Guidance on Cancer Services

Improving Outcomes in Brain and Other CNS Tumours

The Evidence Review

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Introduction

This document contains a summary of the evidence reviewed for the production of the recommendations in Guidance for Commissioning Cancer Services – Improving Outcomes in Brain and Central Nervous System Tumours – The Manual. As with previous documents in this series, the topic areas are dealt with in the same order as in the Manual to facilitate cross referencing.

The purpose of the review is to determine the current evidence on interventions and models of care to guide and improve service provision for people with brain and Central Nervous System (CNS) tumours.

An assessment of need for cancer services for patients with brain and CNS tumours in England and Wales was undertaken as background to this service guidance and accompanies this document on the CD-ROM.

Methodology

Searching for evidence

The stages in the identification and retrieval of evidence are as follows:

1. Clinical question development

The members of the Guidance Development Group (GDG) were asked to consider the issues covered in the project scope and to submit clinical questions covering these issues. Questions were submitted to the National Collaborating Centre for Cancer (NCC-C).

2. Literature searching

Systematic search strategies were constructed by the Information Specialist to identify published evidence for the research questions set by the GDG. A sample search strategy is provided as Appendix A. The search period ended at the end of April 2005.

Unlike clinical guidelines which focus on specific clinical questions, the research questions for this service guidance addressed broad issues of service provision.

Consequently, there was a wide range of topic areas for consideration. For this reason and, due to the large number of research questions, the questions were prioritised by the Lead Researcher/GDG Chair/GDG Clinical Lead for either full searching (using search strategies as shown in Appendix A) or 'high level' searching. High level searching involved identifying evidence from other suitable sources, examples of which are provided in Appendix B.

Studies were selected for critical appraisal according to the hierarchy of evidence (Scottish Intercollegiate Guidelines Network 2002; National Institute for Health and Clinical Excellence 2005), relevance to the research questions and applicability to service provision within the NHS in England and Wales.

Identified titles and abstracts were initially screened for relevance to the clinical question by the Information Specialist and thereafter by the Researcher. Definite inclusion/exclusion criteria were not employed for articles, because of the nature and variability of the literature on service delivery. Only articles in English were selected for critical appraisal. In some instances help from a member of the GDG was enlisted to verify the relevance of selected articles and as a supplementary check on the completeness of the search. In general no formal contact was made with the authors for each paper identified, but occasionally communication was made for clarification of specific points.

3. Critical appraisal

The identified studies were critically appraised and graded for quality using the methodology from the NICE Guideline Development Methods Manual (National Institute for Health and Clinical Excellence 2005) and the information relevant to the questions was extracted and entered into the evidence tables. The evidence grade appended to each study in the evidence table reflects both the study design (e.g. randomised controlled trial (RCT), case series study) and also a judgement of the study methods applied, accepting the study design (i.e. good, fair, poor). In this way the quality of the evidence to support the recommendations made in the manual is explicit. The evidence grading scheme used is shown as Appendix C.

Owing to practical limitations it was not possible for the team of researchers undertaking this review to double review each study.

4. Synthesising evidence

As a general comment, evidence quality for many of the research questions is poor. There were very few RCTs relevant to the majority of the clinical questions. This is a widely acknowledged problem with health service research and every effort was made to maximise the retrieval of relevant high quality literature. Where available, evidence from good quality systematic reviews and meta-analyses was appraised and included in the evidence tables; not all studies in the reviews were individually appraised.

The evidence tables recommended for use in the NICE methodology manual were modified to accept the type of studies identified for service guidance. In addition to the evidence tables a brief evidence summary is provided with each table titled, *Summary of the supporting evidence for the recommendations*. The relevant research questions are included at the beginning of each section and also at the top of each evidence table. References are included at the end of this document.

Other sources of evidence

Key strategic documents pertinent to brain and CNS tumours were also identified as sources of evidence. Relevant national and international guidelines were accepted as sources of evidence and were appraised for quality using the Appraisal of Guidelines Research and Evaluation tool (AGREE).

GDG member and stakeholder submissions

A small volume of evidence was identified by individual GDG members or by stakeholders during consultation period(s). This evidence, like that from other sources, was critically appraised.

Complementary paper

One complementary paper was written for this guidance, titled ‘The role of Neuropsychiatry in the treatment of neuro-oncology patients’. This paper sets out current patterns of referral and treatment with regard to the role of neuropsychiatry in brain and CNS cancer, and is attached as Appendix D.

Recommendations

Drafting recommendations

The GDG members were allocated specific topic areas and asked to review the evidence tables pertaining to the topic and draft recommendations for the service guidance.

Agreeing recommendations

Once an early draft of the guidance was produced, the GDG members were asked to review the draft document and consider whether:

a) there appeared to be any major gaps in the synthesised evidence.

b) the recommendations were justified from the evidence presented and whether they were sufficiently practical and precise so that health service commissioners and the relevant front line healthcare professionals could implement them.

During the development of this guidance no formal consensus methods were used. Consensus was achieved by informal means during GDG meetings and correspondence outside the meetings.

In this guidance, recommendations are not graded.

Writing of the guidance

The first formal draft version of the guidance was coordinated by the Chair and Clinical Lead of the GDG in accordance with the decisions of the GDG. The draft guidance was circulated for consultation according to the formal NICE stakeholder consultation and validation process prior to publication.

Chapter 1 Multidisciplinary teams

The question

In patients with a radiological diagnosis of a malignant brain or CNS tumour what is the best MDT model to ensure all get an appropriate opinion?

The nature of the evidence

Indirect evidence, from the improving outcomes service guidance series, supports the multidisciplinary team model of the management of patients with cancer. The literature search, however, uncovered little direct evidence about multidisciplinary team models for patients with brain or CNS tumours.

- A UK study (Commission for health improvement & Audit Commission 2001) audited the proportion of trusts with regular MDTs for patients with brain and CNS tumours. The study also recorded the staff structure of the MDTs.
- A UK review (Clarke 2003) considered the role of the clinical nurse specialist in the management of patients with high grade glioma. Another UK review article (Hill 2000) considered clinical nurse specialists in general cancer care.
- American reviews (Burger *et al.* 1997) looked at the role of the multidisciplinary team in the management of patients with low grade and high grade brain tumours.
- A DOH publication defined standards for generic cancer MDTs.
- A UK paper (British Association of Head and Neck Oncologists. 2001) reported proposed standards for multidisciplinary meetings for patients with head or neck cancer.

Summary of the supporting evidence for the recommendations

There is good evidence that multimodal treatment is often necessary for people with brain and other CNS tumours (see for example chapters four to ten) – but evidence about the structure of teams to deliver this treatment is consensus based. There were no studies evaluating the effectiveness of MDTs in this patient group. The

inclusion of clinical nurse specialist as a core member of the MDT is supported by expert opinion.

Table 1.1 In patients with a high grade brain or CNS tumour what is the best multidisciplinary team model?

Abbreviations MDT, multidisciplinary team;

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Commission for health improvement & Audit Commission 2001)	NHS Cancer Care in England and Wales	Survey MDT working in 22 NHS trusts (within 9 networks) in England and Wales.		Less than 30% of trusts reported regular patient-planning MDTs for neurological/brain and CNS patients. Where an MDT was present the percentage membership was:- Lead physician/surgeon 100% Pathologist 83% Non-surgical oncologist 81% Other surgeon/physician specialising in same cancer 78% Nurse specialist 74% Radiologist 69% Palliative care nurse 34% Palliative care doctor 31% Medical trainees 23% Therapy radiographer 10% Information specialist 9% Service manager 9% Dietician 9% Ward nurses 7% Speech therapist 4% Physiotherapist 4% Social worker 4%	Small sample. The evidence is drawn from supporting data document 5 – multidisciplinary team working	Cross sectional survey	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Trials/audit 1% Pharmacist 1% OT 1%			
(Clarke 2003)	Patients with glioma UK	Review of literature on the role of the neuro-oncology nurse specialist		There is some observational evidence to indicate a role for a neuro-oncology nurse specialist in the coordination of care, directing patient care and in research. The nature of the illness predicates a need for good supportive care. There is evidence to indicate that the nurse specialist has a pivotal role to play in this.	*Only relevant to nurse specialist*	Expert opinion/review	4-
(Hill 2000)	Cancer nurse specialists			The author concludes that clinical nurse specialists, working with specific cancer populations, are likely to provide better information and support for patients. There is a lack of evidence, however, to define the exact role and specification of the cancer nurse specialist.		Expert opinion	4-
(British Association of Head and Neck Oncologists. 2001)	Patients with head and neck cancer UK	Development of service standards		This paper outlines the minimum standards to be achieved by a head and neck cancer unit. It proposes a functional centre comprising associated units all of which will adopt the same standards and commitment to quality. The paper also proposes a suggested pathway for patients, describing various levels of care through which patients may pass as appropriate together with minimum standards relating to those levels. The skills and training required by various clinicians at different levels are outlined. The paper also describes a multidisciplinary clinic and multidisciplinary	*Some relevance to question. Developed by consensus*	Guidelines	4+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				meeting (MDM), seen as the core service to patients and describes appropriate standards relevant to the clinic. RESULTS RELEVANT TO MDT: The MDM should include audit, the formulation and planning of research and the rehearsal of clinical presentation The meetings should discuss pathological diagnosis, patient management and review success of rehabilitation strategies The meetings should also monitor patient outcomes, review 'new' patient treatments and review treatment plans of patients who have tumour recurrence The meetings should also be used for review of clinical activity and to review survival and also to review the 'process system' of the service – to identify delays in the service, diagnostic errors etc. During the meeting 'new' patients can be presented and treatment planning discussed			
(Burger *et al.* 1997)	Patients with low grade neoplasms or nonneoplastic lesions	Development of checklist to avoid misinterpretation of low grade neoplasm or nonneoplastic lesions as biologically aggressive.	Inappropriate over-treatment (administration of chemotherapy and/or radiotherapy) of low grade neoplasms or nonneoplastic lesions.	Authors discuss the following conditions in which over treatment may occur:- Pilocytic astrocytoma; pleomorphic xanthoastrocytoma; ganglion cell tumours; desmoplastic infantile ganglioma; neurocytic neoplasms; dysembryonic neuroepithelial tumours; haemangioblastoma; demyelinating disease; infarction; progressive multifocal leukoencephalopathy;	*Does not address MDT models. Some evidence given for statements. The authors discuss the roles of the different specialists*	Expert opinion	4+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				gliosis; pineal cyst;cerebral contusion. The authors stress the importance of the consideration clinical, radiological and pathological features which can suggest a low grade or benign tumour. They advocate an interdisciplinary review of patients with suspected CNS tumours, before any treatment plan made.	*in obtaining the correct diagnosis and subsequent treatment*		
Department of Health. National Manual of Quality Measures for Cancer Peer Review. Topic 2 – The generic multidisciplinary team (MDT). DoH 2004	All patients with cancer UK	Standards for generic MDT		Detailed description of standards and measures of compliance.	*These generic MDT standards will be replaced with site specific ones as such guidance becomes available.*	Expert opinion/consensus	4+
Christie Hospital NHS Trust. Central nervous system	All patients with CNS tumours UK	Development of care pathway		The pathway describes 9 milestones that a patient requiring CNS cancer care may meet during the disease process together with aspects of care that can be expected at each stage. Appendices describe the function of the neuro-oncology nurse specialist, criteria for referral to professions allied to medicine and levels	*Highly relevant to question*	Consensus/ evidence based development care pathway	4++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
cancer care pathway. 2000				of care identified by the Working Group.			

Chapter 2 Presentation and referral

The question

Does early diagnosis improve outcome – is tumour size important?

The nature of the evidence

All the studies identified by the search were observational in design

- A retrospective cancer registry based study of people with CNS tumours (Northern and Yorkshire Cancer Registry and Information Service & University of Leeds 1998) in an English Region.
- An American prospective study of the diagnosis of brain tumour in primary care (Becker *et al.* 1993).
- Retrospective case series of patients with: acoustic neuroma (Moffat & Hardy 1989); spinal tumours (HogenEsch & Staal 1988); and high grade glioma (Salander *et al.* 1999).

The studies quantified diagnostic delay using

- The interval from GP referral to treatment (Northern and Yorkshire Cancer Registry and Information Service & University of Leeds 1998).
- The interval between first presentation with a headache and performance of the first CT scan (Becker *et al.* 1993).
- Tumour size (as an indirect indicator of delay) (Moffat & Hardy 1989)

The reported outcomes were

- Overall survival (Northern and Yorkshire Cancer Registry and Information Service & University of Leeds 1998).
- Postoperative morbidity (HogenEsch & Staal 1988; Moffat & Hardy 1989)
- Delayed or missed diagnosis (Becker *et al.* 1993; Salander *et al.* 1999)

Summary of the supporting evidence for the recommendations

None of the studies directly addressed the question, although three studies considered the relationship between diagnostic delay and outcome. The Northern and Yorkshire registry study (Northern and Yorkshire Cancer Registry and Information Service & University of Leeds 1998) measured the interval between GP referral and treatment. For people with low grade glioma there was no relationship between this interval and survival, whereas a shorter interval was associated with poorer overall survival for those with high grade glioma. The authors identified confounding factors–patients with very poor prognosis were more likely to receive urgent palliative treatment, whereas the time taken to plan radical therapy increased treatment delay in those with better prognosis.

HogenEsch and Staal (HogenEsch & Staal 1988) stated that patients with greater preoperative duration of symptoms were more likely to have postoperative morbidity in their case series, but they did not use statistical analysis. The study of Moffat and Hardy (Moffat & Hardy 1989) reported a positive relationship between the size of an acoustic neuroma and postoperative morbidity. However, it is unclear how tumour size relates to diagnostic delay.

There is observational evidence that some patients with intradural tumours of the spinal cord experience considerable delays in diagnosis that can affect their postoperative outcome (see section on patients with spinal cord tumours, chapter 9).

The NICE *referral guidelines for suspected cancer* reviewed evidence about the diagnostic difficulties and delays when people with brain tumours present to primary care. The reviewers concluded that there was insufficient evidence to reach any strong conclusions. Their evidence about the influence of delay on outcomes was limited to patients with spinal cord compression from non-CNS tumours. The review concluded that the initial symptoms of brain tumours (such as headache and dizziness) are often not specific and diagnostic delays can result (Salander *et al.* 1999; Becker *et al.* 1993).

Table 2.1 Does early diagnosis improve outcome?

Abbreviations: GP, general practitioner; CT, computed tomography; A&E, accident and emergency.

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Northern and Yorkshire Cancer Registry and Information Service & University of Leeds 1998)	Treatment practices in the former Yorkshire Region during 1986-1994. The registry recorded 2948 new patients with tumours of the CNS during the study period.	None	The interval from GP referral to start of treatment. Length of management interval Surgery to radiotherapy interval Overall survival.	Interval from GP referral to treatment: 49.1% of patients with CNS tumours were treated within one month of referral by GP. This proportion was highest for patients with high grade glioma (60.7%). For the majority of patients with meningioma (56%) and LGG (56%), this interval exceeded one month. Interval from GP referral to treatment generally increased in the latter third of the study period, which the author interpreted as due to longer waiting times for a hospital appointment. Impact on survival: For patients with LGG there were no significant difference in survival associated with interval of referral by GP to treatment (p>0.2). For patients with meningioma and for patients with HIGH GRADE GLIOMA, survival was significantly shorter for patients treated within a month of referral (p=0.02 and p-0.001 respectively). The authors concluded that this finding was because patients with more urgent symptoms and poorer prognosis necessitated urgent referral and treatment. Length of management interval: 62.3% of all patients with CNS tumours were treated within two weeks of their first attendance in hospital.	*The author emphasises that referral data was more likely to be available for good prognosis patients and less likely for patients with high grade glioma or aged >60 years. Given that planning of treatment in the good prognosis group takes longer than planning palliative care, referral intervals may be over estimated.* *Date of GP referral was available for 30% of patients with CMS tumours, date of first hospital visit for 98.6% and date of*	Retrospective population based case series	3++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Surgery to radiotherapy interval: 61% of patients with glioma commenced radiotherapy within 4 weeks of surgery. This value was 46.1% for patients with LGG and 64% for patients with HIGH GRADE GLIOMA. The authors attributed this to the longer time requirement to plan radical, as opposed to palliative treatment. Over the study period the proportion of patients for whom this interval exceeded four weeks increased. No significant effect upon survival was observed according to this interval.	*first treatment for 88.1%.*		
(Becker *et al.* 1993)	Fifty-eight practices reporting 712,750 patient visits. Patients with a new diagnosis of intracranial tumour, subarachnoid haemorrhage, or subdural haematoma. USA	The aim of the study was to study the signs and symptoms with which these patients presented to primary care physicians, and estimate the extent to which a more aggressive investigative strategy for patients with headaches would have led to earlier diagnosis.	Diagnostic delay. The authors defined delayed diagnosis as an interval between first presentation with a headache and first CT scan greater than two weeks.	25 new intracranial tumours were reported during the recording period. These were 8 benign neoplasms, 12 primary malignancies and 5 secondary malignancies. 12/25 (48%) of the patients with intracranial tumour reported headache. Four patients with brain tumours visited their primary physician with a headache one month or more before a diagnostic CT scan was performed. Diagnosis was delayed in only four patients with headache caused by a brain tumour. Authors conclude that over-reliance on the symptom of headache as an indicator of serious intracranial disease could lead to under-diagnosis. The study did not identify a large number of patients for whom a clinically significant delay in diagnosis occurred. Over 70% of the patients with headaches due to subarachnoid haemorrhage, tumour, or subdural haematoma were		Prospective audit	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				correctly identified by GPs			
(HogenEsch & Staal 1988)	13 adults (6 female, 7 male, mean age 40yrs [14-60 yrs]) with tumours of the cauda equina. NETHERLANDS	Surgical excision of the tumour in all 13 cases and radiotherapy in 4 cases.	Post operative morbidity.	The initial and most prominent sign was pain, localised at the lower back. The duration of symptoms (before definitive diagnosis) ranged from 0.2 to 25 years. The authors state that preoperative duration of symptoms was an adverse prognostic factor for improvement of symptoms, but their analysis was qualitative.		Retrospective case series	3-
(Moffat & Hardy 1989)	66 patients (39 female, 27 male, mean age 51 years [19–72]) with acoustic neuroma. 3% had small (intracnalicular) tumours, 38% had medium (10–25 mm) tumours and 59% had large (>25cm) tumours. UK	Complete surgical excision of tumour	Post operative morbidity	Deafness was the most common presenting symptom (present in 73% of patients). 59% of patients had large tumours; 38% medium size and 3% small tumours. 60/66 patients had a good results defined as completely independent and working. Tumour size and post operative morbidity The facial nerve was preserved in 100% of the patients with small tumours, 83% of those with medium tumours and 51% of those with large tumours. Two patients with large tumours died in the perioperative period. Two patients with large tumours experienced paresis of the IX, X and XI cranial nerves.	*Only 2 patients (3%) had small tumours. There is no statistical analysis of tumour size as a prognostic factor.*	Retrospective case series	3-
(Salander *et al.* 1999)	28 patients (18 men, 10 women, mean age 55 years) with malignant gliomas	Description of symptom development	Barriers to diagnosis of cerebral tumours	20/28 patients presented to primary care. Eight were immediately referred to A & E. Persistent and intense headache and seizure were the most common symptoms at diagnosis.. Headache was	*Small sample size. Insufficient details of methods.* *Low relevance to*	Prospective qualitative study	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	and their spouses. SWEDEN			persistent in half of the ten cases, and was accompanied by vertigo and/or vomiting. Doctors immediately referred two patients for a CT scan. The others were diagnosed as 'sinusitis', work related, vestibulitis, pregnancy, and headache due to tension. Severe or unusual symptoms were associated with shorter times to diagnosis. Less unusual symptoms such as headache were attributed to trivial causes and postponed help seeking. Physician factors in the diagnostic process that affected the time lag for referral were related to the fact that headache, for instance, had numerous reasonable causes that seemed more likely than a brain tumour. The authors conclude that time to diagnosis is not just a matter of symptomatology. Spouses are an important provider of information	*question. Does not discuss tumour size.*		+/-

Chapter 3 Diagnosis

The questions

a) Do new diagnostic techniques alter diagnosis and affect patient management?

b) What is the optimal biopsy technique for intracranial tumours?

c) Should all patients be biopsied?

d) Is interpretation by a neuroradiologist better than a general radiologist

e) Which molecular diagnostic tests currently have clinical utility for the management of adult brain tumours?

f) Does intra-operative biopsy with on site pathology improve diagnostic accuracy?

The nature of the evidence

a) Do new diagnostic techniques alter diagnosis and affect patient management?

There were insufficient research resources to perform full health technology appraisals of the diagnostic imaging techniques used in people with suspected brain tumours. Research concentrated on existing systematic reviews of such technologies.

Studies of position emission tomography included systematic reviews (Matchar *et al.* 2003; Reske & Kotzerke 2001), review articles (Ho, I & Maisey 2002; Jerusalem *et al.* 2003; Hojgaard 2003) and primary studies (Braun *et al.* 2002; Herholz *et al.* 1998; Tralins *et al.* 2002; Sasaki *et al.* 1998)

Studies of the use of magnetic resonsance spectroscopy included systematic reviews (Blue Cross Blue Shield Association 2003; Jordan *et al.* 2003), reviews (Galanaud *et al.* 2003) and primary studies (Rijpkema *et al.* 2003; Burtscher *et al.* 2000; Ishimaru *et al.* 2001; Negendank *et al.* 1996).

Other primary studies compared the use of MRI and CT in the follow up of patients with high grade glioma (Galanis *et al.* 2000) and the use of single position computed

tomography in patients with brain tumours (Lamy-Lhullier *et al.* 1999; Beauchesne *et al.* 2004).

b) What is the optimal biopsy technique for intracranial tumours?

Three studies included comparisons between biopsy techniques for intracranial tumours:

- image guided freehand versus image guided stereotactic(Wen *et al.* 1993)
- frameless versus frame based stereotactic biopsy (Dorward *et al.* 2002)
- stereotactic versus freehand biopsy (Lee *et al.* 1991)

Observational studies reported one or more of the following outcomes for patients undergoing biopsy of intracranial tumour (Bernays *et al.* 2002; Bohinski *et al.* 2001; Dorward *et al.* 2002; Fountas *et al.* 1998; Frighetto *et al.* 2003; Grunert *et al.* 2002; Paleologos *et al.* 2001; Bernstein & Parrent 1994; Boviatsis *et al.* 2003; Fontaine *et al.* 2000; Hall 1998; Kim *et al.* 2003; McGirt *et al.* 2003; Sawin *et al.* 1998):

- morbidity and mortality associated with the biopsy,
- diagnostic yield –the proportion of biopsies which a diagnosis could be made
- diagnostic accuracy –comparing the biopsy diagnosis with the resection diagnosis, in the subgroup of patients who had tumour resection.

c) Should all patients be biopsied?

There was a lack of studies comparing the outcomes of patients who were biopsied with similar patients who were not biopsied.

Observational studies reported the morbidity, mortality and diagnostic yield associated with current image guided biopsy techniques (See evidence for previous question)

Three studies compared the accuracy of the diagnosis of malignancy of intracerebral tumours from CT scans with that from biopsy (Bell *et al.* 2002; Choksey *et al.* 1989; Nishio *et al.* 1991).

Observational studies (Laws *et al.* 2003b; Buckner 2003), an RCT(Vuorinen *et al.* 2003) and two systematic reviews (Grant & Metcalfe 2004; Taylor *et al.* 2004) compared the outcomes of patients with high grade glioma who had surgical resection with those who had biopsy only.

A review article (Samadani & Judy 2003) considered evidence for the safety and usefulness of stereotactic biopsy of brainstem lesions.

An observational study (Stranjalis *et al.* 2003) considered the role of biopsy in patients whose intracerebral lesions were presumed inoperable.

d) Is interpretation by a neuroradiologist better than a general radiologist

The research team identified four studies as follows:

- A UK audit of neuroradiology second opinions (Flynn *et al.* 2005)
- A UK study comparing the accuracy of diagnosis of high grade glioma from brain CT by radiologists and neuroradiologists (Bell *et al.* 2002)
- One UK study of good quality reported a comparison of the original radiological reports with reviews by a specialist oncological radiologist (Loughrey *et al.* 1999) but only around 3% of patients in this study had a brain tumour.
- An American study comparing the evaluation of emergency head CT scans by neuroradiologists and general radiologists (Erly *et al.* 2002).

None of the studies was designed to compare the diagnostic abilities of general radiologists and neuroradiologists.

e) Which molecular diagnostic tests currently have clinical utility for the management of adult brain tumours?

The following articles were included in the evidence table:

- An observational study of the methylation status of the MGMT promoter and survival in patients with glioblastoma receiving adjuvant temozolomide (Hegi *et al.* 2005)

- Four observational studies (Smith *et al.* 2000; Cairncross *et al.* 1998; Ino *et al.* 2001; Sasaki *et al.* 1998) and two review articles (Engelhard *et al.* 2003; Reifenberger & Louis 2003) of allelic loss of 1p or 19q and prognosis in patients with oligodendroglioma (in most cases anaplastic oligdendroglioma)

- An observational study of the use of tumour gene expression profiles to predict prognosis in high grade gliomas (Fuller *et al.* 2002) and a review article of the molecular classification of gliomas (Louis *et al.* 2001)

e) Does intra-operative biopsy with on site pathology improve diagnostic accuracy?

Seven observational studies compared the intraoperative diagnosis of CNS tumours based on biopsy, with that based on paraffin sections (the gold standard). The intraoperative diagnosis was based on

- frozen sections (Regragui *et al.* 2003; Brommeland *et al.* 2003; Shah *et al.* 1998; Martinez *et al.* 1988).

- cytological techniques (Shah *et al.* 1998; Savargaonkar & Farmer 2001; Firlik *et al.* 1999; Martinez *et al.* 1988)

- a combination of frozen sections and cytology(Brommeland *et al.* 2003) (Di Stefano *et al.* 1998; Martinez *et al.* 1988)

Three studies addressed whether intraoperative pathology improved the proportion of biopsies yielding tumour tissue (Regragui *et al.* 2003) (O'Neill *et al.* 1992)(Ellison D, unpublished data 2004).

One study reported a survey of the preferred methods of intraoperative diagnosis of American neuropathologists (Firlik *et al.* 1999)

Summary of the supporting evidence for the recommendations

a) Do new diagnostic techniques alter diagnosis and affect patient management?

Individual case series highlight the potential usefulness of new diagnostic imaging technologies, such as MR spectroscopy, SPECT and PET in the management of

CNS tumours. Meta-analysis of such studies, however, is problematic due to small sample sizes, non-standardised techniques and differences in study populations.

Two evidence-based technology appraisals of MR spectroscopy (Blue Cross Blue Shield Association 2003; Jordan *et al.* 2003) for the evaluation of brain tumours reported that there was insufficient high quality evidence to conclude that MR spectroscopy could replace biopsy in the diagnosis of brain tumours.

There is consensus supporting the usefulness of PET in distinguishing between brain tumour and radiation necrosis. An evidence-based technology appraisal (Matchar *et al.* 2003) estimated the sensitivity of PET in this context as between 76% to 83%, with specificity from 50% to 62%. The review also estimated the sensitivity of PET for distinguishing high grade from low grade gliomas, as ranging from 69% to 100%, with specificity from 57% to 100%. In the absence of studies directly comparing the accuracy of PET with conventional MR for distinguishing low and high grade gliomas, however, it is difficult to estimate whether the addition of PET would improve the pre-operative evaluation of tumour grade.

b) What is the optimal biopsy technique for intracranial tumours?

There was little evidence directly comparing frame based and frameless image directed techniques. The range of the reported outcomes for each technique were as follows.

In biopsies described as frameless, stereotactic and image directed(Bernays *et al.* 2002; Bohinski *et al.* 2001; Dorward *et al.* 2002; Fountas *et al.* 1998; Frighetto *et al.* 2003; Grunert *et al.* 2002; Paleologos *et al.* 2001):

- Perioperative morbidity ranged from 0 to 13%
- Perioperative mortality ranged from 0 to 3%
- Diagnostic yield ranged from 89 to 100%

In biopsies described as stereotactic and image directed (Bernstein & Parrent 1994; Boviatsis *et al.* 2003; Fontaine *et al.* 2000; Hall 1998; Kim *et al.* 2003; McGirt *et al.* 2003; Sawin *et al.* 1998):

- Perioperative morbidity ranged from 3 to 5%
- Perioperative mortality ranged from 0 to 3%
- Diagnostic yield ranged from 92 to 100%
- One study reported diagnostic accuracy (comparing biopsy diagnosis with resection diagnosis) as 79%

One study reported diagnostic accuracy in a mixture of frame based and frameless stereotactic biopsies as 62% (Jackson *et al.* 2001).

A case series (Wen *et al.* 1993) observed little difference in the morbidity and mortality associated with image directed freehand and stereotactic biopsies, although there was no adjustment for case mix differences in the analysis. A second series (Lee *et al.* 1991) noted lower mortality and morbidity with frame based stereotactic biopsy than with freehand.

The study of (Dorward *et al.* 2002) observed similar morbidity and mortality in frameless and frame based stereotactic biopsies, but with shorter operation time and hospital stay in the frameless group.

c) Should all patients be biopsied?

There was a lack of direct evidence to answer this question.

Studies comparing the accuracy of the diagnosis of malignancy of intracerebral tumours from CT scans with that from biopsy suggest that CT diagnosis is not accurate enough to replace biopsy in these patients (Bell *et al.* 2002; Choksey *et al.* 1989; Nishio *et al.* 1991).

An evidence based guideline (Mintz *et al.* 2004) (see treatment of metastases section) considered the issue of stereotactic biopsy of presumed solitary brain metastases before initiation of treatment and identified two primary studies. In one study of patients with a known systemic malignancy and a CT scan reported as being consistent with a single brain metastasis, 11% of cases were diagnosed as either primary brain tumours or non-neoplastic lesions following biopsy. The authors concluded that all patients should undergo biopsy. A second study, however,

reported the rate of MRI misdiagnosis in patients undergoing surgical resection of presumed solitary brain metastases as 2%.

Evidence from observational case series can be used to estimate the morbidity and mortality associated with current biopsy techniques (see previous question).

The review article of Samadani (Samadani & Judy 2003) concluded that stereotactic biopsy should be performed for brainstem lesions. The conclusion was based on observational evidence for the safety of the procedure and the variety of pathology in this location.

An observational study (Stranjalis *et al.* 2003) questioned the use of biopsy in patients whose intracerebral lesions were likely to be inoperable.

There was a lack of evidence about the biopsy of presumed low grade glioma.

Studies comparing biopsy with surgical resection in patients with high grade glioma suggest a survival benefit for those undergoing surgical resection.

d) Is interpretation by a neuroradiologist better than a general radiologist

There is some evidence of disagreement in the reports of general radiologists and neuroradiologists. It is difficult to interpret its significance, however, without knowing the levels of diagnostic disagreement between neuroradiologists themselves.

An audit of neuroradiology second opinions (Flynn *et al.* 2005) noted major discrepancy with the referring radiologist in 9% of cases. A comparison of the accuracy of diagnosis of high grade glioma from CT scan by radiologists and neuroradiologists (Bell *et al.* 2002) did not observe a statistically significant difference between the two groups. The study reported relatively low sensitivity for the overall diagnosis of high grade glioma from CT.

The remaining studies provided indirect evidence. A study of emergency head CT scans (Erly *et al.* 2002), found 9% disagreement between the reports of general and neuro-radiologists. A study of specialist onocological radiology review of cross sectional imaging (Loughrey *et al.* 1999) noted that reporting of MRI and CT studies performed at referring centres was often incomplete.

e) Which molecular diagnostic tests currently have clinical utility for the management of adult brain tumours?

Observational study evidence suggests that loss of 1p 19q of heterozygosity predicts response to chemotherapy and survival in patients with oligodendroglioma (Cairncross *et al.* 1998; Ino *et al.* 2001; Sasaki *et al.* 1998; Smith *et al.* 2000).

A recent trial (Hegi *et al.* 2005) identified a potential role for molecular diagnostic testing in predicting the response of patients with glioblastoma to temozolimide. Methylation status of the MGMT promoter was a prognostic factor for overall survival in people with glioblastoma. Patients whose glioblastoma contained an unmethylated MGMT promoter may benefit less from the addition of temozolomide therapy to radiotherapy than patients whose tumours had a methylated MGMT promoter.

f) Does intra-operative biopsy with on site pathology improve diagnostic accuracy?

Consistent evidence supports the usefulness of intraoperative neuropathology to confirm the adequacy of biopsy specimens. A UK case series (O'Neill *et al.* 1992) described how the diagnostic rate for stereotactic CT-guided biopsy of intracranial lesions was improved from 87% to 94% by the introduction of intraoperative cytopathology. Two UK audits (Ellison D, unpublished data 2004; Bristol Audit of intraoperative histopathology, unpublished data) both showed increased diagnostic yield following stereotactic biopsy if an intra-operative histological procedure was done to confirm that sufficient tissue had been obtained for diagnostic purposes.

Six observational studies (Shah *et al.* 1998; Regragui *et al.* 2003; Savargaonkar & Farmer 2001; Brommeland *et al.* 2003; Martinez *et al.* 1988; Di Stefano *et al.* 1998) examined the accuracy of the intraoperative histopathological and cytopathological diagnosis of central nervous system tumours. Agreement between intraoperative diagnosis based on frozen sections and the definitive diagnosis occurred in between 87 and 90% of cases. Intraoperative diagnosis using both histopathological and cytopathological techniques, was more accurate, with 91 to 95% concordance.

Table 3.1 Do new diagnostic techniques alter diagnosis and affect patient management?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Galanis *et al.* 2000; Rijpkema *et al.* 2003)	231 patients (out of 268 with sufficient follow-up data) with high-grade gliomas (85% grade 4, 15% grade 3). 94% pure astrocytic, 6% also had oligodendroglial elements. Mean age 55 years.	Follow-up with neurological examination and neuroradiological investigations (either MRI or CT)	Proportion of symptomatic (new or worsening symptoms) and asymptomatic (no change in baseline symptomatology) patients. Proportion of patients with progression detected on MRI or CT imaging. Factors associated with survival.	177 (77%) patients became symptomatic. 54 (23%) were asymptomatic. In all asymptomatic patients, progression was detected on MRI or CT scan none was detected on neurological examination alone. MRI detected asymptomatic progression more often than CT (31/91[34.1%] with MRI versus 23/119 [19.3%] with CT, P < 0.01). Asymptomatic patients were more aggressively treated with surgery (P < 0.0001) and second-line chemotherapy (P < 0.0002). Multivariate analysis showed that treatment at recurrence was the most important predictor of survival time following first progression.	The authors concluded that MRI was more likely to detect asymptomatic recurrence than CT scanning. They recommend routine surveillance neuroradiological imaging for patients with high-grade gliomas. *Patients had either MRI or CT imaging.* *MRI and CT not compared in same population and this may have influenced results. Characteristics of excluded patients similar to included patients. Duration of follow-up was*	Retrospective observational study	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					not reported.		
(Braun *et al.* 2002)	32 patients with 34 intracranial lesions detected by MRI. The pathophysiology of lesions had to be unclear or tumour delineation could not be exactly defined by MRI All lesions were treated surgically 26 patients had tumours (14 malignant and 7 benign gliomas), 3 had gliomas without further histological typing, 1 had Ewing sarcoma, 1 had non-Hodgkin lymphoma. Germany	^{11} C methionine positron emission tomography (PET)	Number of lesions with increased methionine uptake and histology of these lesions. Number of methionine negative lesions and histology of lesions. Sensitivity. Specificity, postive predictive value (PPV), negative predictive value (NPV) of ^{11}C methionine PET	27/34 lesions showed increased methionine uptake. Histology of these lesions was: 1 gangioglioma; 6 gliomas WHO II; 12 gliomas WHO III; 2 glioblastomas; 2 low grade gliomas (no further typing); 1 glioma in quiescant stage (was suspected recurrence but necrosis was found); and 2 metastatic lesions. 7/34 lesions were methionine negative. Histology was: 2 gliosis; 1 metastatic Whipples; 4 tumours (2 astrocytomas; 1 DNT; 1 astrocytoma WHO III) Diagnostic accuracy of ^{11}C methionine PET for Tumour: Sensitivity: 87%. Specificity: 75% PPV: 96% NPV: 43% 11 C methionine PET data was integrated into cranial neuronavigation in 25 patients.	*Pilot study. Analysis on basis of lesions and not patients. No details of the number and experience of observers reading scans. No details of intra-observer variation.*	Diagnostic accuracy study	3
(Herholz *et al.* 1998)	196 patients with suspected brain tumours had 11C methionine uptake measured. Mean	^{11}C-methionine PET scan. CT or MRI performed	Methionine uptake index according to grade of glioma.	99 patients had diagnosis confirmed as astocytoma, oligoastroctyoma, or oligodendroglioma. Malignant astrocytomas (grade 3 or 4) had signficantly higher methionine uptake (28 patients,	The authors concluded that the high sensitivity of 11C methionine	Diagnostic accuracy study	2

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	age 45 years; 55% male. 15 patients were excluded due to inconclusive clinical data. Results for 99 untreated patients with suspected glioma and histological diagnosis were used to assess C-methionine uptake. 84 patients were used to assess CT scans or MRI	within a few weeks of PET scan.	Influence of corticosteroid dose on methionine uptake. CT and MRI scans assessed for contrast enhancement according to grade of glioma. Power of PET to discriminate between non tumours and tumours was assessed.	3.0) than low grade astrocytoma (47 patients, 1.7) which had a signficantly higher methionine uptake than nontumour lesions (24 patients, 1.3). There was no signficant effect of steroids on methionine uptake in low grade astrocytomas; uptake significantly but moderately reduced in glioblastomas. Moderate or intense enhancement more commonly seen on CT or MRI with high grade compared with low grade gliomas (10/21[48%] v 6/41[15%]). Enhancement found in 9/22[41%] of non tumour lesions. Using threshold of 1.47 for methionine index uptake correctly classified 79% of scans as tumour or nontumour. Sensitivity 76%, specificity 87%.	uptake is useful for evaluation and follow-up of low-grade gliomas. *Not all eligible patients were included- doubtful cases were excluded.* *Cases without CT or MRI scans were also excluded.* *Some patients had more than one PET- not clear if this was allowed for in comparing PET with MRI and CT.* *No details given of the number and experience of observers reading scans. Agreement between observers was not mentioned.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Ho, I & Maisey 2002)	Aim: to *examine the current indications and data supporting the use of PET in oncology* For primary brain tumours gives 8 references Inclusion criteria not explicitly defined in terms of participants. Included section on primary brain tumours as well as a variety of other cancers (lung, colorectal, lymphoma, melanoma, breast, head and neck, oesophagus and gastric, testicular, and soft tissue)	^{18} F-2-fluoro-2-deoxy-D-glucose (FDG) PET . Mentions C-methionine in brain tumour section	Inclusion criteria not explicitly defined in terms of outcomes. Outcomes mentioned included: diagnostic accuracy.	*The following statements were not supported by any critical evaluation of evidence.* For primary brain tumours: Says major use of PET is in differentiation of tumour recurrence from post-therapy necrosis. FDG-PET can detect high grade recurrence and high FDG uptake in recurrent tumours is associated with decreased survival. FDG does not provide information about tumour extent. 11 C-methionine outlines tumour extent but does not provide prognostic information. Additional uses of PET include detection of low grade to high grade transformation and to improve accuracy of biopsy sampling.	The authors concluded that PET is a powerful and now well established method for functional imaging. *More a source of background information.* *Not a systematic review and hence has the potential for bias*. *There was no search strategy, inclusion criteria, details of the number of studies identified, full details of the included studies or critical analysis of the evidence*.	Review	4
(Tralins *et*	27 patients aged > 18	Patients were treated	Exploration of the	Mean actuarial time to tumour progression was 43	The authors	Observational	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
al. 2002). Aim: to assess use of ^{18}F- FDG PET scans in predicting tumour progressi on and survival in patients with glioblatom a mulitiform e	years with a diagnosis of glioblatoma mulitiforme and Karnofsy Scale score > 60. Mean age 46 years (range 23 to 72 years), mean KS 96 (range 70 to 100). 38 patients recruited but 11excluded (8 had not yet received first follow-up, 2 could not undergo MRI and 1 progressed before PET). All ^{18}F- FDG PET scans read by single experienced observer (aware of clinical characteristics but 'generally' unaware of of patients' condition over course of radiotherapy). Washington State, USA	with standard conformational fractionated radiotherapy (1.8 to 59.4 Gy per fraction) with volumes determined by MRI. At doses of 45 to 50.4 Gy patients underwent 18F- FDG PET scan for boost target delineation. Criteria for metabolically active areas using ^{18}F- FDG PET scan were defined.	effect of the following variables on tumour progesssion and survival: age; KS; MRI-based volumes; and ^{18}F-FDG PET volumes. Concordance between MRI and ^{18}F- FDG PET volumes	weeks. Mean actuarial survival after diagnosis was 70 weeks. The mean abnormal area defined by ^{18}F- FDG PET scan was significantly smaller than the area defined by T1 weighted MRI gladolinium enhancement volume (P = 0.0018) and TI weighted MRI gadolinium enhancement plus resection cavity volume (P =0.0001). 21 patients showed increased ^{18}F- FDG PET uptake, 6 patients did not. 16 patients had tumour progression after radiotherapy. 12 of these patients showed abnormal ^{18}F- FDG PET uptake. Of the 6 with no abnormal ^{18}F- FDG PET uptake, 4 had tumpur progression. Mutlivariatee analysis showed than only ^{18}F- FDG PET scan was a signficant predictor of time to tumour progression (P = 0.0022) and survival (P = 0.018).	concluded that compared with MRI, ^{18}F- FDG PET delineated unique volumes for radiation dose escalation. ^{18}F-FDG PET volume predcited survival and time to tumour progression. *Small sample size-authors described this as a pilot study.* *Absence of abnormal upake does not appear to indicate that tumour progression in unlikely since 4/6 with no initial abnormal uptake went on to tumour progression.*	study	
(Sasaki *et al.* 1998)	23 patients with astrocyte tumours (7 had	Tracers assessed were:	Each tracer and T1 uptake was	^{201} TI uptake increased with the grade of tumour and differed significantly among groups (grade II: 1.51	The authors concluded that ^{201}	Observational study	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
Aim: to compare Thallium-201, carbon-11 methionine (MET), Fluorine-18 fluorodeoxyglucose (FDG), and ^{201} TI single-photon emission tomography (SPET) in patients with astrocytic tumours.	astrocytoma, grade II; 10 had anaplastic astrocytoma, grade III; 6 had glioblastoma, grade IV), age ranged from 16 to 73 years. Diagnosis was made pathologically. All patients had undergone surgery. Japan	Thallium-201, carbon-11 methionine (MET) and Fluorine-18 fluorodeoxyglucose (FDG) ^{201} TI single-photon emission tomography (SPET), MET positron emission tomography (PET) and FDG PET were performed.	evaluated for its ability to determine histological grade and extent of astrocytoma	(0.36); grade III: 2.58 (1.50); grade IV: 7.65 (3.84)) MET uptake in grade II was significantly lower than grade III or IV (grade II: 1.49 (0.44); grade III: 3.29 (1.44); grade IV: 3.20 (0.92)) FDG uptake did not differ among groups.	TI was more useful than either MET or FDG in evaluating the histological grade of astrocytoma although TI did not reliably differentiate between some grade III and II tumours. MET was very useful in detecting astrocytomas and their extent and for differentiating benign from malignant but was not useful enough at distinguishing the histological grade. FDG was not useful. *Small sample size all patients with known astrocytoma. Appears to be more a pilot study*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					than a diagnostic accuracy study.		
(Jerusalem *et al.* 2003). *Aim: to discuss the most promising indications for PET in oncology, the shortcomings and the important questions to be answered before PET is introduced into routine practice*	Mentioned studies of patients with brain tumours, lung cancer, pancreatic masses, colorectal cancer, Hodgkins and non-Hodgkins lymphoma, seminoma, germ cell carcinoma, head and neck cancer, melanoma. *The type of cancer was not always specified for studies presented in this report*	The use of PET was discussed under the following headings: potential clinical applications of 18F-FDG PET examined in qualitiative studies (screening; differentiating benign from malignant tumours; detection of primary site; staging at initial diagnosis and relapse; end of treatment evaluation; rountine follow-up); and quantitative PET studies (use of standardised uptake value as a new prognostic factor; measurement of clinical and subclinical response).	N/A	Says that although PET may be useful in other tumours, the available data are too scarce to allow recommendaitons. RE: brain tumours (P1530) The evaluation of brain tumours is the longest established oncological application of PET. Says CT / MRI are limited in their ability to differentiate recurrence of cerebral gliomas from benign posttherapuetic lesions. PET has been shown to be more accurate in monitoing therapeutic response but 18F-FDG is clearly not the best radiotracer. Says 11C-methionine is a better radiotracer but its use is restricted to PET centres with on-site cyclotrons. One reference given for brain tumours	The authors concluded many studies have shown high accuracy using 18F-FDG PET for the detection and stanging of malignant tumours and for monitoring therapy it is important to assess the impact of these techniques on patient outcome and to show cost-effectiveness from the societal viewpoint. *Non systematic overview.* *The authors quote results from selected studies but provide no details of how*	Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					these studies were selected for inclusion or critical evaluation of the evidence.		
(Hojgaard 2003). *Aim: not specifically stated. / to examine the extent to which the HTA concept addresses the criteria for high quality health care set out by the WHO (high professional*	Oncology patients	PET	Usefulness of HTA reports	*Discussion about different conclusions reached by HTAs in various countries about the value of PET in oncology*. Summarised below Wuff and Gotzsche (2000) recommended that studies of the efficacy of a new diagnostic test should compare the test result with the presence or absence of disease. However, the correct diagnosis can be difficult to determine. Previously new diagnostic tests were introduced without evaluation. Author asserts that HTA reports have had a very large influence on the introduction and use of PET in clinical oncology. Norway HTA 2000: no documented evidence supporting PET Denmark HTA 2001: no evidence regarding the clinical use of PET. Danish National Board of Health 2002: dedicated PET is useful in oncology.	The author concluded that 'new diagnostic imaging techniques such as PET and PET/CT should be used on the basis of scientific evaluation rather than HTA reports, as their value is questionable. The HTA concept needs to be developed and improved and achieve a higher degree of reliability and the conclusions should not be regarded as infallible. The important issue is whether a new	Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
standard; minimal patient risk; effective use of resources ; high patient satisfaction; coherent patient treatment) .				FDA in USA approved PET Other HTA reports published in UK, Australia, Canada, Scotland, Spain, Germany, anf France All are members of INAHTA and claim to use the same methodology. The reports reached different conclusions. The author asks if HTA reports can be trusted given that they reached different conclusions using the same methodology. The authors considers the 2 crucial questions to be: is it appropriate to require documentation which shows better survival due to PET when such data have not been required before the introduction of other technologies?. And Is it appropriate to demand RCT for documentation purposes? Should the assessment of a diagnostic tool be linked to patient outcome in the first place? The author suggests that HTA reports have lagged behind research and technological developments.	method will improve diagnosis for the patients, as treatment benefit based on new diagnostic gain may follow some years later.		
(Matchar *et al.*	13 studies met the inclusion criteria.	The aim was to evaluate the clinical	The usefulness of PET for: guidance	Guidance of biopsy The search did not identify any studies that directly		Systematic review (for	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
2003)	Inclusion criteria Studies of PET for patients with suspected or confirmed brain tumour, English language articles reporting primary data and published in a peer review journal (not abstracts), studies including at least 12 human subjects (not animal studies). If the study was of diagnostic accuracy then a reference standard had to be obtained on all patients.	usefulness of PET in for patients with brain tumours or, cervical, small cell lung, ovarian, pancreatic or testicular cancer.	of biopsy; distinguishing tumour recurrence from radiation necrosis and for distinguishing high from low grade gliomas in patients with indeterminate biopsy.	addressed how PET may affect biopsy performance for patients with recurrent brain tumour. Distinguishing tumour recurrence from radiation necrosis This was the most commonly reported use for PET in the management of people with brain tumours. The sensitivity of PET for this use ranged from 76% to 83% with specificity from 50% to 62%. Authors comment that 'while the specificity may not be sufficient to rule in recurrence (and rule out necrosis), it may be adequate in some cases to rule in radiation necrosis (and rule out recurrence.)' Distinguishing high-grade from low-grade gliomas when a new brain tumour is deemed indeterminate by biopsy None of the studies identified examined the performance of PET in clarifying the grade of tumour for patients with indeterminate (grade II/III) biopsy. However, four studies provided data on patients with definite biopsy grade; these provide estimates of sensitivity for high-grade tumour ranging from 69% to 100%, and specificity from 57% to 100%. It was unclear, however, to what extent PET performance for patients with truly indeterminate biopsy results would resemble the reviewed studies.		health technology appraisal).	
(Reske &	122 relevant papers were	The review aimed to	The authors	For patients with brain tumours, the panel	The authors	Systematic	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
Kotzerke 2001)	identified Subcommittees (made up of an oncologist with anatomical site specific expertise, a radiologist and a nuclear medicine expert) appraised the papers. An expert panel compiled and graded the results of these committees to indicate areas of clinical usefulness of PET.	identify areas of clinical usefulness of PET in oncology.	considered the following outcomes: technical capacity, diagnostic accuracy, diagnostic impact, therapeutic impact and patient outcome.	considered the following applications of PET to be supported by good evidence • differentiation of recurrence and scar in high grade gliomas • detection of tumour dedifferentiation in recurrence, • localisation of tumour site for biopsy The panel considered the following applications of PET to be supported, but by weaker evidence • tumour grading • estimation of postoperative tumour mass • differentiation of cerebral lymphoma and toxoplasmosis	derived the results for CNS tumours from an earlier review and consensus conference in 1998 (not appraised here because it is in German). The 1998 review could contain studies using outdated technology (e.g. non PET-CT).	review and consensus conference	
(Rijpkema *et al.* 2003)	15 patients with oligodendroglial tumours (8 high grade and 7 low grade). Mean age 39 and 45 years. All patients were previously untreated. 6 patients with low grade astrocytoma used as control	MRI and Short echo time ^{1}H MR spectroscopic imaging (MRSI)	Metabolic profile of the following metabolites: N-acetylaspartate plus N-acetylaspartate (NAA); creatinine plus phosphocreatinine (Cr); choline containing compounds (Cho); myo-inositol (Ino);	Glx was signitficantly higher in low grade oligodendrogliomas than low grade astrocytomas (ratios: 1.48 [0.41] versus 1.30[0.38], P < 0.05). There was no significant difference between high grade and low grade oligodenrogliomas for any of the main metabolites (NAA, Cho, Cr, Ino, Glx). Lipid plus lactate levels were significantly higher in high grade compared with low-grade oligodendrogliomas (arbitrary units: 24.7[12.4] versus 5.2[2.4], P < 0.01)	The authors concluded that MRSI could be used to monitor any change of low-grade oligodendrogliomas into higher malignancy tumours. *Very small sample size. No details of*	Observational study	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Netherlands		glutamine plus glutamate (Glx). Results expressed as ratio of tumour to contralateral white matter. The sum of lactate plus lipid levels was also measured.		*the number of observers reading results or blinding of observers. No diagnostic accuracy data. No determi*nation *of cut off points with maximum ability to differntiate tumour type. Overlap of values between tumours seen on scatter plots Appears to be exploratory study. Sample was either either low-grade or high grade with no indeterminate lesions so may not be representative of general population*		
(Galanaud *et al.* 2003) Aim: to discuss	Not explicitly stated. Article included intracranial tumours and tumour-like processes; multiple sclerosis;	Not explicitly stated. Article included sections on: proton magnetic resonance spectroscopy (MRS);	Discusses the place of advanced MRI analysis in managing patients with diseases of	Only relevant sections are reported. The authors stated that 'conventional MRI is the imaging method of choice for intracranial tumours'.	The authors concluded that multimodal analysis of MRI provide a powerful tool for	Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
the potential impact of advanced MRI analysis in the clincail managem ent of common brain pathologie s.	ischaemic stroke; epilepsy; and Alzheimer's disease and other dementias.	diffusion weighted imaging (DWI); magnetisation transfer imaging (MTI); MR perfusion imaging; and functional imaging.	the central nervous system.	They quoted results from one study that showed that DWI and MRS could distinguish cystic tumours from brain abscesses. And mentioned a second study (105 tumours) that showed promising results for multimodal MRI analysed with neural networks.	analysing data from MRI and MRS. *There was no search strategy, inclusion criteria, details of the number of studies identified, or adequate details of the included studies or critical analysis of the evidence*.		
(Burtscher *et al.* 2000). Aim: *to evaluate the diagnostic accuracy of proton MR spectrosc opy in*	26 patients with suspected intracranial malignant tumours scheduled for brain biopsy; had to have tumours that were difficult /impossible to classify on the basis of clinical and neurological findings and be unsuitable for open biopsy or open resection.	MRI proton MR spectroscopy Stereotactic biopsy Three observers (neurosurgeon, neuroradiologist, spectroscopist) blinded to final histopathological diagnosis retrospectively	Distribution pattern of pathological spectra (defined as NAA/Cho ratio <1) across lesion. Patterns were classified as limited to those in the region of contrast enhancement and those outside the region of contrast enhancement.	Distribution patterns could not be evaluated for 5 patients (3 with poor spectral quality, 1 with volume of interest not covering target point; 1 with only 1 single volume spectroscopy measurement taken) Gliomas and lymphomas showed pathological spectra outside the area of contrast enhancement. There was no significant correlation between different tumour types and signal ratios. MR spectroscopy improved diagnostic accuracy by	The authors concluded that MR spectroscopy can improve diagnostic accuracy by differentiating circumscribed brain lesions from histologically infiltrating processes. *Full description of*	Observational study	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
intracranial tumours.	Mean age 52 years; range 31 to 80 years. Histopathological diagnoses were: 4 low grade astrocytomas; 13 high grade astrocytomas; 4 lymphomas; 4 miscellaneous nonmetastatic circumscribed tumours; and 1 unclear. Sweden	analysed data. They ranked preoperative differential diagnosis as definite, probable, possible, not probable or excluded. Neurologists' preoperative diagnosis was based on all neuroloradiological and clinical data available. The spectroscopist re-evaluated and ranked the preoperative diagnoses proposed by the neuroradiologist.	Diagnosis based on MR spectroscopy compared with histopathological findings by comparing the number of correctly ranked differential diagnosis for each observer and using the percentage of correct diagnoses for the 3 observers.	differentiating infiltrative from circumscribed tumours (infiltrative v circumscribed lesions: 5 cases of increased accuracy; 3 cases of unchanged accuracy; 0 cases of decreased accuracy) MR spectroscopy did not improve diagnostic accuracy in terms of differentiating types of infiltrative or circumscribed lesions (different infiltrative lesions: 0 increased accuracy; 11 unchanged accuracy; 4 decreased accuracy; different circumscribed lesions: 0 increased accuracy; 1 unchanged accuraccy; 1 descreased accuracy).	*methods used to arrive at diagnoses. Small sample size. 5/26 cases could not be evaluated.No diagnostic accuracy statistics.*		
(Ishimaru *et al.* 2001) Aim: to assess the ability	31 patients with high-grade gliomas (11 anaplastic and 20 glioblastomas, age range 12 to 82 years) and 25 patients with metastases (from lung, breast,	Singe-voxel proton magnetic resonance spectroscopy (MRS) using short point-resolved spectroscopy with echo times (TE) of	Spectographic peaks for lipids, N-acetyl-aspartate (NAA), creatinine (Cr) and choline-containing compounds (Cho)	A Cho peak was present in all but one of the high-grade gliomas and in 4 of the 25 metastases smaller than 17 mm. All the gliomas but one showed a Cr peak (with or without NAA). A Cr peak was not present in 21 of 25 metastases or in one glioblastoma (the one with no Cho peak).	The authors concluded that single-voxel proton MR spectroscopy will help differentiate between high-	Observational study	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
of singe-voxel proton magnetic resonance spectroscopy in distinguishing between high-grade gliomas and metatases.	ovarian, colon, fibrous histiocytoma, age range 32 to 88 years). Japan	136 and 30 ms Lipid peaks evaluated at short TE. Other peaks evaluated at long TE	for tumours and metastases.	Lipid or lipid/lactate mixed signals were present in all metastases and glioblastomas. None of the astrocytomas showed a lipid peak. Findings show that intramural CR suggests a glioma and absence of CR suggests metastases. A definite lipid signal suggests glioblastoma or metastases and no lipid signal may exclude metastases.	grade gliomas and metastases. *This seems to have been more a pilot study that a diagnostic accuracy study. No details were given of the methods used to read images, the number or experience of radiologists, or blinding of radiologists to diagnosis. No diagnostic accuracy statistics were reported.*		
(Negendank *et al.* 1996) Aim: to examine the	86 patients with newly diagnosed or recurrent primary glial type tumours. Tuours had to be assessable (acceptabel quality of MRI spectrum), occupy at least 50% of	1H –magnetic resonance spectroscopy (1H MRS). Institutions provided blinded MRI	Metabolic profile by tumour type. Choline, creatinine, N-acetylyaspartate, lipids and lactate were measured.	Metabolic characteristics varied considerably within each tumour type and there was overlap between tumour types. This made it impossible to distinguish between high and low grade tumours. Mobile lipids were present in 41% of anaplastic	The authors concluded that it was not possible to distinguish between high and low grade tumours. They stated that mobile lipids may	Observational study	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
feasibility of using metabolic features to characterise glial brain tumours	the volume of the 8-cc MR spectroscopy voxel on MRI and be confirmed histologically at some point. Patients were from 15 institutions 19 patients with astrocytoma; 22 with anaplastic astrocytoma; 34 with gioblastoma multiforme; 6 with oligodendroglioma; 5 with ependymoma. Age ranged from 3 to 75 years. 31 patients had recurrent tumour and 25 of these patients had received radiation treatment. Multicentre International study	spectroscopy data processing plus independent review of histological type.		astrocytomas and glioblastoma multiformes but only 16% of astrocytomas.	correlate independently with prognosis. *Appears to be well conducted and clearly presented*.		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Lamy-Lhullier *et al.* 1999) Aim: to assess the use of 99mTc-sestamibi SPECT in the differential diagnosis of tumour recurrence and radionecrosis of subtentorial glial tumours in adults. Full publication in French. Data extracted from	22 patient with astrocytoma (grade 2 to 4), oligodendroglioma (grade 2 to 3) or mixed (grade 2 to 3).	99mTc-sestamibi SPECT compared with stereotactic biopsy or clinical course at 6 months	CI and MI indices measured . CI defined as the ratio of mean counts in lesion to mean counts in contralteral choroid plexus. MI defined as theratio of mean counts in lesion to contralateral mirror area. Sensitivity, specificity, positive predictive and negative predictive value for tumour recurrence were calculated	12/22 patients showed increased uptake of tracer. 11/12 patients presented with recurrence. In 10 patients without fixation, 4 were false negatives. Sensitivity for tumour recurrence was 73%; specificity was 85%. positive predictive value was 91%; negative predictive value was 60%.	The authors concluded that a positive SPECT conclusively diagnosed recurrence, but a negative SPECT did not equate with absence of recurrence. *Report published in French. Data only extracted from English language abstract .Very small sample size. No details of the number of observers reading scans or characteristics of patients in abstract.*	Prospective diagnostic accuracy study	3 insufficient information in abstract to classify

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
English language abstract.							
(Beauchesne *et al.* 2004) Aim: to assess the use of ^{99m}Tc-sestamibi (MIBI) brain SPECT in measuring residual tumpur volume at the end of cranial irradiation.	57 patients with supratentorial malignant gliomas (13 patients had grade 3 and 44 had grade 4 using Stainte Anne-Mayo classification). Median age 61 years. 24 patients underwent total macroscopic tumour resection, 10 patients had incomplete resection, 23 patients had stereotactic biopsy. Patients then had radiotherapy and chemotherapy France	^{99m}Tc-sestamibi (MIBI) brain SPECT performed at the end of radiotherapy in all patients. CT scan performed in 56 patients Two independent neurologists reviewed the CT scans.	Metabolic tumour volume (MTV) calculated from transverse, coronal and sagittal slices. Median survival time. CT findings Tc-MIBI findings. Relationship between survival time and other factors including age, KPS score, MTV, complete tumour resection, and CT findings.	Multivariate analysis showed that predictors of survival were: age (P = 0.002), complete tumour resection (P = 0.03), KPS score (P = 0.001) and MTV (P = 0.02). Patients with MTV < 32cm^3 had significantly longer survival than patients with MTV ≥ 32 cm^3 (358 versus 238 days, P = 0.05). Approximately 50% (26/56) of CT scans within 10 days post radiotherapy were classified as doubtful or suggestive. Tc-MIBI scan was negative in one of these patients and positive in the other 25 patients.	The authors concluded that ^{99m}Tc-MIBI brain SPECT may help determine the prognosis of patients with glioma at the end of radiation therapy. *No details of how many observers performed or analysed Tc-MIBI scans or if they were blinded to CT results.*	Prospective observational study	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Blue Cross Blue Shield Association 2003)	Inclusion criteria Studies using hydrogen proton MRS (1H MRS), sample size at least 10 patients, a method of confirmation of the MRS diagnosis, the criteria for a positive MRS test were stated and sufficient information was available to evaluate the diagnostic performance of the test.	The aim was to evaluate the clinical usefulness of hydrogen proton magnetic resonance spectroscopy in the evaluation of people with suspected brain tumours.	The primary outcomes were morbidity and mortality associated with the diagnosis and treatment of indeterminate brain lesions.	Seven studies met the eligibility criteria, with 271 patients. Limitations and differences in the study methods meant that statistical combination of the results was inappropriate. For example, investigators used different strength magnets (0.5 to 1.2 Tesla), there were different criteria for a positive test result, and the patient populations were different. Evidence was insufficient for the investigators to conclude whether MR spectroscopy affects health outcomes in people with suspected brain tumours. The reported sensitivity of MRS ranged from 79% to 100% and specificity from 74% to 100%. Positive predictive values ranged from 92% to 100% and negative predictive values range from 60% to 100%.		Systematic review (for health technology appraisal).	2+
(Jordan *et al.* 2003)	96 studies (published before November 6, 2002) were included in the review. Inclusion criteria Hydrogen proton magnetic resonance spectroscopy (1H MRS) on patients with suspected or known brain tumours. Only in	The aim was to evaluate the clinical usefulness of hydrogen proton magnetic resonance spectroscopy in the evaluation of people with suspected brain tumours.	Technical feasibility and optimization (85 studies), diagnostic accuracy (8 studies), diagnostic thinking impact (2 studies), therapeutic choice impact (2 studies). No studies reported patient outcome or	The review concludes that 'Human studies conducted on the use of MRS for brain tumours demonstrate that this non-invasive method is technically feasible and suggest potential benefits for some of the proposed indications. There is a paucity of high quality direct evidence demonstrating the impact on diagnostic thinking and therapeutic decision making. In addition, the techniques of acquiring the MRS spectra and interpreting the results are not well standardized.'		Systematic review (for health technology appraisal).	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	vivo studies with a minimum of six adult human subjects were included. Exclusion criteria Studies of only healthy patients or studies of exclusively HIV/AIDS patients. Studies of phosphorus or other types of MRS were excluded		societal impact.				

Table 3.2 What is the optimal biopsy technique?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Bernays *et al.* 2002)	During July 1996-November 2000, 113 consecutive patients (median age 53 years, 6 months – 78 yrs) with an intracranial lesion detected by CT or MR.patients	Frameless stereotactic biopsy with aid of open MR system to investigate supratentorial lesion. A CT scan was performed 1 day post-operatively to evaluate postoperative complications.	Morbidity, mortality, frequency post-operative haemorrhage & histological yield. Size and location of lesions.	The median volume of the lesions was 33.5 cm and 31.9% were deep seated. A specific neuropathological diagnosis was made in 111/114 biopsies. In 2/114 cases haemorrhage was found with no neurological worsening. Morbidity with neurological worsening was seen in 3/114 cases; it was transient in 2 and in 1 craniotomy was required. There was 1 death. The authors conclude that open intraoperative MR imaging transforms a blind conventional stereotactic procedure into a visually controlled procedure.	*Adequate description of methods, insufficient details of patient selection.* *Enhancement of the biopsy process by the use of intraoperative MRI guidance, is an expensive refinement which may have a place where real-time biopsies are failing to produce results. The overall yield was 97.4% and is only succeeded where PET directed biopsies of active areas are performed. The morbidity and mortality remains the same.*	Case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Bernstein & Parrent 1994)	300 consecutive stereotactic biopsies for intra-axial lesions performed by 1 neurosurgeon	CT guided stereotactic biopsy	Complications	19/300 patients, developed complications. 5 patients died from intracranial hypertension. All 5 patients, had GBM. In the 14 other patients the neurological deficit was severe. Mortality or major morbidity was thus 3.0% and minor morbidity was 3.3%.	*Outdated. illustrates risks in the biopsy of patients, with intracranial swelling*	Case series	3
(Bohinski *et al.* 2001)	40 patients with Grade II glioma	Safety and efficacy of a shared resource intraoperative MRI design for the detection of residual glioma after an image-guided frameless stereotactic resection (IGFSR)	Extent of resection. Morbidity and mortality	In 19 patients (47%) intraoperative MRI studies confirmed that adequate resection had been achieved after IGFSR. Intraoperative MRI showed accessible residual tumours in the remaining 21 patients (53%), all of whom underwent additional resections. One patient developed a superficial wound infection. Five patients experienced worsening neurological status post-operatively; 1/5 patients died of a pulmonary embolus. The authors conclude that use of a shared MRI operating room may represent a more cost effective approach than dedicated intraoperaitve units for some hospitals.	*Small patient numbers. Considerable morbidity (5/40 patients), although authors state that only in 1 patient related to technique.* *Relevance to UK?*	Historical case series	3
(Boviatsis *et al.* 2003)	11 patients, mean age 49.9 yrs, range 24-71 yrs with brain stem lesions	CT guided stereotactic biopsy	Diagnostic accuracy. Mortality.	There was no surgical mortality. Precise histological diagnosis was obtained in all patients. The authors conclude that their results are consistent with a review of the relevant published literature.	*Small number of patients.*	Historical case series	3-
(Dorward *et al.* 2002)	September 1996-April 1999, 155 stereotactic biopsy procedures were performed. 79 (mean age 52.1 years,	Comparison of frameless ST biopsy over frame based procedure	Histological diagnosis. Morbidity and mortality; cost analysis	There were no significant differences in the demographics, lesion site, size and pathologies between the 2 groups. Operating theatre occupancy and anaesthetic time were both significantly shorter for the frameless series than the frame based (p=<0.0001). The rate of surgical complications was 8.8 in the frame	*Selection of technique was dependent on availability of the image guidance system. Other*	Retrospective cohort study	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	range 15-96 years) of these were performed with a stereotactic frame and 76 (mean age 54.9 years, range 25-79 years) with a novel technique of frameless ST biopsy. The imaging modality used to target the biopsy was CT in 89% of frame based biopsy and 32% of frameless. MRI was used in 11% of framed based cases and 68% of frameless ones.			based and 6.6% in the frameless. There was 1 death in each series. The overall complication rates in the frameless series was significantly lower than in the frame based series (p= 0.018) [22 patients in the framed vs 11 in the frameless procedure; 1/22 died from a haemorrhage – 22% vs 14%]. This resulted in a lower use of |ITU bed occupancy (p=0.02), shorter mean LOS (p=0.0013) and significant cost savings (p=0.0022) for the frameless ST biopsy group, despite the increased use of more expensive MRI in these cases.	*methodological problems. Preferred technique throughout study period was frameless biopsy with framed biopsy used when frameless unavailable. i.e no case selection for either procedure.* *N.B. Frame based ST biopsy is current gold standard. Method is safe (mortality , 1%, morbidity 3-4%) and effective (diagnostic yield > 95% compared with freehand (CT directed) burr hole biopsy (mortality > 5%, morbidity 15%, diagnostic yield 85%)* *Authors define frameless ST as 'a*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					system by which an instrument may be advanced directly to a pre-selected discrete target, without deviation or collateral brain injury'. Frameless ST is a useful term when applied strictly to point-targeted arm-based IGS techniques. *Time becomes relevant where theatre use is at a premium or there are problems with support stafff generally frameless biopsy requires a GA, whereas ST is usually done under LA.*		
(Fenchel *et al.* 2003)	All neurosurgical patients			The authors conclude that intraoperative MR imaging is a safe and effective technology. It is particularly useful		Expert opinion	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				for ensuring that biopsies yield diagnostic tissue and for assessing completeness of tumour resection. In surgery for LGG the technique is accepted practice but in HGG its usefulness to monitor resection remains controversial.			
(Fontaine *et al.* 2000)	Between December 1991 and October 1996, 100 MR guided stereotactic biopsies on patients with intracranial lesions	Use of MR guided biopsies where CT guiding was considered too dangerous or impossible i.e. lesions located in functional or highly vascularised areas & in the brain stem. I	Histological diagnosis. Morbidity and mortality.	MR guided biopsy allowed a diagnosis to be made in 92/100 cases. In 8 cases the biopsy was negative. 3 patients had transient worsening of their neurological problems. Two patients had permanent loss of motor function. The authors conclude that the percentage of negative results in their study was similar to other published series. The authors address the disadvantage of MR information being non-linear. Vascular areas i.e. sylvian fissure, brain stem, pineal region will be associated with higher morbidity	*Insufficient details of patients included in series. The results are suggestive of superiority of MR guided versus CT biopsy. No direct comparison between CT and MR accuracy.*	Historical case series	3-
(Fountas *et al.* 1998)	21 patients, aged 41-76 years, mean age 61.6 yrs., with preoperative diagnosis of a brain tumour.	Frameless ST biopsy – results and complications	Morbidity. Extent of surgical resection	Both preoperatively and postoperatively all patients had a brain CT or MRI. Total tumour resection was obtained in 20/21 patients. There were no major complications. Mean LOS was 2.8 ± 0.3 days. Gross neurological examination remained stable. In 11 patients KPS at 6 months was stable; in 7 KPS was increased at 3 months and at 3 months was decreased in 3.	*Small patient numbers. Insufficient details given*	Historical case series.	3-
(Frighetto *et al.* 2003)	4 patients, mean age 61.2 yrs, range 29-89 years, presenting with parasellar	Image guided frameless stereotactic biopsy	Diagnostic yield; morbidity	There was no mortality. Diagnosis was made in all 4 patients.	*Very small studiy. Of limited relevance to the question.*	Historical case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	lesions				*Inadequate description of patients*		
(Fritsch *et al.* 1998).	65 consecutive patients undergoing ST biopsies of intracranial lesions. 5/65 were children aged 1-10 yrs and 60 patients were aged between 18-83 yrs (mean age 46 yrs)	Stereotactic biopsy of intracranial brain lesions	Diagnostic yield; morbidity.	The diagnostic yield was 98.5 ± 1.5%. 1 patient developed clinical findings of meningitis 10 days after ST biopsy and died 1 month after biopsy. No patient had transient or permanent neurological deficits.	*Discussion and conclusions not consistent with results. Poor quality study*	Historical case series	3-
(Gildenberg 2000)	Patients, with brain tumours	Use of stereotaxis and image guided surgery		The authors conclude that there is increasing evidence that patients, operated on with imaging guidance have a more benign course and shorter LOS than techniques not using imaging. .		Expert opinion	4
(Goncalves-Ferreira *et al.* 2003)	30 patients (27 adults, 3 children) undergoing ST biopsy of focal brainstem lesions	Stereotactic biopsy	Diagnostic yield; morbidity and mortality	A specific diagnosis was obtained in 26/28 patients; in 2 patients there was no pathology. Morbidity was restricted to 2 patients consisting of transient cranial nerve defects.	*Small study; inadequate description of methods.*	Historical case series	3-
(Grunert *et al.* 2002)	1997-2000, 49 patients, aged between 8 and 79 years, mean age 50.7 years	Frameless ST biopsy guided by an optical navigation system (Radionics)	Diagnostic accuracy, morbidity and mortality. Theatre time; surgery time.	Diagnostic accuracy was 89% (44/49 patients). In the remaining 5 patients no tumour was found. There was no mortality; 3 patients had transient neurological deficit. There was a mean non significant reduction in theatre time of ¾ hour for navigation guided biopsies compared with framed ST biopsies	*Abstract does not match results. Possible reduction in theatre time important for service guidance.*	Historical case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Hall 1998)	134 ST biopsies performed between February 1991-December 1996 in 122 patients, mean age 41 years (3-83 years) with intracranial lesions	Safety and efficacy of ST biopsy with CT or MRI guidance	Diagnostic yield; mortality and morbidity	85 (63%) lesions were biopsied with CT guidance and 49(37%) with MRI guidance. Diagnostic yield was 96%; reasons fro diagnostic failure were lesion location adjacent to the ventricular system, inaccurate targeting and inability to penetrate the tumour. 1 patient sustained a neurological deficit and 1 died from haemorrhage. The authors conclude that ST frame biopsies are safe and effective for the diagnosis of intracranial lesions.		Historical case series	3-
(Jackson *et al.* 2001)	81 patients (mean age 48, range 15-81 yrs) with suspected glioma underwent 82 biopsies.	Limitations of stereotactic biopsy.	Diagnostic yield, diagnostic accuracy. Morbidity and mortality	Frameless CT guided biopsy was the most common method of biopsy; some underwent frame-based and frameless MRI-guided biopsies. Patients, not experiencing tumour mass effect underwent surgery. Gross total resection (demonstrated by computer assisted volumetric analysis) was achieved in 46/81 (57%). Diagnoses based on biopsy or resection in the same patient differed in 40/82 cases (49%). Review by 3 neuropathologists reduced the discrepancy to 30/82 (38%). Major complications occurred in 10/81 (12.3%) surgical patients and 3/81 (3.7%) undergoing biopsy. The authors conclude that ST biopsy is frequently inaccurate in providing a correct diagnosis and is associated with additional risk and cost (*no cost data given)*. Expert neuropathological opinion is required if ST biopsy is performed.	*Authors address the question of selection bias in their series. Biopsies were performed at different institutions. 3..7% stereotactic morbidity with approx. 4% mortality is the EORTC recognised risk from ST biopsy.* *The paper provides evidence that resection gives better biopsy yield*	Historical case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					than biopsy.		
(Kim *et al.* 2003)	308 biopsies in 300 patients (mean age 41, range 3-79 years) with intracranial lesions	CT guided stereotactic biopsy	Diagnostic yield; mortality and morbidity	Diagnostic yield was 91.7% (275/300 patients). Univariate (p=0.01) and multivariate (p= 0.02)analyses confirmed that neoplastic lesions were more likely to be diagnosed than non-neoplastic lesions. Location and Multiplicity were not significant. Craniotomy after the St biopsy was performed in 30 patients and the diagnoses of the 2 procedures were identical. There were 2 deaths (0.6%0. New neurological deficits developed in 19 patients,. The permanent morbidity rate was 3.9% (12/308 procedures)	*Patient selection bias since the most difficult cases were selected for ST biopsy Adequate description of methods; appropriate use of statistics. Results of the intraoperative histology using frozen sections not clear and no conclusions should be made on the statistical significance.*	Historical case series	3
(Kratimenos & Thomas 1993)	72 patients aged between 2 and 60 years with mass lesions of the brainstem. All patients underwent preoperative cerebral angiography, high resolution contrast enhanced CT and	Role of image directed biopsy in diagnosis and management of brainstem lesions	Histological diagnosis. Morbidity and mortality	Histological diagnosis was obtained in 52/72 cases. Haematoma was diagnosed in 16. There were no deaths and morbidity was low – no increased neurological deficit occurred in any patient following the procedure. Transient deterioration occurred in 2 patients. 1 patient required early aspiration of haemorrhage	*Low relevance to question. High risk of confounding. Yardstick for data for ST biopsy in a difficult and relatively rarely biopsied area usually done by specialised*	Historical case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	preoperative MRI.				*centres.*		
(Lee *et al.* 1991)	From July 1988-Decmber 1989 at Oxford Centre 45 cases (mean age 50yrs' SD 16)were selected for ST biopsy and 41 (mean age 53 yrs; SD 17) cases for freehand biopsy. In the Birmingham Unit from October 1986-September 1989, 108 ST biopsies were performed on 103 patients(mean age 51 SD 18)	Two centre study comparing:- Birmingham where all biopsies are performed stereotacitically Oxford where 'difficult lesions' i.e. small size and deep or eloquent site are treated stereotactically; other tumours were biopsied freehand	Mortality and morbidity. Diagnostic accuracy	ST biopsy had a lower incidence of both mortality (2.6%) and morbidity (1.3%) than freehand (7.8 and 7.8%) while diagnostic accuracy was 92.1% and 64.9% respectively. Multivariate analysis of the diagnostic yield and complication rate of the ST group showed no relationship to patient age or sex, diameter or depth of lesion, diameter:depth ratio or to the surgeon. Similar analysis in the FH group indicated a trend towards improved diagnostic yield with > diameter:depth ratio. Morbidity and mortality was > in patients aged > 60 years (p=<0.05). The author concludes that ST biopsy is superior to freehand for all intracranial biopsies regardless of size or site.	*Groups were not completely comparable - > subcortical cases in the freehand biopsy group; ST groups had > deeply situated lesions. Inevitable problems associated with retrospective observational studies – confounding, selection bias etc No concomitant therapy was recorded. True comparison not feasible; high risk of confounding.*	Retrospective comparative study with historical control	2-
(McGirt *et al.* 2003)	43 cases (age not given) of astrocytic brain tumours	MRI guided stereotactic biopsy followed by open resection of the lesion, Comparison of histological diagnosis	Accuracy of diagnosis by resection or ST biopsy.	All biopsies and histological diagnoses were made by the same surgeon and pathologist. In the 23 patients undergoing resection within 60 days post biopsy, the biopsy diagnosis was the same as the diagnosis by resection in 18 (79%) cases. In 4 patients GBM was undergraded as anaplastic astrocytoma in 4 patients	*Methodological problems = ST biopsy relied on single specimens without serial biopsy specimens.*	Historical case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		from biopsy with histology after tumour resection		and in 1 patient GBM was misdiagnosed as radiation necrosis. In 20 patients, undergoing resection (> 60days) because of radiological tumour progression (mean 7 months post biopsy) 6/6 (100%) biopsy obtained diagnoses of glioma grade correlated with resection diagnosis, while only 6/14 (43%) biopsy obtained diagnoses of radiation necrosis correlated with resection diagnosis of progression (p=<0.01), Fisher Exact Test (FET). When resection was performed at < 60 days there was no statistical difference between biopsies correlating versus not correlating to subsequent resection specimens.	*Small patient numbers. No details of statistical methods but use of FET is appropriate.*		
(Paleologos *et al.* 2001)	Patients (mean age 53.7, range 16-83 yrs) with intracranial lesions (108 = tumours, 14, non-tumour)	125 frameless stereotactic biopsies. 86 were MRI guided and 39 CT directed.	Complications. Diagnostic yield	Complications were described as minor or severe depending upon need for additional surgery and/or produced a permanent (>30d) neurological deficit. 13/125 patients developed complications, 10 of which were related to surgery. Although not statistically significant there was an association between complications and patient age (>40 yrs; p=0.32) and anatomical or functional locations of the lesions (p=0.52 and 0.51 respectively) Histological yield was obtained in 122/125 cases.	*Well described study details. Higher morbidity from frameless biopsy.*	Historical case series	3
(Savitz 2000)	60 cases of suspected neoplasm.	CT guided needle biopsy	Morbidity, mortality. Diagnostic accuracy was 55/60 patients.	All patients were given steroids and prophylactic antibiotics. Post operative haemorrhage occurred in 2/128 freehand CT guided procedures (1.6%). Overall morbidity and mortality (0.5%) were not reported separately for the brain tumour patients	*Poor quality study. Authors conclusions not backed by data.*	Historical case series	3-
(Sawin *et*	225 patients, mean	CT and MRI guided	Diagnostic yield;	CT images were used in 197 cases (87.6%) with MRI	*Adequate*	Historical	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
al. 1998)	age 47.4 years, range 3-84 with intracranial lesions over 13.5 years	stereotactic biopsy.	mortality and morbidity risk factors for biopsy associated complications	reserved for 28 patients in whom lesions were not adequately seen with CT. A definitive diagnosis was obtained in 95.6% of cases. 12 patients, (5.3%) suffered morbidity ranging from persistent neurological deficit with significant functional loss to transient gaze palsy. 1 patient died. Univariate and multivariate analyses demonstrated a significant increased risk of morbidity was associated with preoperative use of anti-platelet agents, chronic corticosteroids, deep seated lesions, malignant gliomas and repeat biopsy (p=<0.05)	*description of methods; inappropriate use of multivariate analysis (only 12 patients,). Length of study time introduces problems with changes to techniques etc and although patient numbers appear large it represents only 1.4 ST biopsies per month. Does provide data on morbidity and mortality and points out a priori definable risks e.g. clotting status platelets, aspirin use etc.*	case series	
(Seliem *et al.* 2003)	From October 1987-August 2002 130 CT guided fine needle aspiration biopsy	Safety of CT guided freehand biopsies	Diagnostic accuracy	A diagnosis was obtained in 97/130 FNABs (75%). There was no morbidity or mortality. FNAB was most effective in diagnosing GBM and AA, metastases and lymphomas. Authors conclude that use of a fine needle	*No control group using regular size biopsy needle. No patient details.*	Historical case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	(FNABs) of suspected brain and CNS tumours.			for biopsy is safe and relaible.			
(Wen *et al.* 1993)	167 biopsies performed in 154 patients (mean age 45 years, 2-87 yrs) with intracranial lesions.	2 groups:- CT guided freehand biopsy (69 patients, 75 biopsies) Stereotactic biopsy (60 patients, 66 biopsies [34 CT-guided & 32 MRI guided])	Biopsy related morbidity and mortality. Diagnostic failure	There was an equal distribution of sexes in the CT guided group but a preponderance of male patients, in the stereotactic group. Patients who underwent freehand CT guided biopsies were older mean age 49.5 years vs 40.6 years. 14 of the stereotactic and 12 of the CT guided biopsies were of deep lesions and were excluded from analysis. There were no biopsy-related deaths among the patients who underwent freehand CT guided biopsy and 1 death in the stereotactic biopsy group. Freehand CT guided biopsy was associated with 5% morbidity, compared with 6% morbidity for stereotactic biopsy. Chi-squared analysis of morbidity and mortality showed no statistically significant difference between freehand CT guided and stereotactic biopsy groups. There was a statistically significant difference in mean lesion diameter in the two groups (mean 3.9 cm vs 2.6 cm ; p= <0.001) Seven freehand CT guided biopsies (9%) and 12 stereotactic biopsies (18%) did not yield a pathological diagnosis. There was no statistical difference in the size or location of the lesions in either the freehand CT guided biopsy group or those in the CT and MRI guided stereotactic biopsy groups. There was however, a statistical difference (p=<0.05) in diagnostic failure	*Patient attrition details not described.* *The statistically significant difference in tumour size (3.9 in CT guided freehand vs 2.6 in stereotactic) between the 2 groups makes comparison difficult. The authors also discuss the occurrence of selection bias of the operating surgeons. ST biopsies all performed by 1 specialist surgeon. The tumours biopsied and their situation were not*	Retrospectiv e cohort study	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				rates.	*comparable. Study by Lee et al 1991 is more reliable.*		
(Zhao *et al.* 2003)	465 craniotomies, 290 tumours.	Assessment of the value of frameless stereotaxy in craniotomy procedures.	Accuracy; morbidity and mortality	For the 465 procedures the calculated location error ranged from 1.2 to 3.5 mm (mean 2.4mm); lesion error averaged 1.8mm and the success rate of locating the lesion was 100%. Four cases of inaccuracy were observed due to brain shift. 253/ 290 tumours were completely resected (87.2%). There were no postoperative deaths. Postoperative complications occurred in 17 cases (3.6%) and neurological complications in 22 cases (4.8%). The authors conclude that brain shift remains a problem with frameless techniques but the addition of MRI can compensate for this	*Inadequate details given of patients and study. No attempt to discuss patient selection bias etc. Unsure of applicability of system used to UK.* *Often open biopsy shows a similar morbidity to stero or needle biopsy because visual as opposed to coordinate based biopsy is the difference between blind high precision and open direct vision. Also choice of biopsy should be appropriate for patient concerned*	Historical case series	3-

Table 3.3 Should all patients be biopsied?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Bell *et al.* 2002)	All patients in an 18 month period from three neuroscience centres who had a suspected diagnosis of solitary intracerebral tumour on CT (1997-1999). UK	Consultant radiologists or neuroradiologists were asked after CT diagnosis of a tumour whether :- The solitary lesion represented a tumour If a tumour was considered was it a primary or secondary Whether the tumour was benign or malignant What was the 'best guess diagnosis' Diagnosis confirmed by histopathology.	Accuracy of the diagnosis of tumour histology from brain CT by radiologists and neuroradiologists Histological diagnosis from biopsy was the gold standard (reference) diagnosis.	265/324 (80%) had verification of the radiological lesion; in 4 (1.5%) the biopsy tissue was non-diagnostic. In 36 patients pathology forms were lost. In the remaining 63 cases biopsy was not performed. There were 221 CT scans with a best guess diagnosis and a definitive pathology. The three most common histological diagnoses were categorised as: malignant glioma, 135 patients low grade glioma, 25 patients metastasis 39 patients 22 others had other diagnoses. Identification of tumour from CT scan When radiologists were asked if the lesion represented an intracerebral tumour their overall accuracy was 0.81 with a positive predictive value (PPV) of 0.93. Separate results for radiologists versus neuroradiologists are not reported. Diagnosis of high grade glioma from CT scan The overall sensitivity was 0.51, with specificity of 0.74. There was no significant difference between histological diagnostic accuracy of specialist neuroradiologists and general radiologists in the ability to diagnose high grade glioma on CT (p>0.05, statistical test not reported).	*Methodology and results not well described.* *It does not appear that general radiologists and neuroradiologists looked at the same cases.*	Prospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Diagnosis of low grade glioma from CT scan The overall sensitivity was 0.44, with specificity of 0.90. Diagnosis of low grade glioma from CT scan The overall sensitivity was 0.44, with specificity of 0.90.			
(Buckner 2003)	Patients with high grade gliomas	Recursive partitioning analysis of literature	Survival	The author concludes that gross total resection is associated with significantly improved survival compared with biopsy only.	*Low relevance to question.*	Expert opinion	4
(Choksey *et al.* 1989).	300 patients with intracerebral mass lesions of known pathology	2 subgroups:- a) one with appearances so specific for malignant glioma that biopsy was unnecessary. b) one with appearances that were characteristic of malignancy, but not specific for glioma 3 neuroradiologists reviewed the CT scans	Diagnostic accuracy	When diagnosing malignancy all neuroradiologists made errors (12 errors /600 results; 2%) and 9 benign tumours were diagnosed as malignant. When diagnosing malignant gliomas 1/3 neuroradiologists made errors whilst 2/3 were more accurate with their diagnoses. The investigators identified criteria pathognomic for gliomas. Using these criteria the neuroradiologists could correctly identify a small proportion of patients (20% of glioma patients) with malignant gliomas. In all other patients, biopsy was required.	*Dated, techniques now improved. Referral bias, increased proportion of patients with equivocal scans referred for specialist opinion..*	Retrospective cohort study	2-
(Grant & Metcalfe 2004)	Patients (presumably adults, but not specified) with presumed isolated supratentorial	Stereotactic biopsy Surgical resection	Time to death, Median survival Time to progression Quality of life	Only one small, low quality RCT identified, (Vuorinen 2003) that included 30 participants, age ≥ 70 years and KPS ≥ 60%. Survival appeared better in resected group p = 0.035. but insufficient evidence to answer the question.	*A high quality review that found only one low quality RCT that fulfilled inclusion*	Systematic Review	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	malignant glioma. Not just "high grade" glioma. Sterotactic biopsy Surgical resection				*criteria. The value of tumour resection compared with stereotactic biopsy alone is uncertain*.		
(Laws *et al.* 2003b)	666 patients, with malignant glioma enrolled in Glioma Outcomes Project. Decmber 1997-October 2000.	Extent of resection. Patients were followed up until death or up to 24 months	Length of survival	Improved survival was obtained in patients, who had undergone resection compared with biopsy. The biopsy patients however, included more older patients, and those with impaired performance and virtually all of the multifocal and bilateral tumours. In order to analyse effect of these differences an analysis was performed eliminating from both groups patients, aged > 65, those with KPS < 70 and those with multifocal or bilateral tumours. The advantage for resection was significant (p=0.0015). The authors conclude that despite selection bias the data support resection as a major factor in survival after surgery for malignant gliomas.	*Insufficient details of analyses given.* *Gives guidelines for when to biopsy and when to resect*	Expert opinion and historical case series	3/4+/-
(Nishio *et al.* 1991)	31 patients (mean age 18.1 yrs, 3-50 yrs.) with brain stem gliomas between 1965-1990	Role of biopsy	Diagnostic accuracy	No consistent correlation was found between CT and histological diagnoses. The authors conclude that all patients should be biopsied because of the inaccuracy of CT	*Small patient numbers. High possibility of bias and confounding. Long study time, techniques now improved.*	Historical case series	3-
(Samadani & Judy 2003)	Adult patients with brainstem lesions	Meta-analysis of studies performing ST biopsy.	Diagnostic accuracy	The literature search revealed 14 articles of patients who had undergone ST biopsy. 4 studies were excluded. The authors conclude that empiric treatment	*Poor quality study. No details of searching,*	Meta-analysis of retrospectiv	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		12 patients with brainstem lesions. Comparison of MRI findings with biopsy histopathology obtained using ST biopsy.		of adult brainstem lesions should not be performed because of the wide spectrum of diverse pathology. ST biopsy is safe and effective.	*inclusion & exclusion criteria, metanalyses etc. Not certain it is a metanalysis..*	e case series	
(Stranjalis *et al.* 2003)	69 patients (mean age 52 yrs, range13-73 yrs)with presumed inoperable cerebral lesions	CT guided stereotactic biopsy..	Diagnostic accuracy. Contribution of biopsy to the final management and survival.	55/69 patients (80%) died from their malignancy within 6 months after the biopsy was performed. The preoperative imaging diagnosis was consistent with the histological diagnosis in 60 patients (87% accuracy). The authors conclude:- o that the biopsy did not alter either the therapeutic management or the mortality due to the natural course of the disease. o the mandatory biopsy of patients with inoperable malignant tumours should be re-evaluated. o stereotactic biopsy carries a risk of contributing either to tumour growth acceleration or converting a benign glioma to a malignant one neurosurgeons should adhere to the proposed criteria: o younger patients with MRI suspicion of LGG but with considerable anxiety about their diagnosis. o suspicion of either an abscess or a radiosensitive lesion o metastasis of unknown primary o pineal lesions with the exception of the elderly	*Small numbers. Patient selection bias.*	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				o patients with a high probability of malignant gliomas on MRI should not undergo biopsy			
(Taylor *et al.* 2004)	Adults with supratentorial malignant glioma	Systematic review of published literature (1985 to June 2003) Stereotactic biopsy Gross total resection Subtotal or partial resection	Survival Prognostic factors for survival Complications of surgery Quality of life	One Cochrane review, one systematic review, one small RCT, six prospective phase II studies, 11 retrospective studies identified. Prognostic factors for survival: Evidence from 6 retrospective studies and 1 prospective phase II study. Most commonly identified factors: extent of resection, age, KPS . Biopsy versus resection: One RCT, 6 retrospective studies and 1 prospective phase II. RCT was of low quality and included only 30 patients (age ≥ 70 years, KPS ≥ 60%). All studies reported results that showed statistically significant benefit of tumour resection compared with biopsy (including in patients over 65 years). Gross total resection (GTR) versus subtotal (STR) or partial resection (PR) Five retrospective studies and five prospective studies identified. All studies suggested improved survival for patients who had GTR compared to STR or PR. But only 2 studies reported that patients were similar for age and KPS before surgery. Complications: Only one study reported complications. Biopsy (88 patients). Haematoma 3%, Death in 30 days: 4%.	*Lack of high quality evidence precludes comment on the value of GTR compared with biopsy alone or STR/PR* *The RCT was small, and all other studies non-randomised and so very likely to be subject to selection bias.* *It is not clear what selection biases operate in these non-randomised studies.* *Small studies, non randomised, with selection biases.*	Systematic review	2^{++}

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Resection (40 patients) Death in 30 days: 2%. QOL or functional status: 4 retrospective studies, 1 prospective. No consistent patterns of improvement or deterioration in functional status after GTR or less than GTR.			
(Vuorinen *et al.* 2003).	30 patients, 60 yrs with malignant glioma. 7/30 patients did not have glioma on further investigation. Results for 23 patients presented. Ten patients were randomised to undergo resection and 13 to biopsy.	Resection versus biopsy	Median survival	The authors observed longer median survival for the patients undergoing resection compared with biopsy (24 weeks versus 12 weeks; p= 0.035).	*Some methodological problems with the trial:-* *23% of patients included in the trial did not have glioma* *small sample size* *no mention of whether study was powered to detect a significant difference between the groups.* *method of randomization not described* *no intention to treat analysis* *no stratification for age or KPS*	Randomised controlled trial	1⁻

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					error in methods section – states KPS > 60 when In fact some patietns = to 60 *patients in two arms not equal.* *study underpowered*		

Table 3.4 Is interpretation by a neuroradiologist better than a general radiologist

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Flynn *et al.* 2005)	506 referrals for neuroradiology second opinion. Audit period lasted from 1st Jan 2004 to 31st Dec 2004. Referrals were from 14 hospitals. Modality was 59% MR, 41% CT. 86% had MR as first imaging and 8% had both MR and CT. UK	Neuoradiologist second opinion.	Correlation between initial report and second opinion. The investigators classified each case as: inconclusive; complete concurrence; minor discrepancy or major discrepancy. They also noted the source of each referral (radiologist, neurologist, neurosurgeon or other).	Source of referrals Radiologist (n=78), neurologist (n=374), neurosurgeon (n=77) and other (n=77). Concordance of reports Inconclusive (usually due to incomplete or absent primary report) 141/506 (27.9%) Complete concurrence 241/506 (47.6%) Minor discrepancy 75/506 (14.8%) Major discrepancy 45/506(8.9%) Major discrepancies in diagnosis included: missed sub arachnoid haemorrhage, missed infarcts, tumours called infarcts, mesial temporal sclerosis overcalled and cord multiple sclerosis lesions missed.	Authors comment that there is likely to be some discrepancy between specialist neuroradiologists.	Prospective case series (audit).	3
(Loughrey *et al.* 1999)	124 patients attending a regional oncology centre over a 1 year period, who had review of cross sectional imaging. Study included 129 (87%) CT studies and 19 (13%) MRI studies. The authors selected the patients	Specialist oncological radiology review of cross sectional imaging. The authors define 'specialist oncological radiologists' as those based in a cancer centre (the Christie Hospital).	Technical adequacy of cross sectional imaging studies. Agreement between outside and review reports.	Technical adequacy: Coverage was adequate in 94% of cases. A calibration rule was absent in 9% of cases. Comparison of outside and review reports: Only 33% of outside reports provided dimensions of measurable disease. Specific comment was made by outside reports on the appearance of the liver, lungs and bones in 77%, 55% and 16% of appropriate cases. A fundamental difference in interpretation arose in	RCR 1994 CT guidelines were considered as national standard practice and used to judge the adequacy of pre-referral imaging. Delayed specialist radiological	Prospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	at random from a series of 526. The most common diagnoses were non-Hodgkin's lymphoma (17%), Hodgkin's disease (11%) and colorectal carcinoma (11%). From the figures presented, the proportion of patients with brain tumour is probably less than 3% in this series. UK			41/122 (34%) of reports. The specialist review upstaged disease in 15 cases, downstaged disease in 6 patients and excluded disease in 2 patients. Additional sites of disease were noted in 8 patients and excluded in 6 patients. In 4 cases of disagreement the independent arbiter agreed with the original (non-specialist) report. Common sites of disagreement were the mediastinum, pelvis, retroperitoneum, axilla and neck. No specific tumour type appeared associated with difficulty in radiological interpretation. Impact on management: Specialist radiological review affected management in 9/122 patients (7%). 4 patients underwent additional investigative procedures and treatment was changed in 5 patients. In 7% of cases the delay between initial cross sectional imaging and specialist review was 6 months, the extent of the patient's disease was likely to have changed and the review findings of limited value. Authors' conclusions Specialist oncological radiology review of outside cross-sectional imaging changed radiological staging in 19% of cases but had little impact on patient management. Oncological cross-sectional imaging techniques in the North West of England are of high quality, probably helped by recent RCR guidelines.	reviews were of reduced relevance to patient management.		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Bell *et al.* 2002)	All patients in an 18 month period from three neuroscience centres who had a suspected diagnosis of solitary intracerebral tumour on CT (1997-1999). UK	Consultant radiologists or neuroradiologists were asked after CT diagnosis of a tumour whether :- The solitary lesion represented a tumour If a tumour was considered was it a primary or secondary Whether the tumour was benign or malignant What was the 'best guess diagnosis' Diagnosis confirmed by histopathology.	Accuracy of the diagnosis of tumour histology from brain CT by radiologists and neuroradiologists Histological diagnosis from biopsy was the gold standard (reference) diagnosis.	265/324 (80%) had verification of the radiological lesion; in 4 (1.5%) the biopsy tissue was non-diagnostic. In 36 patients pathology forms were lost. In the remaining 63 cases biopsy was not performed. There were 221 CT scans with a best guess diagnosis and a definitive pathology. The three most common histological diagnoses were categorised as: malignant glioma, 135 patients low grade glioma, 25 patients metastasis 39 patients 22 others had other diagnoses. Identification of tumour from CT scan When radiologists were asked if the lesion represented an intracerebral tumour their overall accuracy was 0.81 with a positive predictive value (PPV) of 0.93. Separate results for radiologists versus neuroradiologists are not reported. Diagnosis of high grade glioma from CT scan The overall sensitivity was 0.51, with specificity of 0.74. There was no significant difference between histological diagnostic accuracy of specialist neuroradiologists and general radiologists in the ability to diagnose high grade glioma on CT (p>0.05, statistical test not reported). Diagnosis of low grade glioma from CT scan	*Methodology and results not well described.* *It does not appear that general radiologists and neuroradiologists looked at the same cases.*	Prospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				The overall sensitivity was 0.44, with specificity of 0.90. Diagnosis of low grade glioma from CT scan The overall sensitivity was 0.44, with specificity of 0.90.			
(Erly *et al.* 2002)	1324 consecutive head CT scans ordered in the emergency department of a university hospital. USA	Emergency head CT scan, interpreted by one of 18 radiology residents (doctors in a 4 year radiology specialization program) and by one of 5 neuroradiologists (with a certificate of added qualification). The authors considered the neuroradiologist's report the gold standard.	Agreement between the reports of the radiology residents and the neuroradiologists. The confidence levels of the radiology residents.	The neuroradiologists interpreted 770/1324 (58%) of the scans as normal, and 554/1324 (42%) as abnormal. Agreement The agreement between the radiology residents and neuroradiologists was 91%. In 7% of cases there was insignificant disagreement (with no potential for adverse patient outcome). In 1.5% of cases there was significant disagreement: either with potential for adverse patient outcome, or a major diagnostic error. The residents rated their confidence in their initial reports. There was a significant relationship between level of confidence and disagreement; the less confident the resident was in the diagnosis the more likely it was that the neuroradiologist would disagree. As residents progressed through their 4 year training, they were significantly more confident in their diagnoses. There were 3 disagreements related to neoplasms; this represented 3/113 (2.7%) disagreements and 3/1324 (0.2%) scans.	The analysis does not allow for fallibility on the part of the neuroradiologist (the gold standard diagnosis).	Retrospective case series	3+

Table 3.5 Molecular pathology

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Cairncross *et al.* 1998)	39 patients, mean age 46 yrs (25-75), 18 male, 21 female with anaplastic oligodendrogliomas. Karnofsky scores 70 (60-90) at start of chemotherapy (CT). All tumour diagnosis confirmed by imaging. CANADA	Analysis of alterations in 1p,10q, 19q,TP53 & CDKN2A .	Response to chemotherapy and recurrence free survival.	Allelic loss of:-chromosome 1p occurred in 24 (67%) of 36 informative DNA pairs. Chromosome 19q in 28 (82%) of 34 informative pairs. Allelic losses of 1p and 19q were closely associated with one another (p=0.008) Loss of chromosome 1p was associated with improved response to CT (p,0.001, 95% CI 0.018-0.199) The association of chromosome 19q and chemotherapy response was not significant (p=0.126 95%CI 0.085-0.734) Loss of 1p and 19 q was significantly associated with response to CT (p<0.001, (95% CI 0.044-0.331) Univariate and multivariate analyses demonstrated that losses of both 1p and 19q were strongly associated with longer overall survival. The 5 year survival rate for patients with allelic loss on 1p and 19q was 95%.	*Retrospective analyses of small numbers of patients from a single centre.* *For survival analyses the patients were censored at their last follow up.* *Patients who were alive without evidence of disease progression were treated as censored for the analysis of recurrence free survival.* *Inappropriate use of Cox models with small numbers. Patients not homogenous*	Case series	3+
(Engelhard *et al.* 2003)	Patients, with oligodendroglioma and anaplastic	Review of published literature on clinical features, treatment	-	Molecular markers and prognosis: Allelic loss on chromosome arm 1p , especially if	*Useful review of literature*	Literature review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	oligodendroglioma	and prognosis.		accompanied by loss on 19q, is apredictor of response to chemotherapy and survival both in high and low grade oligodendrogliomas. Other molecular markers that have prognostic value include – topoisomerase IIa, cyclooxygenase isoenzyme-1, p16 and especially p53 mutations in anaplastic oligodendrogliomas.			
(Fuller *et al.* 2002)	30 primary human glioma (glioblastoma grade !V, anaplastic astrocytoma grade III, oligodendroglioma WHO grade III and anaplastic oligodenroglioma, grade III) tissue samples. USA	Profiling using cDNA arrays of the gene expression	Stratification of tumours using gene expression data. Survival	The multidimensional scaling plot indicated that the tumours sorted according to grade. Three glioblastoma tumours formed a separate cluster away from the 9 other GM. Review of their histology indicated ahigh grade glioma meeting current WHO criteria for glioblastoma. Follow up (3,21 & 26 months) indicated that they have better median survival compared with the median glioblastoma survival of 12months. SURVIVAL: 15/30 deaths occurred during follow up. The authors conclude that the results show a close correlation between MDS clustering and survival.	*Small study. Poor description of methods. Likely to be subject to bias.. Use of Cox regression model not appropriate for small samples. Interesting preliminary data but require confirmation and improved statistics*	Case series	3-
(Ino *et al.* 2001)	50 patients with anaplastic oligodendrogliomas	Sampling taken at time of diagnosis	Survival. Analysis of response to chemotherapy.	Patients with 1p/19q loss but without any other genetic alterations had a median survival of 10 years. All 21 tumours with 1p loss had visible responses to CT ($p<0.0001$). Duration of response to PCV was also linked with combined 1p/19q status.	*Patient group more homogenous than Cairncross 1998 study*	Historical case series	3+
(Jacobs *et al.* 2002)	Glioma patients	Molecular imaging		The authors conclude:- Gene co-expression strategies are being used with MRI and PET imaging techniques to delineate biologically active glioma tissue amenable for	*Not relevant to question*	Review	4-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				gene and cell therapeutic strategies to detect glioma progression and early recurrence to preserve neurological function during NS, brach- and radiotherapy These methods may determine how much PET-imageable vector mediated gene transduction is necessary to reach a certain therapeutic response.			
(Louis *et al.* 2001)	Glioma patients	Use of molecular methods for classification of gliomas		Discusses the feasibility of a molecular classification for diffuse gliomas.	*Indirect relevance to question*	Review	4+
(Reifenberger & Louis 2003)	Oligodendroglioma patients	Review of molecular genetics of oligodendrogliomas and oligoastrocytomas.		The authors propose: that for clinical trials for gliomas the obligatory central pathology should be supplemented by molecular analyses in order to avoid the possibility of unrecognised genetic heterogeneity obscuring an effect of therapy the greater use of molecular analyses in the routine neuropathological assessment of oligodendroglial tumours will improve diagnostic accuracy. Diagnostic testing for 1p/19q loss should be performed in only 3 clinical settings.: after a diagnosis of anaplastic oligodendroglioma; for a small cell malignant glioma in which the differential diagnosis is anaplastic oligodendroglioma versus small cell glioblastoma and after a diagnosis of WHO grade II oligodendroglioma. N.B. the authors do not believe that 1p/19q loss can be	*Comprehensive review of major published literature. Authors views backed by current evidence*	Review	4+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				used as an absolute diagnostic criterion for the diagnosis of oligodendroglioma. The results of the 3 major studies Cairncross, Ino & Smith) on survival and correlation with 1p/19q status indicate that there is a powerful association between 1p/19q status and survival in high grade and possibly low grade oligodendroglial tumours.(Sasaki) Currently clinical 1p/19q evaluations are being performed at relatively few institutions worldwide. For the next 10 years it is unlikely that routine molecular testing will become available in hospital pathology laboratories Data on poor prognosis in oligodendrogliomas must be viewed as preliminary and their clinical utility is unproven The clinical relevance of 1p/19q status in astrocytomas and oligoastrocytomas remains unproven			
(Sasaki *et al.* 1998)	44 patients with Grade II gliomas, diagnosed as oligodendrogliomas by referral pathologists.	Evaluation of 1p status	Response to chemotherapy	14/44 cases had been treated with CT at the time of clinical or radiological progression. 13 cases were evaluated. 10/11 cases with 1p LOH had responses to PCV. Neither case that maintained both copies of 1p had responses. The authors suggest that the results suggest that tumour genotype could predict chemosensitivity in the setting of recurrent tumours that were initially diagnosed as low grade lesions	Small patient numbers.	Historical case series	3-
(Hegi *et al.* 2005)	Patients were originally recruited for	One group received temozolomide at	Overall survival, progression free	MGMT status For the 206 patients whose MGMT status could be	A low propotion of patients had their	Observational study	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	an RCT of temozolomide for glioblastoma (EORTC trial 26981/22981 and NCIC trial CE.3). Methylation status of the MGMT promoter was determined using methylation-specific polymerase chain reaction with paraffin sections of glioblastoma tissue. Adequate paraffin embedded tissue was available for 307/573 (54%) patients; of these MGMT methylation status was successfully determined for 206/573 (36% of the overall population). EUROPE/CANADA	75mg per square meter of body surface area daily during fractionated radiotherapy (60 Gy), and at a dose of 120mg per square meter of body surface area for 5 days of every 28 day cycle after radiotherapy. The control group received radiotherapy only. Most patients, however, received additional second line / salvage chemotherapy including temozolomide. 59% of patients in the control group received temozolomide, but the analysis was by intention to treat.	survival.	ascertained, patients with methylated MGMT promoter had significantly better overall survival than those who did not (p<0.01, log rank test (univariate analysis)). Patients with methylated MGMT promoter Univariate analysis showed a significantly better survival in those who received temozolomide in addition to radiotherapy, compared to those who received radiotherapy alone (p=0.007, log rank test). Median survival was 21.7 months for those assigned to the temozolomide plus radiotherapy group and 16 months (figure from graph) for the radiotherapy only group. Patients with unmethylated MGMT promoter Univariate analysis of survival in those who received temozolomide in addition to radiotherapy, compared to those who received radiotherapy alone approached significance (p=0.06, log rank test). Median survival was 12.7 months for those assigned to the temozolomide plus radiotherapy group and 11.8 months for the radiotherapy only group. On multivariate analysis the interaction of MGMT status and treatment group was did not significantly predict overall survival (p=0.29). The methylation status of the MGMT promoter, however, was a significant prognostic factor for overall survival (p<0.001).	MGMT methylation status determined (36%). Possible bias if there was a systematic reason why adequate tissue for PCR was unavailable (e.g. tumour size), or MGMT promoter status could not be determined (although the Cox regression included other prognostic variables). Authors report that the success of the PCR technique was highly variable and dependent upon the institution. The investigators did not design the study for the MGMT status by treatment group	(using data from RCT)	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					analysis and it was probably underpowered.		
(Smith *et al.* 2000)	79 patients, with astrocytomas; 52 oligodendrogliomas and 31 mixed oligoastrocytomas..	Loss of 1p and 19q alleles	Survival	116/162 patients, analysed. The oligodendroglial phenotype was highly associated with loss of 1p (p= 0.0002), loss of 19q (p <0.001) and combined loss of 1p and 19q (p<0.0001). combined loss of 19 and 19q was a statistically significant predictor of prolonged survival in patients with pure oligodendrogliomas (log rank, p=0.03). This favourable association was not demonstrated in patients, with astrocytoma or mixed oligoastrocytoma.	*Well described study. Appropriate use of statistics.*	Historical case series	3+

Table 3.6 Intraoperative pathology

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Brommeland *et al.* 2003)	153 patients (group B) whose intraoperative diagnosis was based on frozen sections and imprint cytology (1999 to 2001). A comparison group (group A) of 153 patients, diagnosed using frozen sections only (before 1999), was also included. Mean age was 53 years (range 2 to 87 years). Inclusion criteria Patients undergoing stereotactic or open biopsy of a brain tumour at a university hospital. NORWAY	Open or stereotactic biopsy. There were 117 craniotomies and 36 stereotactic biopsies in group B; there were 100 craniotomies and 53 stereotactic biopsies in group A.	Accuracy of intraoperative diagnosis (the diagnosis based on paraffin sections of the biopsy specimen was the gold standard).	The study allowed four diagnostic categories: high grade astrocytoma, low grade astrocytoma, metastasis or lymphoma and benign lesion. Group A (frozen sections only) Accuracy was 103/117 (88%) for open biopsies and 30/36 (83%) for stereotactic biopsies. Overall accuracy was 133/153 (87%). Group B (frozen sections and imprint cytology) Accuracy was 94/100 (94%) for open biopsies and 45/53 (89%) for stereotactic biopsies. Overall accuracy was 139/153 (91%). There was no significant difference between group A and B in terms of diagnostic accuracy or between open and stereotactic biopsies (using Chi squared test).	*There were more open biopsies in group A. Are paraffin sections from a stereotactic biopsy specimen equivalent to those from open biopsies?*	Retrospective case series	3-
(O'Neill *et al.* 1992)	245 patients (133 men and 112 women)	CT-guided stereotactic biopsy	Diagnostic rate, mortality rate,	Diagnostic rate In the series of 142 patients without intraoperative	*Accuracy of diagnosis is not*	Retrospective case	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	with a mean age of 56 years (range 7 to 85 years). Patients received a stereotactic CT-guided biopsy of their intracranial mass lesion between 1986 and 1991. The first 142 patients did not have intraoperative cytology, whereas the subsequent 103 patients did. UK	with or without intraoperative smear cytology	improvement rate, perioperative morbidity and permanent morbidity.	cytology, there were 21 non-diagnostic biopsies (15%). 4% of patients had a second biopsy. In the 103 patients who had intraoperative smear cytology there were 6 non-diagnostic biopsies (6%). No patients had a second biopsy. Mortality Overall mortality rate 3.3% (8/245 patients). These patients had high grade primary tumours (n=6) or metastases (n=2). Immediate morbidity The authors reported morbidity immediately after the procedure in 27 patients (11%). Permanent morbidity 16 patients experienced permanent deficit following the biopsy. Improvement of symptoms The authors reported an immediate improvement in the condition of 34 patients. Another 14 patients did not improve immediately but showed later improvement in condition. The overall improvement rate was 20%.	*evaluated.*	series	
(Regragui *et al.* 2003).	1315 frozen sections of CNS tumours performed 1988-1999 MOROCCO (in French)	Comparison of diagnostic accuracy of frozen sections with data reported in the literature.	Diagnostic accuracy	When the false positives and false negatives were excluded (46/1315) the agreement between intraoperative and paraffin section for the presence of tumour tissue was 96.6% . The agreement for benign or malignant lesions was 92.6%. The most frequent errors occurred in the diagnosis of	*No control group. Used data from published series.*	Retrospectiv e case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				gliomas, haemangioblastomas and metastases. The authors emphasise the importance of close cooperation with the neurosurgeon and histopathologist..			
(Savargaonkar & Farmer 2001)	103 cases (60 males, 43 females, 17 were children < 20yrs) of CNS intra-operative consultations(January 1997-June 1999) for the diagnosis of CNS lesions. USA	Comparison of frozen sections and cytology techniques	Diagnostic accuracy	In 18 cases the biopsies were stereotactic, in 52 open biopsies and in 33 non-specified. Agreement was 94% between the intraoperative diagnosis and the final diagnosis. Most discrepancies occurred in the diagnosis of meningiomas. The cytology technique was more useful for astrocytomas, small round cell tumours and some metastases. The frozen section technique was better for the diagnosis of meningiomas, reactive lesions, ependymomas and most metastases. The authors conclude that the use of both techniques is beneficial.	*Small numbers to make comparisons on.*	Retrospective case series	3-
(Shah *et al.* 1998).	183 CNS tumours January 1995-June 1996 INDIA	Comparison of squash preparation and frozen sections with paraffin sections.	Diagnostic accuracy	In 156 cases the smears were adequate. The cytological study gave a diagnostic accuracy of 89.7% (140.156) and the frozen section 90.4% (141/156); p=0.9877. The authors conclude that the accuracy of the squash smear technique approaches that of frozen sections and with the advent of stereotactic biopsies may be the only technique available.	*Poorly described study. Insufficient details of patients methods and results. No definition of term 'adequate'*	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Ellison D, unpublished data 2004)	Audit of 133 stereotactic biopsies for adult brain tumours and took place over approximately 9 months.73 (55%) had intra-operative histopathology and 60 (45%) did not have intraoperative histopathology. UK	Stereotactic biopsy, either with or without intraoperative histopathology (frozen sections).	Satisfactory diagnosis rate.	Overall the rate of satisfactory diagnosis was 113/133 (85%) biopsies and of unsatisfactory diagnosis was 20/133 (15%) biopsies. For biopsies with intraoperative histopathology, 93% produced a satisfactory diagnosis and 7% an unsatisfactory diagnosis. The corresponding rates for biopsies without intraoperative histopathology were 75% and 25%. Intra-operative histological assessment judged 74% of first biopsies to be satisfactory - immediate repeat biopsy increased the final proportion of satisfactory biopsies to 93%. Reasons for unsatisfactory diagnosis even after intra-operative histology (5 patients): repeat biopsy also (normal, reactive or necrotic), biopsy associated haemorrhage or patient not in theatre.		Prospective case series (audit)	3+
(Bristol Audit of intraoperative histopathology, unpublished data)							
(Di Stefano *et al.* 1998)	85 biopsies of nervous system tumours.	Biopsy: stereotactic (n=15) or craniotomy (n=70). In all cases	Diagnostic accuracy (authors used paraffin sections for	The intraoperative diagnosis agreed with the paraffin section diagnosis in 81/85 cases (95%).		Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	ITALY	the investigators used both imprint cytology and frozen sections for intraoperative diagnosis	the gold standard diagnosis).				
(Firlik *et al.* 1999)	595 stereotactic brain biopsies from the records of a single institution. The authors also conducted a survey of 148 neuropathologist randomly selected from the directory of the American Association of Neuropathologists. USA	Stereotactic biopsy with intraoperative cytological diagnosis.	Agreement between intraoperative cytological and final histological diagnosis. The proportion of biopsies yielding diagnostic specimens. The survey of neuropathologists examined the preferred methods for intraoperative diagnosis.	Survey of neuropathologists There was a response rate of 62% to the survey. 23% of respondents chose frozen section alone as their preferred method of intraoperative diagnosis. 13% chose a cytological technique alone (touch, smear or crush preparation) as their favoured method. 64% used a combination of frozen sections and cytology. Diagnostic agreement There was complete agreement (in both histological type and malignancy) between the intraoperative and final diagnosis in 308/595 biopsies (52%). There was at least partial agreement (either histological type or malignancy) in 89% of cases, and no agreement in 11% of cases. Adequacy of specimens Diagnostic specimens were obtained in 544/595 biopsies (91%). 523/543 (96%) of these diagnostic specimens were correctly interpreted as abnormal. 20/543 (4%) were false negative for abnormality.		Retrospective case series and cross-sectional survey.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Martinez *et al.* 1988)**.**	100 CNS biopsies in which both frozen sections and touch preparations were used for intraoperative diagnosis. USA	Stereotactic or surgical excisional biopsy, with both frozen section and cytology (touch prep.) intraoperative diagnosis.	Intraoperative diagnostic accuracy (using paraffin section diagnosis as the gold standard).	In 76 cases a specific intraoperative diagnosis was made using cytology, compared to 88 cases using frozen sections. Non specific diagnoses (accurate judgement of malignancy and glial or non glial histology) were achieved in a further 18 and 11 cases respectively. In 5 cases, the touch preparation was non diagnostic - when firm tumours did not transfer many cells to the slide. When the two techniques were used in combination, the specific and accurate diagnosis was made in 95% of cases.		Retrospective case series	3+

Chapter 4 Management of patients with low grade glioma

The questions

a) In patients with low grade glioma, what is the evidence that surgery improves outcome, in terms of survival, quality of life or functional status?

b) In patients with low grade glioma, what is the evidence that chemotherapy improves outcome, in terms of survival, quality of life or functional status?

c) In patients with low grade glioma, what is the evidence that radiotherapy improves outcome, in terms of survival, quality of life or functional status?

The nature of the evidence

a) In patients with low grade glioma, what is the evidence that surgery improves outcome, in terms of survival, quality of life or functional status?

Two multicentre observational studies (from Europe (Pignatti *et al.* 2002) and America (Shaw *et al.* 2002)) considered the extent of surgical resection as a prognostic factor for the overall survival of adults with low grade glioma. Keles and co-workers (Keles *et al.* 2001)reviewed studies of the influence of surgical resection on the overall survival of adults with low grade glioma.

b) In patients with low grade glioma, what is the evidence that chemotherapy improves outcome, in terms of survival, quality of life or functional status?

Three prospective case series (Brada *et al.* 2003; Buckner *et al.* 2003; Quinn *et al.* 2003) from the UK and USA documented tumour response and the toxicity of chemotherapy in people with low grade glioma.

One American RCT (Eyre *et al.* 1993) examined the addition of chemotherapy to radiotherapy for people with low grade glioma.

c) In patients with low grade glioma, what is the evidence that radiotherapy improves outcome, in terms of survival, quality of life or functional status?

Two multicentre RCTs, from Europe (Karim *et al.* 1996) and America (Shaw *et al.* 2002), compared standard with high dose radiotherapy. A European multicentre RCT (Karim *et al.* 2002; Van Den Bent *et al.* 2005) and an American case series (Hanzely

et al. 2003) compared early with delayed radiotherapy. The studies recorded overall survival, progression free survival and toxicity. The RCTs enrolled adults with low grade non-pilocytic astrocytoma, oligodendroglioma or mixed oligoastrocytoma. The case series included only those with low grade non-pilocytic astrocytoma.

Summary of the supporting evidence for the recommendations

a) In patients with low grade glioma, what is the evidence that surgery improves outcome, in terms of survival, quality of life or functional status?

Prospective trials of radiotherapy for low grade glioma did not find the extent of tumour resection significantly affected overall survival (Pignatti *et al.* 2002; Shaw *et al.* 2002). However Keles and co-workers (Keles *et al.* 2001) reported that more extensive surgical resection was a positive prognostic factor in four of the five case series in their review.

The inconsistency of the evidence could be partly due to selection bias. The studies did not randomly choose patients for extensive surgical resection. Instead patients were likely to have been selected on the basis of other prognostic factors (such as age, tumour size and site). The prospective trials (Pignatti *et al.* 2002; Shaw *et al.* 2002) tend to support this idea. Considered on its own, extent of resection was a statistically significant predictor of overall survival. When the investigators adjusted for other prognostic factors (using multivariate models) extent of surgery was no longer statistically significant. In these studies, however, the extent of resection was a qualitative measure, typically the surgeon's intraoperative estimation.

b) In patients with low grade glioma, what is the evidence that chemotherapy improves outcome, in terms of survival, quality of life or functional status?

There was little evidence about the role of chemotherapy for people with low grade gliomas. Eyre and co-workers (Eyre *et al.* 1993) closed their RCT early because they could not recruit enough patients. Their (underpowered) analysis did not demonstrate an overall survival benefit for CCNU chemotherapy. Prospective case series (Brada *et al.* 2003; Buckner *et al.* 2003; Quinn *et al.* 2003) suggest a role for chemotherapy in the treatment of low grade gliomas. But these were preliminary studies without comparison groups.

The results of ongoing randomised trials of chemotherapy for people with low grade glioma (EORTC trial 22033–26033 and RTOG trial 98–02) should strengthen the evidence in this area.

c) In patients with low grade glioma, what is the evidence that radiotherapy improves outcome, in terms of survival, quality of life or functional status?

Two RCTs comparing standard with high dosage therapy (Karim *et al.* 2002; Shaw *et al.* 2002) did not observe an effect of dosage on overall survival. The trial of Shaw and co workers (Shaw *et al.* 2002) observed an objective response to radiotherapy in 32% of patients.

Delaying postoperative radiotherapy until tumour progression does not appear to adversely affect the overall survival of people with low grade glioma (Karim *et al.* 2002; Van Den Bent *et al.* 2005; Hanzely *et al.* 2003). Early radiotherapy may improve tumour control (Karim *et al.* 2002; Van Den Bent *et al.* 2005; Hanzely *et al.* 2003) – but it is unclear what impact early radiotherapy has on quality of life.

Table 4.1 Surgery for people with low grade glioma

Abbreviations: EORTC, European organisation for research and treatment of cancer; MMSE, mini mental status examination.

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Shaw *et al.* 2002)	Investigators randomized 108 patients to the low dose arm of the trial and 103 to the high dose arm. For reasons of ineligibility (n=5) and patient compliance (n=3), 101 patients began the low dose therapy and 102 the high dose therapy. The investigators stratified the randomization by: grade; histology; completeness of surgical resection; age; tumour size; and institution (the trial was multi-centre). Inclusion criteria Age more than 18 years; histologically proven Kernohan	Localized radiotherapy, either low dose (50.4 Gy in 28 fractions) or high dose (64.8 Gy in 36 fractions).	Survival, time to tumour progression (TTP), tumour response and toxicity.	The study did not demonstrate a benefit from higher dose radiotherapy in terms of overall survival or tumour progression. Gross total resection of the tumour was a positive prognostic factor for time to tumour progression but not for overall survival. Overall survival Median follow up for the 120 patients still alive was 6.4 years. Overall 5-year survival was 72% in the low dose radiotherapy arm was compared to 65% in the high dose arm. The authors used multivariate analysis (CART and Cox models) to identify prognostic factors for overall survival. The CART model identified 5 survival groups based on histology, tumour size, age and MMSE score. Cox analysis identified non-oligo/mixed histology, tumour size>5cm, age>40, non-Mayo Clinic institution and MMSE 28-30 as significant adverse prognostic factors ($p<0.05$) for survival. High dose radiation was not a prognostic factor for survival. Time to progression Cox analysis identified non-oligo/mixed histology, tumour size>5cm, age>40, MMSE 28-30 and incomplete gross tumour resection as significant adverse prognostic factors ($p<0.05$) for time to tumour		Prospective observational study.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	grade 1 or 2 astrocytoma, oligodendroglioma or mixed oligoastrocytoma within 3 months of study entry; Exclusion criteria Pilocytic astrocytoma. USA			regression. High dose radiation was not a prognostic factor for tumour progression. Tumour response Imaging data for tumour response to radiotherapy were available for 177 patients. In the standard dose group there were 2 complete responders and 27 partial responders. In the high dose group there was one complete responder and 26 partial responders. In all 32% of the 177 patients showed objective tumour response to radiotherapy. Toxicity The most commonly reported toxicities were dermatitis (31%), alopecia (at least 24%), lethargy (7%), otitis (6%), nausea (3%) and neurological toxicity (3%). The authors report grade 3 to 5 toxicity in 13% of the patients (13% in the low dose arm, 14% in the high dose arm).			
(Pignatti *et al.* 2002)	The investigators used data from 2 EORTC RCTs of radiotherapy for the treatment of low grade glioma: trial 22844 (322 patients) and trial 22845 (288 patients).	Data were collected during two EORTC trials of radiotherapy.	Overall survival: the time from randomization until death from any cause.	The investigators used data from EORTC 22844 to construct a Cox proportional hazards regression model for survival, which they validated with data from EORTC 22845. Their final prognostic model contained 5 factors: age, largest diameter of the tumour, tumour crossing the midline, histology type and neurological deficits before surgery.	The authors selected variables for their model on the basis of univariate screening ($p<0.10$), and a backward and forward elimination process.	Prospective observational study.	3++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Inclusion criteria Age 16 to 65 years; histological diagnosis of low grade oligodendroglioma, astrocytoma or mixed oligoastrocytoma; Karnofsky score at least 60; WHO performance score 2 or less. Exclusion criteria Totally excised pilocytic astrocytoma; pregnancy; gross hepatic, cardiovascular or renal disease; any other cancers in the previous 5 years (excluding curable skin cancer); major functional neurological deficit.			More extensive surgery was a positive prognostic factor on univariate analysis ($p<0.05$) but did not feature in the final model. This suggests that extensive surgery was more likely in patients with a better prognosis (with smaller more superficial tumours).	The authors note that in the trials the extent of surgery was based on the surgeon's intraoperative estimation, not on imaging, and this may have introduced variability in this measure. The authors also comment that extensive surgical is more likely to uncover unrecognized high grade tumours than a biopsy alone. Thus there may be more undetected high grade tumours in patients who receive biopsy alone.		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Keles *et al.* 2001)	The authors searched MEDLINE (1970-2000) for relevant studies. The search identified 30 potentially relevant papers; 5 of these met the authors' criteria for quality and relevance. Inclusion criteria Studies reporting extent of resection and survival in adult patients with hemispheric low grade gliomas. Exclusion criteria Predominantly non-hemispheric gliomas; studies not in the English language; series containing children; pilocytic or gemistocytic astrocytoma; series with less than 75 patients or small	Surgical resection of low grade glioma	Overall survival	In univariate analysis all 5 studies reported extent of surgical resection a significant prognostic factor for survival. In multivariate analysis 4/5 studies reported extent of resection a significant prognostic factor. 4/5 of the studies evaluated the extent of resection using the surgeon's intraoperative impression. One study used postoperative imaging. Patient selection was a potential source of bias: one study excluded patients who had only biopsy or those who died within 30 postoperative days. Patients were not randomly selected for surgery, but in the belief that surgery was necessary.	The case series from 70s and 80s - possible changes in patient management (e.g. MRI)?	Systematic review of case series.	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	numbers of events						

Table 4.2 Chemotherapy for people with low grade glioma

Abbreviations: CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1 nitrosourea; HQOL, health related quality of life; PFS, progression free survival;

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Buckner *et al.* 2003)	The trial registered 31 patients:3 received only chemotherapy; 25 both chemotherapy radiotherapy; 3 were ineligable. Age was 23 to 62 years, median 36 years. Eligibility criteria: supratentorial low-grade oligodendroglioma (n=17) or mixed oligoastrocytoma (n=11). All patients had biopsy or incomplete resection, with measurable tumour on post operative MRI scan. Exclusion criteria:	Chemotherapy (PCV): procarbazine, lomustine and vincristine. Most patients also received radiotherapy.	Toxicity, tumour regression, and overall survival.	Toxicity 75% of patients experienced grade 3 or 4 leukopenia and 64% grade 3 thrombocytopenia. 46% of patients experienced mild to moderate anorexia, 61% nausea, 57% vomiting and 29% diarrhoea. Neurologic toxicity was usually mild to moderate but was severe in approximately 4% of patients. Tumour Regression 25 of the 28 patients had pre and post chemotherapy MRI scans (to allow estimation of tumour regression). 13/25 patients were deemed to have tumour regression by blinded central neuroradiology review (52%; 95% CI, 31% to 72%). The patients' treating physicians reported 6/25 (29%) patients had tumour regression. Overall survival Kaplan-Meier estimates of the 1, 2 and 5 year overall survival were 100%, 96% and 89% respectively. 1,2 and 5 year recurrence free survival was 91%, 62% and undefined respectively.	Discrepancy between neuroradiologists and oncologists assessment of tumour response to chemotherapy. How does tumour response relate to other outcomes for this group?	Prospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	those with macroscopic complete resection; those with tumours of the pons, medulla or optic chiasm; those with pilocytic astrocytoma; those whose tumours with 3 or 4 elements; pregnant or lactating women; prior malignancy; active infection; prior oncological treatment; or Eastern Cooperative Oncology Group performance scores of 3 or 4; USA						
(Quinn *et al.* 2003)	By the date of the analysis the investigators had enrolled 46 patients. 59% of the group were male. Median age of the group was	Temozolomide administered orally once a day for 5 consecutive days, starting at a dose of 200mg/m^2/day. Treatment cycles	Toxicity and progression free survival. Tumour response was evaluated by the principal investigator using MRI scans	Before starting temozomolide therapy 52% of patients had tumour resection, 15% prior radiotherapy and 22% prior chemotherapy. Toxicity The toxicities were limited to myelosupression: 3 episodes of grade 3 neutropenia; 2 episodes of grade 3		Prospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	41years (range 7 to 61 years). 35% of the patients had astrocytoma, 43% oligodendroglioma, 11% pilocytic astrocytoma and 11% mixed glioma. Inclusion criteria: primary supra- or infratentorial low grade glioma; measurable progressive disease on CT or MRI, or neurologically; age at least 4 years; KPS at least 70; adequate pre-treatment bone marrow, renal and hepatic function. Exclusion criteria: pregnancy; HIV positivity; patients recovering from surgery; frequent vomiting; poor medical risk due to	were repeated every 28 days.	before odd treatment cycles.	thrombocytopenia. One patient had grade 4 neutropenia and thrombocyotpenia and died of an intracerebral haemorrhage. Progression free survival 16 patients showed tumour progression. Median progression free survival (PFS) was 22 months. 6 month PFS was 98% (95% CI, 94% to 100%) and 12 month PFS was 76% (95% CI, 63% to 92%). On univariate analysis prior radiotherapy or chemotherapy was an adverse prognostic factor for PFS. The investigators observed a complete or partial tumour response to chemotherapy in 28 of the 46 patients, corresponding to a response rate of 61% (95% CI, 43% to 77%).			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	other systemic disease; active infection requiring antibiotics. USA						
(Brada *et al.* 2003)	30 patients entered the study. Tumour response was evaluable in 29. Median age was 40 years (range 25 to 86 years). 2/30 patients had KPS<70. Inclusion criteria: age more than 18 years; histologically confirmed grade II: astrocytoma, oligodendroglioma or mixed oligoastrocytoma; stable or progressive disease; satisfactory haematological and biological parameters (defined in earlier temozolomide trials).	Temozolomide 200mg/m^2/day for 5 days, given every 28 days, with a maximum of 12 cycles. Dose and frequency were adjusted according to standard toxicity criteria.	Toxicity; tumour response determined using imaging and clinically(seizures and HQOL); survival.	Toxicity 24/29 patients completed 12 months of treatment. Reasons for stopping treatment were: disease progression (n=3); skin eruption (n=1) and early death (n=1). There were 11 episodes of grade III/IV haematological toxicity in 6 patients. 2 patients had grade III constipation and one had grade III nausea and vomiting. Tumour response (imaging) 3 patients had a partial response, 14 minimal response, 11 stable disease and one progressive disease. Tumour response (clinical) 27 patients had a history of seizures and 14 of these had reduced seizure frequency during chemotherapy. 27/28 patients had improvement in at least one HQOL domain. Improvement in HQOL was more likely in treatment responders than non-responders (66% vs. 44%, p<0.01). Tumour control and survival 9 patients had progressive disease either during (n=3)		Prospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Exclusion criteria: previous radiotherapy or chemotherapy; those with imaging or histological evidence of high grade transformation; those requiring urgent surgery or radiotherapy; pregnancy.			or after completion of chemotherapy (n=3). PFS at 2 years was 76% and at 3 years was 66%. 2 year actuarial survival was 87% and 3 year actuarial survival was 82%.			
(Eyre *et al.* 1993).	The investigators enrolled 60 patients. 6 were excluded because their tumours were high grade. 19 patients received radiotherapy alone and 35 received radiotherapy and chemotherapy. Median age was 36 years (range 22 to 73 years) for the radiotherapy group. Median age was 39 years (range 17 to 72 years) for the	Radiotherapy alone (55 Gy in 32 fractions) or radiotherapy and CCNU chemotherapy (110mg/m^2 every 6 weeks).	Overall survival. Tumour remission. Toxicity.	Overall survival Using a log rank test, there was no significant difference in the survival of the two groups (p=0.7). Median survival for the RT+CCNU group was 7.4 years compared to 4.5 years for the RT only group. Other univariate (log rank) analyses suggested that age and performance status were potential prognostic factors (p<0.01). Tumour remission 54% of patients in the RT+CCNU had complete or partial remission compared to 79% in the RT only group. The difference was not statistically significant. The authors judged remission using tumour size on CT scan, neurological function and performance status. Toxicity	Study closed early due to slow accrual and the rejection of the hypothesis of a 50% survival improvement in the CCNU group. No details of randomization, allocation concealment or blinding. Length of follow-up not reported.	RCT	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	radiotherapy and chemotherapy group. Inclusion criteria Histological diagnosis of grade I or II primary brain tumour (according to Kernohan and Sayre), with incomplete resection. Exclusion criteria Cystic cerebellar astrocytoma USA			All patients experienced toxicity, usually as a result of radiotherapy. The investigators reported severe (grade 3) or life threatening (grade 4) haematological toxicity in 12% of patients receiving CCNU.			

Table 4.3 Radiotherapy for people with low grade glioma

Abbreviations: CART, classification and regression tree; MMSE, mini mental status examination; TTP, time to tumour progression; CT, ; MRI, ; PFS , progression free survival; RT, radiotherapy; DSS, disease specific survival;

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Shaw *et al.* 2002)	Investigators randomized 108 patients to the low dose arm of the trial and 103 to the high dose arm. For reasons of ineligibility (n=5) and patient compliance (n=3), 101 patients began the low dose therapy and 102 the high dose therapy. The investigators stratified the randomization by: grade; histology; completeness of surgical resection; age; tumour size; and institution (the trial was multi-centre). Inclusion criteria Age more than 18	Localized radiotherapy, either low dose (50.4 Gy in 28 fractions) or high dose (64.8 Gy in 36 fractions).	Survival, time to tumour progression (TTP), tumour response and toxicity.	The study did not demonstrate a benefit from higher dose radiotherapy in terms of overall survival or tumour progression. Overall survival Median follow up for the 120 patients still alive was 6.4 years. Overall 5-year survival was 72% in the low dose radiotherapy arm was compared to 65% in the high dose arm. The authors used multivariate analysis (CART and Cox models) to identify prognostic factors for overall survival. The CART model identified 5 survival groups based on histology, tumour size, age and MMSE score. Cox analysis identified non-oligo/mixed histology, tumour size>5cm, age>40, non-Mayo Clinic institution and MMSE 28-30 as significant adverse prognostic factors ($p<0.05$) for survival. High dose radiation was not a prognostic factor for suvival. Time to progression (progression free survival) Cox analysis identified non-oligo/mixed histology, tumour size>5cm, age>40, MMSE 28-30 and incomplete gross tumour resection as significant adverse prognostic factors ($p<0.05$) for time to tumour regression. High dose radiation was not a prognostic	Incomplete reporting of randomisation, allocation concealment and blinding.	RCT	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	years; histologically proven Kernohan grade 1 or 2 astrocytoma, oligodendroglioma or mixed oligoastrocytoma within 3 months of study entry; Exclusion criteria Pilocytic astrocytoma. Multicentre trial, USA			factor for tumour progression. Toxicity The most commonly reported toxicities were dermatitis (31%), alopecia (at least 24%), lethargy (7%), otitis (6%), nausea (3%) and neurological toxicity (3%). The authors report grade 3 to 5 toxicity in 13% of the patients (13% in the low dose arm, 14% in the high dose arm).			
(Karim *et al.* 1996)	The investigators randomized 379 patients, but included 343 (91%) in the analysis. 171 patients received low dose radiotherapy and 172 high dose. Minimum length of follow up was 4.5 years (median 6.2 years). The investigators excluded 36 patient from the analysis because of:	Localized radiotherapy, either low dose (45 Gy in 25 fractions) or high dose (59.4 Gy in 33 fractions).	Overall survival and progression free survival (PFS). The investigators determined tumour progression using clinical and radiologic (CT and later MRI in some patients) examination during follow up.	Overall survival There was no evidence of improved survival in the high dose group. The investigators used multivariate analysis (Cox regression) to identify the following adverse prognostic factors: Extent of the primary tumour (increasing T classification); poor neurologic status; increased age; incomplete surgical resection of tumour; Progression free survival Adverse prognostic factors were: Extent of the primary tumour (increasing T classification); astrocytoma histologic type; poor neurologic status; incomplete surgical resection of tumour.	Incomplete reporting of randomization, allocation concealment and blinding.	RCT	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	incomplete data (n=16); wrong tumour location or type (n=11); poor performance score (n=4) and prior treatment or delay in radiotherapy (n=5). Inclusion criteria Age 16 to 65 years; histological diagnosis of low grade oligodendroglioma, astrocytoma or mixed oligoastrocytoma; Karnofsky score at least 60; WHO performance score 2 or less. Exclusion criteria Totally excised pilocytic astrocytoma; pregnancy; gross hepatic, cardiovascular or renal disease; any other cancers in the previous 5 years			Toxicity The investigators report only qualitative results. Radiotherapy had to be interrupted for more than 1 week in 13 of the low dose patients and in 26 of the high dose patients. Treatment was discontinued for 9 high dose patients.			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	(excluding curable skin cancer); major functional neurological deficit. Multicentre study (EORTC trial 22844), Europe						
(Karim *et al.* 2002)	The investigators randomized 311 patients to the trial. They found only 290 were eligible and assessable: 150 in the radiotherapy arm and 140 in the observation only arm. Inclusion criteria Age 16 to 65 years; histological diagnosis of low grade oligodendroglioma, astrocytoma or mixed oligoastrocytoma; Karnofsky score at least 60; WHO performance score 2 or less.	The treatment group received postoperative radiotherapy (54Gy given over 6 weeks) within 8 weeks of surgery. The comparison group did not receive postoperative radiotherapy until their tumour showed signs of progression.	Overall survival and time to tumour progression (progression free survival), measured from the date of randomization. Toxicity. Median follow up was 5 years (range 14 months to 11 years). The investigators defined tumour progression as clinical-neurologic deterioration confirmed by evidence of tumour activity clinically and on CT scan (in some cases MRI was used).	Overall survival There was no significant difference in the overall survival of the treatment and control groups (p=0.49, log rank test). The 5 year overall survival was 63% in the treatment group compared to 66% for the controls. Time to tumour progression (progression free survival) Time to tumour progression was significantly longer in the treatment group (p=0.02, log rank test). The 5 year progression free survival was 44% for the treatment group and 37% for the controls. Toxicity Grade 3 acute reactions: erythema (1%) and headache (1%). 1% of the patients experienced grade 4 erythema.		RCT	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Exclusion criteria Totally excised pilocytic astrocytoma; pregnancy; gross hepatic, cardiovascular or renal disease; any other cancers in the previous 5 years (excluding curable skin cancer); major functional neurological deficit. Multicentre study (EORTC trial 22845), Europe						
(Van Den Bent *et al.* 2005)	The investigators randomized 311 patients to the trial, 154 to the radiotherapy arm and 157 to the observation only arm. 303 patients were both eligible and assessable.	Intervention The treatment group received postoperative radiotherapy (protocol stated 54Gy given over 6 weeks in 30 fractions) within 8 weeks of surgery. The comparison group did not receive	Overall survival and time to tumour progression (progression free survival), measured from the date of randomization. Median follow up was 7.75 years. The investigators defined tumour progression	Overall survival The investigators found no difference between the overall survival of the control and treatment groups (p=0.873, log rank test), in an intention to treat analysis. Progression free survival Patients in the treatment group had longer progression free survival (p<0.001, log rank test). Median progression free survival was 5.3 years (95% CI 4.6 to 6.3 years) for the treatment group compared with 3.4 years (95% CI 4.6 to 6.3 years).	Authors suggest postoperative radiotherapy could be deferred for patients in good condition, provided they are carefully monitored.	RCT	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Inclusion criteria Age 16 to 65 years; histological diagnosis of low grade oligodendroglioma, astrocytoma or mixed oligoastrocytoma; Karnofsky score at least 60; WHO performance score 2 or less. Exclusion criteria Optic nerve glioma, brainstem glioma, third ventricular glioma and mostly infratentorial glioma; totally excised pilocytic astrocytoma; pregnancy; gross hepatic, cardiovascular or renal disease; any other cancers in the previous 5 years (excluding curable skin cancer); major functional neurological deficit.	postoperative radiotherapy until their tumour showed signs of progression.	as clinical-neurologic deterioration confirmed by evidence of tumour activity clinically and on CT scan (in some later cases MRI was used).				

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Multicentre study (EORTC trial 22845), Europe						
(Hanzely *et al.* 2003)	The investigators reviewed 166 patients from their institutional database, and included 97 patients in the analysis. Mean age for the early RT group (n=36) was 36 years, range (19 to 50 years). Mean age for the no early RT group (n=61) was 37 years, range (14 to 85 years). Inclusion criteria Cases where the 2 neuropathologists agreed on the diagnosis of WHO grade II supratentorial, non-pilocytic astrocytoma.	Early radiotherapy (if the patient received RT following histological confirmation of their tumour) or late radiotherapy (if it was delayed until their tumour progressed).	Disease specific survival and progression free survival (both measured from the time of diagnosis). Median follow up of surviving patients was 6.7 years (range 2.3 to 12.8 years). The date of tumour progression was based on clinical deterioration and/or radiographic worsening (not further defined).	Disease specific survival (DSS) The investigators did not identify significant prognostic factors (at $p<0.05$) for DSS using multivariate analysis. Age and extent of surgical resection approached significance, but early RT did not appear to influence DSS. Progression free survival (PFS) On multivariate analysis, only early RT was significantly associated with better PFS ($p<0.01$, Cox regression). The 5 and 10 year progression free survival rates were 52% and 31% in the early RT group compared to 40% and 12% in the no-early RT group.		Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Exclusion criteria Oligodendral features, loss to follow up (n=6), early postoperative death (n=3; not further defined). USA						

Chapter 5 Management of patients with high grade glioma

1 Surgery

The question

In patients with HGG, what is the evidence that surgery improves outcome, in terms of survival, quality of life or functional status?

The nature of the evidence

Fourteen studies were identified, as follows:

- Three systematic reviews: two of high quality and one of low quality
- One randomised, controlled trial, of poor quality
- Two observational studies of good quality
- Six observational studies of fair quality
- Two observational studies of poor quality

One systematic review was undertaken in the UK. The majority of studies (ten) are from the US and one study each is from Canada, Finland and Germany. Applicability to the UK is therefore limited.

The studies are predominantly of patients with HGG, particularly glioblastoma multiforme and supra-tentorial malignant glioma. One study is of patients who underwent craniotomy for primary neoplasm.

Summary of the supporting evidence for the recommendations

There is no high quality evidence to suggest better outcomes for patients with HGG arising from surgery over stereotactic biopsy, and this finding is reflected in the rigorous systematic review of RCT evidence by Grant & Metcalf (2004). Whilst one randomised, controlled trial concluded that survival is significantly longer following resection compared with biopsy, this study had methodological flaws. Observational study evidence reaches no consensus on whether surgery or biopsy alone provides

the best outcomes for patients with HGG, and this is reflected in two systematic reviews of observational studies. Where surgical resection is undertaken, observational study evidence is suggestive of an advantage in terms of survival following gross, total resection over partial resection. This finding was reflected in a low quality systematic review.

Table 5.1 In patients with high grade glioma, what is the evidence that surgery improves outcome, in terms of survival, quality of life or functional status?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Grant & Metcalfe 2004)	Patients (presumably adults, but not specified) with presumed isolated supra-tentorial malignant glioma. Not just "high grade" glioma. Stereotactic biopsy Surgical resection Undertaken in the UK	Stereotactic biopsy Surgical resection	Time to death, Median survival Time to progression Quality of life	Only one small, low quality RCT identified, (Vuorinen 2003) that included 30 participants, age ≥ 70 years and KPS ≥ 60%. Survival appeared better in resected group p = 0.035. but insufficient evidence to answer the question.	*A high quality review that found only one low quality RCT. The value of tumour resection compared with stereotactic biopsy alone is uncertain*.	Systematic Review	1 ++
(Long *et al.* 2003)	All adult (4723) patients, undergoing craniotomy for tumour in 33 acute care hospitals between 1990-1996. 1740 with primary malignant neoplasms, 1071 with secondary malignancies and 1912 with benign	Analysis of effects of regionalisation by analysis of the cost and outcome of craniotomy for tumours and to compare the results in academic medical centres versus community based hospitals. Hospitals were categorised as	Mortality, length of stay (LOS) and costs	The mortality rate was 2.5% at high volume centres and 4.9% at low volume hospitals with an adjusted RR of 1.4 (p=<0.05), assuming equivalence of disease severity. Adjusted LOS in high volume centres was 6.8 days compared with 8.8 days in low volume centres (p= <0.001). hospital charges were significantly higher at high volume centres than at low volume hospitals. The mortality by diagnosis indicated that the adjusted relative risk for secondary malignancies was significantly lower at high volume centres.. The authors conclude that if all patients had been treated at centres with survival rates equal to those	*Not enough details reported of statistical analyses. In the UK no neurosurgical unit does less than 50 operations of this kind per year, with most performing over 100 per year. Limited relevance*	Historical case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	tumours. US	high volume, >50 craniotomies/year or low volume , 50 craniotomies /yr.		achieved by the high volume centres then 46 patients would have not have died of operation.	*to UK. Not directly relevant to question*		
(Taylor *et al.* 2004)	Adults with supra-tentorial malignant glioma Review undertaken in Canada	Systematic review of published literature (1985 to June 2003) Stereotactic biopsy Gross total resection Subtotal or partial resection	Survival Prognostic factors for survival Complications of surgery Quality of life	One Cochrane review, one systematic review, one small RCT, six prospective phase II studies, 11 retrospective studies identified. Prognostic factors for survival: Evidence from 6 retrospective studies and 1 prospective phase II study. Most commonly identified factors: extent of resection, age, Karnofsky scale. Biopsy versus resection: One RCT, 6 retrospective studies and 1 prospective phase II. RCT was of low quality and included only 30 patients (age ≥ 70 years, KPS ≥ 60%). All studies reported results that showed statistically significant benefit of tumour resection compared with biopsy (including in patients over 65 years). Gross total resection (GTR) versus subtotal (STR) or partial resection (PR) Five retrospective studies and five prospective studies identified. All studies suggested improved survival for patients who had GTR compared to STR or PR. But only 2 studies reported that patients were similar for age and KPS before surgery. Complications:	*Lack of high quality evidence precludes comment on the value of GTR compared with biopsy alone or STR/PR* *The RCT was small, and all other studies non-randomised and so very likely to be subject to selection bias.* *It is not clear what selection biases operate in these non-randomised studies.* *Small studies,*	Systematic review	2 ++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Only one study reported complications. Biopsy (88 patients). Haematoma 3%, Death in 30 days: 4%. Resection (40 patients) Death in 30 days: 2%. QOL or functional status: 4 retrospective studies, 1 prospective. No consistent patterns of improvement or deterioration in functional status after GTR or less than GTR.	*non randomised, with selection biases.*		
(Vuorinen *et al.* 2003)	30 patients, 60 yrs with malignant glioma. 7/30 patients did not have glioma on further investigation. Results for 23 patients presented. Ten patients were randomised to undergo resection and 13 to biopsy. Finland	Resection versus biopsy	Median survival	The authors observed longer median survival for the patients undergoing resection compared with biopsy (24 weeks versus 12 weeks; p= 0.035).	*Some methodological problems with the trial:-* *23% of patients included in the trial did not have glioma* *small sample size* *no mention of whether study was powered to detect a significant difference between the groups.* *method of randomization not*	Randomised controlled trial	1 -

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					described *no intention to treat analysis* *no stratification for age or KPS* *error in methods section – states KPS > 60 when In fact some patients = to 60* *patients in two arms not equal.* *study underpowered*		
(Berger 1994)	92 patients(median age 51 years, 15-80 yrs), with GBM US	A computerised image analysis technique was used to assess the volumetric extent of tumour removal.	Tumour progression. Mortality	All patients had received radiotherapy and 85% of them had received additional chemotherapy. The median time for tumour progression was 30 weeks. Median survival was 61 weeks. Total tumour resection resulted in a median survival duration of 93 weeks versus 63 and 32 weeks for a 50% to 74% and less than 25% resections, respectively. Other variables that reached statistical significance for survival were age and preoperative and postoperative Karnofsky scores. The most powerful predictor of a significant effect on survival in their analysis was time to tumour progression between first operation and re-operation		Historical case series	3 -
(Fadul *et al.*	104 patients (mean age 51, range 19-74	Surgical resection	Morbidity and	Mortality was 3.3% and the medical and neurological morbidity was 31.7%. Functionally significant	*The groups differed*	Case series	3 -

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
1988)	years) with supra-tentorial glioma from 1 centre 109 patients, from 1 centre. 65 % patients, had GBM, 25% anaplastic glioma and 9% LGG. US		survival	neurological worsening occurred in 42 (19.7%) of patients. Patients, with complete resection had fewer acute neurological complications and no greater risk of being neurologically impaired at 1 week than patients with biopsy or less extensive procedures. Re-operation for recurrent tumour carried no greater risk of mortality, neurological deterioration and infection than a first operation. The authors conclude that whenever possible maximal surgical resection should be offered to patients with supra-tentorial gliomas.	*significantly in the proportion of patients undergoing complete resection (p=< 0.0001). Limited relevance to question. Dated*		
(Coffey *et al.* 1988)	91 patients, with GBM (64) or AA (27) between August 1981-June 1986, confirmed by CT or MRI US	Comparison of stereotactic biopsy followed by RT with craniotomy and tumour resection	Mortality and morbidity. Survival.	There were no deaths as a result of the Stereotactic biopsy. 4 patients, died within 30 days after biopsy. 3 patients, had complications after biopsy. The treatment prescribed after biopsy, tumour location, histological findings and patients' age at presentation were statistically significant factors determining patient survival. If adequate RT was not prescribed the median survival was ≤ 11 weeks regardless of tumour site or histology. Median survival for patients, with deep or midline tumours who completed RT was similar in AA (19.4 weeks) and GBM (27 weeks) cases. Cytoreductive surgery had no statistically significant effect on survival. The authors conclude that for patients, with deep or midline malignant gliomas and for selected patients, with lobar tumours in critical areas, stereotactic biopsy followed by RT and non-operative adjuvant therapy is	*Authors discuss the significant confounding effects between the 2 groups and the treatment and selection biases..*	Case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				a rational treatment strategy			
(Devaux *et al.* 1993)	263 patients (163 male, 100 female), mean age 52 yrs (4-83 yrs) with malignant brain gliomas There were 170 grade IV astrocytomas, 17 grade IV mixed oligoastrocytomas, 44 grade III astrocytomas, 22 grade III mixed oligoastrocytomas and 10 malignant oligodendrogliomas US	Stereotactic biopsy in 160, resection in 103 patients, performed by 1 surgeon.	Post operative mortality and morbidity. Overall survival.	9 deaths occurred within 30 days following 179 stereotactic biopsy procedures; 2 deaths were related to surgery; 2 to non-surgical complications and 5 to deteriorating neurological course unrelated to biopsy. There were no postoperative deaths among the 78 patients who underwent stereotactic resection or among the 25 with non-stereotactic resection.	*Good description of methodology with appropriate use of statistics. Obvious* problems *with patient selection bias. The authors plan a randomised study that will further evaluate the role of surgical resection & pre-operative selection factors.*	Historical case series	3 +
(Kreth *et al.* 1993)	Between January 1986-March 1991, 133 patients with GBM Germany	Comparison of surgical resection and RT versus biopsy and RT	Survival	115/133 patients were included in the analysis. The biopsy and resection group did not differ significantly in terms of age, clinical symptoms, tumour size, symptom duration. The mean preoperative KPS was higher (p=0.02), the tumours located more often in the right hemisphere (p<0.01) in the resection group. Midline tumours were found only in the biopsy group. The median survival time for the biopsy plus RT group	*Some significant differences between the 2 groups. Comparison of the 2 groups must therefore be viewed with*	Retrospective comparative study with historical control	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				(4 censored events) was 32 weeks versus 39.5 weeks for the resection and RT group (mean FU period 35.6 weeks). This difference was not significant 9p>0.05). Multivariate analysis indicated that age was the most significant variable in predicting survival length (p<0.01). Preoperative KPS was significant in univariate analysis. The authors conclude that RT is the most effective therapy for GBM	*caution.*		
(Lacroix *et al.* 2001)	416 patients (median age 53 years (SD 14 years)with GBM who underwent craniotomy and tumour resection. Study period June 1993-June 1999. US	Identification of significant independent predictors of survival and to determine whether the extent of resection was associated with increased survival time	Survival	All patients underwent RT in addition to surgical resection. The preoperative KPS was > 80 in 313/416 (75%) of patients. There were 183 (44%)treated patients, and 233 (56%)untreated patients. Before presentation at the Centre, the treated patients had undergone resection or biopsy with or without adjuvant chemotherapy. Median survival was 56 weeks in patients in whom the resection was ≥ 98% and 38 weeks with ≤ 98%; p= 0.02. An additional finding was that on preoperative MRI the degree of necrosis enhancement was significantly associated with survival. The authors conclude that GTR should be performed whenever possible.	*With selected patients, it is possible to demonstrate that GTR is associated with an increase in survival and this correlates with age < 40 years, good KPS and frontal tumours.*	Historical case series	3
(Laws *et al.* 2003b)	666 patients, with malignant glioma enrolled in Glioma Outcomes Project. December 1997-	Extent of resection. Patients were followed up until death or up to 24 months	Length of survival	Improved survival was obtained in patients, who had undergone resection compared with biopsy. The biopsy group however, included more older patients, and those with impaired performance and virtually all of the multifocal and bilateral tumours. In order to	*Insufficient details of analyses given.* *Gives guidelines for when to biopsy and when to*	Historical case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	October 2000. US			analyse effect of these differences an analysis was performed eliminating from both groups patients, aged > 65, those with KPS < 70 and those with multifocal or bilateral tumours. The advantage for resection was significant (p=0.0015). The authors conclude that despite selection bias the data support resection as a major factor in survival after surgery for malignant gliomas.	*resect*		
(Laws *et al.* 2003a)	788 patients, with recently diagnosed malignant glioma. Accrual period 1997-2001 US	Analysis of data from the Glioma Outcomes Project for survival following surgery and prognostic factors.	Length of Survival	565 patients were analysed. Median length of survival was 48.2 weeks (range 0.3-104.3 weeks) for the entire group. Within each tumour grade patients, who underwent resection had improved survival. Among patients with Grade III gliomas, the median survival times were 52.1 weeks after biopsy and 87 weeks after resection (p<0.0001). similarly the median survival times for patients, with GBM was 21 weeks after biopsy and 45.3 after resection (p, 0.0001) Cox proportional hazards model survival data are significantly different for biopsy and resection for patients, within each tumour grade after adjusting for age, KPS, presence of unifocal or multifocal disease, use of CT and use of RT. Age < 60, KPS > 70 and use of CT were important covariates (p< 0.0001; p =0.0003); p=0.0158 respectively)	*No attempt was made to quantify the true extent of resection. The author discusses the limitations of the study such as lack of central pathological review.*	Historical case series	3
(Quigley & Maroon 1991)	Patients with supra-tentorial malignant gliomas.	Review of English language literature 1960-1990 on surgical treatment of	Median survival for:- biopsy subtotal resection	20 studies with a total of 5691 patients. 85% of cases involved GBM. 4/20 reports found the extent of resection was not related to survival on multivariate analyses.	*Inadequate description of methodology. All included studies*	Systematic review	2 -

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	US	supra-tentorial malignant gliomas with > 75 patients..	total resection	8/16 reports did not show an association between extent of resection and length of survival. The remaining four studies did not consider confounders and the results viewed with caution..	*used the surgeon's impression to measure the extent of resection as opposed to using an objective measure of resection, such as MRI or CT.* *Likelihood of confounding due to different age, histology and performance status. High degree of selection bias.*		
(Simpson *et al.* 1993)	645 patients with GBM US	The influence of tumour location, size and extent of surgery on survival in patients, with GBM treated on 3 consecutive prospective randomised Radiation Therapy	Survival	Patients, undergoing GTR had a median survival of 11.3 months compared with 6.6 months for patients, with biopsy only ($p < 0.0001$). There was a significant difference in median survival for partial resection versus biopsy alone (10.4 vs. 6.6 months; $p < 0.001$). Multivariate analyses confirmed a significant correlation of age, KPS, extent of surgery and primary site with survival. The best survival rates occurred in patients, who had at least 3 of < 40 years of age; high KPS; frontal tumours and GTR (17 months median)	*Results difficult to analyse. Numerous potential confounding factors, bias etc.*	Historical case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		Oncology Group trials		The authors conclude that biopsy alone yields inferior survival to more extensive surgery for patients, with GBM treated with surgery and RT.			

2 Radiotherapy

The question

In patients with HGG, what is the evidence that radiotherapy improves outcome, in terms of survival, quality of life or functional status?

The nature of the evidence

Nine studies were identified as follows:

- One systematic review of good quality
- 6 RCTs, 3 of good quality and 3 of poor quality
- Two observational/analytical studies, one of good quality and one of poor quality.

Two studies are from the UK, one of which is the systematic review. Four studies originate form the US and one study each is from Canada, Sweden and Israel. Applicability to the UK is likely to be reasonable but limited.

All studies are of patients with HGG.

Summary of the evidence supporting the recommendations

Evidence from RCTs and a systematic review of RCTs supports the role of radiotherapy as a treatment after surgery in patients with HGG. Radiotherapy has been associated with longer survival compared to BCNU regimen chemotherapy (Walker et al., 1978). Time to tumour progression or recurrence and also survival has been demonstrated as significantly longer in patients treated with CCNU regimen chemotherapy plus radiotherapy compared to chemotherapy alone (Sandberg-Wollheim et al., 1991). Randomised controlled trial evidence is also suggestive of no significant survival advantage arising from whole brain radiotherapy compared with whole brain radiotherapy plus coned radiotherapy, when accompanied by chemotherapy regimens, based upon BCNU (Shapiro et al., 1989). Randomised control trial evidence is suggestive of a survival advantage arising from a 60 Gy radiotherapy regimen versus a 45 Gy regimen (Bleehen & Stenning, 1991). The same level of evidence (Scott et al., 1998) suggests there is no survival advantage

arising from the use of a hyper fractionated radiotherapy regimen (72.0 Gy in 1.2 Gy twice-daily fractions) versus standard radiotherapy (60.0 Gy in 2.0 Gy daily fractions). A case series study by Brada et al. (1999) found no survival advantage arising from intensified dose of radiotherapy (55 Gy in 34 fractions i.e. 2 fractions of 1.6 Gy each per day), compared to conventional radiotherapy.

The systematic review by Laperriere et al. (2004) does not support the use of radiation dose intensification and radiation sensitizer approaches. The same review and randomised controlled trials suggest that the total dose delivered should be in the range of 50-60 Gy in fraction sizes of 1.7-2.1 Gy. (Walker et al., 1978, Scott et al., 1998, Bleehen & Stenning 1991, Chang et al., 1983). Systematic review evidence also supports hypo fractionation of radiotherapy for older patients, and also, in older patients with a poor performance status, supportive care alone (Laperriere et al. 2004). The observational analysis by Curran et al. (1993) found that in patients with HGG aged 50 years or more participating in trials of radiotherapy, performance status at trial entry was the most predictive variable of survival.

Table 5.2 In patients with high grade glioma, what is the evidence that radiotherapy improves outcome, in terms of survival, quality of life or functional status?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Walker *et al.* 1978)	N=303 randomised patients with anaplastic glioma (grades 3 & 4 Kernohan scale) having had definitive surgical resection (maximum delay between surgery and randomisation 6 weeks) Patients recruited from 10 neurosurgical services Israel	Aim - Chemotherapy alone vs. radiotherapy alone vs. radiotherapy and chemotherapy Group 1)Radiotherapy alone (n=93): Whole brain; 50-60 Gy; in 5 fractions per week for 6-7 weeks Group 2)Radiotherapy and chemotherapy (n – 100): Whole brain; 50-60 Gy; in 4 fractions per week for 6-7 weeks BCNU 80mg/m^2 intravenously, on 3 successive days every 6-8 weeks	Median survival time Toxicity	Median survival time Valid Study Group (received any amount of therapy n=222) 1) Radiotherapy alone: Mean survival = 35 weeks 2) Radiotherapy and chemotherapy: Mean survival = 34.5 weeks 3) chemotherapy alone: Mean survival = 18.5 weeks 4) Best conventional care: Mean survival = 14 weeks Groups 1 (radiotherapy alone, p=0001)and 2 (radiotherapy and chemotherapy p=0.001) had significantly longer median survival time compared with both group 3 (chemotherapy alone) and group 4 (best conventional care) Group 3 was not significantly better than best conventional care. No significant difference in median survival time between groups 1 and 2. Adequately Treated Group (received >50Gy RT, >2 courses of chemotherapy, min survival of 8 weeks)	*Study was published in 1978; however, also presented in part at two conferences during 1972 and 1973 (therefore likely that study >30 years old)* *Valid study group analysis may introduce bias in terms of excluding patients. Results should be interpreted with caution.* Protocol violations 27% evenly distributed across all groups *Approximately 90% glioblastoma multiforme (GBM)*	Randomised controlled trial	1 -

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		Group 3) Chemotherapy alone (n = 68): BCNU 80mg/m^2 intravenously, on 3 successive days every 6-8 weeks Group 4) Best conventional care (n = 42)		1) Radiotherapy alone: Mean survival: 37.5 weeks 2) Radiotherapy and chemotherapy: Mean survival 40.5 weeks 3) chemotherapy alone: mean survival = 25 weeks 4) Best conventional care: Mean survival = 17 weeks Toxicity Toxicity included acceptable, reversible thrombocytopenia and leukopaenia	*and 10% anaplastic astrocytoma (AA) in each treatment group* In group 2, 39% of patients received a fourth dose of BCNU compared with only 20% of patients in group 3. After second course group 2 had significantly greater number of courses of chemotherapy compared with group 3 ($p<0.01$) Results should be interpreted with caution. *Doses are approximately 2.1 Gy per fraction (4 fractions per week for 6-7 weeks)*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Sandberg-Wollheim *et al.* 1991)	N = 171 randomised patients with supra-tentorial astrocytoma (grades 3&4 Kernohan scale) having had definitive surgical resection (maximum delay between surgery and randomisation 7 days; maximum delay between surgery and treatment 3 weeks) Patients recruited from one neurosurgical department. Patients were stratified according to age (<50 and >50 years of age) and amount of tumour removed at surgery (subtotal or total macroscopic resection) Sweden	Chemotherapy (CT) alone vs. chemotherapy (CT) and radiation therapy (RT) Group 1 (n=87) CT alone: 1 cycle of CCNU (Procarbazine, vincristine and lomustine) every 56 days to maximum of 10 cycles 1 cycle Procarbazine: 75mg/m^2 given orally daily from day 1 to day 28 Vincristine: 1mg/m^2 IV Lomustine: 50mg/m^2 given orally on day 1 and day 15 Group 2 (n = 84) CT (as above) and RT(whole brain	Time to tumour progression or recurrence (wk) Median survival time (wk) Toxicity	All randomised patients n= 171 Median Time to tumour progression/recurrence (wk) CT alone (n= 87) = 18 weeks CT and RT (n= 84) = 29 weeks P = 0.0036 Median survival time (wk) CT alone (n=87) = 42 weeks CT and RT (n = 84) 62 weeks P = 0.028 Valid study group n = 139 (Valid study group who fulfilled protocol requirements, received at least one course of chemotherapy and/or completed radiation therapy). Median Time to tumour progression/recurrence (wk) CT alone (n = 71) = 20 weeks CT and RT (n=68) = 31 weeks P = (0.0057) Median survival time (wk) CT alone (n = 71) = 47 weeks CT and RT (n = 68) = 66 weeks No significant difference between groups. Patients <50 years of age treated with chemotherapy and radiation therapy had significantly longer mean time to progression (CT and RT = 81 weeks vs. CT	*Valid study group analysis may introduce bias in terms of excluding patients. Results should be interpreted with caution.* *After confirmation of progressive tumour growth, patients were given additional individual treatment. This affects the interpretation of median survival time results.* *Numbers of patients with GBM and AA not reported. *important as GBM has worse prognosis and*	Randomised controlled trial	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		irradiation 58Gy to centre of tumour-bearing hemisphere and 50Gy to contra lateral hemisphere in 27 daily fractions x 5 days per week)		alone = 21 weeks; p0.007) and median survival time (CT and RT = 124 weeks vs. CT alone = 66 weeks; p = 0.0033)(p=0.031). Patients >50 years of age; difference between groups was not significant. Toxicity with CT treatment was primarily delayed bone marrow depression and liver toxicity.	*therefore proportion of both types could bias results.*		
(Shapiro *et al.* 1989)	N = 571 randomised patients with malignant gliomas (80% of whom had glioblastoma multiforme) having had maximum surgical resection (maximum delay between surgery and randomisation/treatment 3 weeks). Karnofsky performance status ≥40 at randomisation Patients recruited from seven institutions	Chemotherapy (CT) and radiation therapy (RT) – comparison of different regimens Group 1) CT (BCNU as single chemotherapy regimen) (80mg/m2/day on 3 successive days for 8 weeks) AND a) (n=51) whole brain RT (6020 rads delivered in 35 fractions over 7 weeks) OR b) (n=53) whole brain RT + coned down RT(4300-rad	Median survival time (months) in: 1) Total randomised population (n=104) 2) VSG Valid Study Group	Three different CT regimens plus a) whole brain radiation alone (n = 148) or b) localised radiation (n = 155) No significant difference in median survival times between CT + whole brain radiation alone compared with CT + whole brain RT plus coned down RT. Total randomised population (p = 0.21) Valid study group (p=0.34) (*see comments below*) Authors concluded that 'Giving part of the radiotherapy by coned-down boost is as effective as full whole-brain irradiation'. Analysis of prognostic factors showed that histopathological category, age at randomisation and Karnofsky performance status at randomisation were all significant prognostic variables (p<0.00001)	*All three groups received radiotherapy in addition to chemotherapy.* *Intention to treat population not reported quantitatively. Only valid study group reported. Valid study group analysis may introduce bias in terms of excluding patients e.g. with short survival times. Results should be*	Randomised controlled trial	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Study compares: BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) alone, versus: alternating courses (every 8 weeks) of BCNU and procarbazine, versus: BCNU plus hydroxyurea alternating with procarbazine plus VM-26 (epipodophyllotoxin). US	whole brain radiation plus 1720 rads coned down to tumour volume). Group 2) Alternating courses (every 8 weeks) of CT (BCNU (80mg/m2/day on 3 successive days for 8 weeks) and procarbazine (150mg/m^2 every day for 28 days) AND a) whole brain RT (n=49) (6020 rads delivered in 35 fractions over 7 weeks) OR b) whole brain RT + coned down (n=50) (4300-rad whole brain radiation plus 1720 rads coned down to tumour volume). Group 3) CT (BCNU plus hydroxyurea		Doses could be adjusted according to evidence of toxicity	*interpreted with caution.* *Trial conducted 1980-1983* *Patients recruited in 1980-81 received whole brain radiation, whereas those recruited in 1982-83 were randomly assigned with 6020-rad whole brain radiation or 4300-rad whole brain radiation plus 1720 rads coned down to tumour volume* *Approximately 80% glioblastoma multiforme (GBM) and 20% anaplastic astrocytoma (AA) in each treatment group*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		(1000mg/m2/day every other day for total of 21 days) in combination for 8 weeks, alternating with procarbazine plus VM-26 (epipodophyllotixin) (130mg/m^2/week for 6 weeks) in combination for 8 weeks AND a) whole brain RT (n=48) (6020 rads delivered in 35 fractions over 7 weeks) or b) whole brain RT + coned down(n=52) (4300-rad whole brain radiation plus 1720 rads coned down to tumour volume).					
(Bleehen & Stenning 1991)	N = 474 randomised patients with malignant gliomas (grade 3 or 4) having had	Aim- Different doses of radiotherapy	Survival rate	At 12 months, survival rates for 45Gy and 60Gy were significantly different; 29% and 39 % respectively	*Distribution of GBM and AA between groups not reported*	Randomised controlled trial conducted	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	neurosurgery (biopsy/aspiration: 43%, partial removal: 41%, total removal: 16%) (maximum delay between surgery and treatment 6 weeks). Recruited from 16 sites. UK	Group 1 (n=156) – 45Gy (in 20 fractions of 2.25 Gy over 4 weeks) localised on tumour and surrounding margin Group 2 (n=318) – 60 Gy (in 30 fractions over 6 weeks) localised on tumour and surrounding margin		At 18 months, survival rates for 45Gy and 60Gy were 11% and 18% respectively. 18 months: 45Gy (11%); 60Gy (18%) 24 months: 45gy (8%); 60Gy (12%) 30 months: 45Gy (5%); 60Gy (8%) 36months: 45Gy (5%); 60Gy (6%) Overall difference in survival corresponds to an improvement in median survival of two months in the 60Gy arm (Hazard ratio 0.81 95% CI 0.66 to 0,99, p=0.04). Adjusting for age, an improvement in median survival of approximately 3 months in the 60Gy group compared with 45Gy (Hazard ratio 0.75 95% CI=0.61; 0.92 p=0.007)	**important as GBM has worse prognosis and therefore proportion of both types could bias results.* *Treatment with adjuvant chemotherapy at relapse was at clinician's discretion. 12 patients in the 45Gy group (9%) received chemotherapy and 21 (7%) in the higher dose group. May bias survival times.* *31 patients excluded from analysis on basis of incorrect histology. Pathology was*	between 1983 and 1988	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					blinded therefore excluding these patients not likely to bias results. N=443 patients included in analysis irrespective of protocol compliance i.e. analysis is intention to treat		
(Laperriere *et al.* 2004)	Newly diagnosed adults with histological confirmation of the following diagnoses: glioblastoma multiforme, malignant strocytoma, malignant astrocytoma grade malignant astrocytoma grade malignant glioma, or gliosarcoma. Canada	Systematic review of the evidence.	Development of evidence based guidelines	43 randomised trials were identified. Five of six randomized studies demonstrated that post-operative radiotherapy improves survival compared with no radiation in patients with malignant glioma. • Seven of eight randomized studies of hyper fractionated versus conventionally fractionated radiotherapy demonstrated no significant survival benefit of hyper fractionated radiotherapy. No randomized trials have examined survival following doses in the 50–60 Gy range. • A high-dose volume incorporating the enhancing tumour plus a limited margin (e.g. 2 cm) has achieved similar survival to volumes incorporating whole brain for part or all of the treatment in two randomized studies. • Radiation dose intensification and radiation sensitizer approaches have not demonstrated survival rates	*Good quality guidelines with high score on AGREE tool in most domains. Well described methodology. Evidence reviewed by only 3 members of the guideline development panel.*	Systematic review/ Guidelines	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				superior to those seen with conventionally fractionated doses of 50-60 Gy in randomized studies. Recommendations • Post-operative external beam radiotherapy is recommended as standard therapy. • The high-dose volume should incorporate the enhancing tumour plus a limited margin (e.g. 2 cm) for the planning target volume, and the total dose delivered should be in the range of 50-60 Gy in fraction sizes of 1.8-2.0 Gy. • Radiation dose intensification and radiation sensitizer approaches are not recommended as standard care. Qualifying Statements • A randomized study has established the equivalence of 60 Gy in 30 fractions to 40 Gy in 15 fractions in older patients (>60 years). • Since the outcome following conventional radiotherapy is so poor in older patients with a poor performance status, supportive care alone is a reasonable therapeutic option in these patients.			
(Scott *et al.* 1998)	712 adults with newly diagnosed malignant glioma US	Randomised controlled trial comparing hyper fractionated radiotherapy of 72.0 Gy in 1.2 Gy twice-daily fractions and 60.0 Gy in 2.0 Gy	Mean survival	No survival advantage for the hyper fractionated arm was observed overall or in any stratified subgroup, and the outcome of the standard radiotherapy arm was in fact superior for all patients under age 50 (mean survival: 21.9 v 19.8 months, P = 0.05) as well as for glioblastoma multiforme patients under age 50 (mean survival: 15.7 v 12.4 months, P = 0.03).	Patients were stratified by age (<40, 40-60, ≥60 years), Karnofsky Performance Status (60-70, 80-100), and histology (glioblastoma	Randomised controlled trial conducted between 11/1990 and 3/1994	1 +

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		daily fractions as standard radiotherapy. All patients received 80 mg/m-2 of carmustine D 1--3 q 8 wks.		Mean survival of the 520 evaluable glioblastoma multiforme patients were 11.2 months and 10.2 months for the standard radiotherapy & hyper fractionated arms (P = 0.44). Among the 107 evaluable anaplastic astrocytoma patients, the mean survival were 49.5 & 43.5 months for the standard radiotherapy & hyper fractionated arms, respectively (P = 0.81), as compared to the predicted mean survival of 35.1 and 49.9 months from prior RTOG trials. No significant treatment-related factors were identified by Cox models for anaplastic astrocytoma patients. Authors conclude there is no indication of a benefit for hyper fractionated radiotherapy in any subgroup.	multiforme versus anaplastic astrocytoma). Arm assignment was equal by all other known pre-treatment variables. The study design was based on observed differences in median survival times in prior RTOG trials testing hyper fractionated and standard radiotherapy regimens for glioblastoma multiforme (12.8 versus 10.0 months respectively) and for anaplastic astrocytoma patients (49.9 versus 35.1 months		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					respectively). *Only abstract available. Factors considered in stratified analyses were stated beforehand.*		
(Chang *et al.* 1983)	N = 626 randomised patients with malignant glioma grade III/IV (Kernohan) having had surgery (resection, biopsy) Recruited from multiple sites (exact number of sites not stated). US	Radiotherapy alone vs. chemotherapy and radiotherapy Group 1 - Whole brain radiation (n = 167) 60Gy, 35 fractions, 7 weeks Group 2 Whole brain radiation (n = 114) 60Gy in 35 fractions over 7 weeks, followed by 10Gy to tumour volume plus margin delivered in 5 fractions over 5 days.	Median survival time and 18-month survival in relation to prognostic variables. Toxicity	Median survival time No significant difference in median or 18-month survival was seen between treatment groups; ** however, for patients in the 40-60 age groups, both BCNU and methyl-CCNU + DTIC were significantly better than radiotherapy alone (RT alone 9.3 months median survival vs. BCNU 11.3 months; Methyl-CCNU + DTIC 9.9 months) Patients with anaplastic astrocytoma had a median survival of 27 months compared with 8 months for patients with glioblastoma. Age was the most significant prognostic factor in determining median survival time. Patients with anaplastic astrocytoma Patients ≤40 years – 39.2 months Patients 40-60 years – 23.9 months Patients ≥60 years – 5.2 months	*Conducted between 1974 and 1979 (30 year old study)* *Intention to treat population not reported. Only 'evaluable' patient (n=535) analysis reported. Such analysis may introduce bias in terms of excluding patients. Results should be interpreted with caution.* *12% of patients*	Randomised controlled trial	1 +

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		*Group 3 – Radiotherapy plus Chemotherapy (n = 185) Whole brain radiation 60Gy, 35 fractions, 7 weeks plus BCNU 80mg/m2 x 3 intravenously every 6-8 weeks Group 4 – Radiotherapy plus chemotherapy (n=160) Whole brain radiation 60Gy, 35 fractions, 7 weeks plus methyl CCNU + DTIC. Methyl-CCNU 125 mg/m2 orally, every 8 weeks DTIC 150mg/m2 x 5 intravenously every 4 weeks		Patients with glioblastoma Patients ≤40 years – 16.7 months Patients 40-60 years – 9 months Patients ≥60 years - 6 months No significant increase in survival in group 2 (60Gy whole brain irradiation + 10Gy localised radiation) compared with 60Gy whole brain irradiation alone Toxicity *Methyl-CCNU + DTIC (group 4) had significantly more nausea (p=0.05), vomiting p=0.02) and thrombocytopenia than BCNU (p=0.005). Methyl-CCNU + DTIC produced severe or worse thrombocytopenia in 23% of patients compared with 6% on BCNU	*had major protocol deviations in delivery of chemotherapy; 37% had minor deviations. 19% of patients had protocol deviations in delivery of radiotherapy.* *Each institution randomised patients to treatments in two or three groups of their choice from the four treatment groups. Numbers of patients in treatment groups not equal.* *47% of group 3 (BCNU group) had tumour size <5cm compared with 22-26% in the other groups.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					*There were 46% anaplastic astrocytoma in the <40 group compared with 14% in the 40-60 group and 7% in the >60 group. *important as GBM has worse prognosis and therefore proportion of both types could bias results.* *68% of patients diagnosed with glioblastoma multiforme (GBM) and 14% anaplastic astrocytoma (AA). 18% of patients did not have reviewed diagnosis undertaken. Distribution of*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					GBM and AA similar in all treatment groups. *60 Gy in 35 fractions = 1.7 Gy per fraction*		
(Brada *et al.* 1999)	211 patients with HGG. UK	Evaluation of efficacy and toxicity of accelerated RT consisting 55Gy in 34 fractions (twice daily) delivered to the enhancing tumour and a 3cm margin.	Survival	201/211 patients completed RT; 39/201 (19%) had deterioration in KPS during RT; this was transient in 11. 27 patients were alive at analysis. Median survival was 10 months with 38% 1-year, 14% 2-year and 8% 3-year survival probabilities. On multivariate analysis age, neurological performance status and extent of surgery were independent prognostic variables. Treatment toxicity attributable to RT was mild. (*no details of how assessed)* The authors conclude that survival of patients receiving accelerated RT is comparable to conventional RT.	*Authors discuss the limitations of the data and their preliminary status.* *No control group, use comparison with patients reported in Bleehan 1991 study.* *Equates to 3.2 Gy per day in 2 fractions of 1.6 Gy.*	Case series	3
(Curran, Jr. *et al.* 1993)	1743 patients entered into 3 RTOG trials (RTOG 74-01, RTOG 79-18; RTOG 83-02) for biopsy proven	To analyse the relative contributions of pre-treatment variables to survival using recursive	Survival	1578/1743 patients were analysed. 26 pre-treatment characteristics and 6 treatment-related variables were analysed. The most significant split occurred by age (<50 vs. >50 years). Patients < 50 were categorised by histology (astrocytomas with anaplastic or atypical foci	*15 year accrual period. 1974-1989. No details about reasons for patient*	Statistical analysis of trial data	3 +

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	supra-tentorial malignant gliomas. US	partitioning analysis. The trials used several RT regimens with & without CT or a radiation sensitizer.		(AAF) vs. GBM and subsequently by normal or abnormal mental status for AA vs. GBM and subsequently by normal or abnormal mental status for AAF patients and by performance status for those with GBM. Performance status was the most important variable for patients > 50 years. Treatment related variables produced a subgroup showing significant differences only for better performance status GBM patients > 50 (by extent of surgery and RT dose). The authors conclude that recursive partitioning technique can be used to refine stratification and design of malignant glioma trials.	*attrition.*		

3 Chemotherapy

Systemic chemotherapy

The question

In patients with HGG, what is the evidence that chemotherapy improves outcome, in terms of survival, quality of life or functional status?

The nature of the evidence

Temozolomide was the subject of NICE guideline in the form of technology appraisal number 23 published in 2001. The guidance recommended that temozolomide may be considered as a treatment for patients with:

- Histologically proven malignant glioma (WHO grades III and IV, or transformed grade II) at first relapse, recurrence or progression (as assessed by imaging).
- Karnofsky performance status greater than or equal to 70 and a projected life expectancy of 12 weeks or more.

The same guideline stated that temozolomide is not recommended for first-line chemotherapy treatment for patients with malignant glioma who have failed primary therapy (surgery and/or radiotherapy), except in the context of a RCT against a standard-treatment comparator. The guideline will be updated in 2007.

The effect of carmustine implants and temozolomide on newly diagnosed HGG is the subject of an ongoing NICE health technology appraisal which is due for publication in November 2007 (carmustine implants and temozolomide for the treatment of newly diagnosed HGG).

Twenty three studies were identified, as follows:

- Eight RCTs, seven of good quality and one of poor quality
- Three meta-analyses, Two of good quality and one of poor quality
- One systematic review without meta-analysis, of poor quality

- Seven case series studies of fair quality
- One survey of fair quality
- Two non-systematic reviews of fair quality
- One expert opinion source, of poor quality.

Four studies originate form the UK. The majority (twelve) are from the US and one study is from Canada. Four studies are from Europe and two studies are international, but predominantly European. All studies were of patients with HGG, of which nine were of patients with recurrent HGG.

Summary of the evidence supporting the recommendations

Chemotherapy with Radiotherapy

Evidence from a recent, high quality meta-analysis supports the use of chemotherapy with radiotherapy in an adjuvant setting (Stewart, 2002). The study demonstrated a 2 month median survival advantage for chemotherapy plus radiotherapy compared with radiotherapy alone (hazard ratio of 0.85; 95% CI 0.78-0.91; p=0.00004) and a 5% increase in 2 year survivors. Similarly, the meta-analysis of RCTs by Fine et al. (1993) concluded that median survival is significantly longer with radiotherapy plus chemotherapy (range 7-46 months, median 12 months) combined compared with radiotherapy therapy alone (range 7-34 months, median 9.4 months, p=0.002). A recent, well conducted, RCT demonstrated benefit from adjuvant chemotherapy with temozolomide and radiotherapy, compared with radiotherapy alone, in improving median survival by 2.5 months (hazard ratio of 0.63; 95%CI 0.52-0.75; p<0.001) and a 16% increase in patients surviving at 2 years (Stupp et al. 2005). Expert review evidence supports the use of nitrosuria as adjuvant chemotherapy in patients with HGG and recurrent HGG.

Single versus multiple drug regimens

Strong evidence is lacking to suggest a survival advantage arising from radiotherapy and multiple chemotherapy regiments over radiotherapy and a single chemotherapy regimen. The meta-analysis of RCTs by Huncharek, Muscat, & Geschwind (1998) found that in patients with high grade astrocytoma, the odds of survival at one year

following treatment with radiotherapy plus single drug chemotherapy were greater than those associated with the use of radiotherapy plus combination chemotherapy, but not significantly so (OR 1.22; 95% CI 0.99-1.36). The RCT by Shapiro et al. (1989) found no significant difference in median survival between patients treated with radiotherapy plus multiple drug chemotherapy based upon BCNU and radiotherapy plus BCNU as a single agent. The RCT by Chang et al. (1983) found no significant difference in survival between treatment groups arising from different combinations of chemotherapy plus radiotherapy compared to radiotherapy alone. However, for patients in the 40-60 year age group, the use of both BCNU and methyl CCNU plus DTIC chemotherapy were associated with significantly longer median survival than was radiotherapy alone. An RCT by Prados et al. (1999) of radiotherapy plus adjuvant procarbazine, CCNU and vincristine (PCV) chemotherapy with or without bromodeoxyuridine was stopped early as interim analysis was suggestive of no survival advantage arising from the addition of bromodeoxyuridine.

Genetic factors

Observational study evidence suggests that in patients with oligodendroglioma, demonstration of 1p 19q loss of heterozygosity not only predicts response to chemotherapy, but also survival (see section on molecular pathology).

Temozolomide

The recent RCT by (Stupp et al. 2005) demonstrated a significant survival benefit from adjuvant chemotherapy with temozolomide and radiotherapy (see above). A previous systematic review concluded that there is very little evidence available from RCTs on the role of temozolomide to treat patients with HGG. However the review concluded that temozolomide may increase progression-free survival and may positively affect health-related quality of life, but has no significant impact on overall survival in patients with HGG (Dinnes et al. (2002). The questionnaire survey of patients with recurrent GBM by Osoba et al. (2000) concluded that treatment with temozolomide was associated with improvement in HRQOL scores compared to treatment with procarbazine. Procarbazine was associated with a deterioration in HRQOL, which was interpreted as arising from toxicity.

There is evidence from observational studies supporting the use of temozolomide as an adjuvant treatment for elderly patients with HGG. The prospective, non randomised study by Brandes et al. (2003) found that radiotherapy plus temozolomide significantly increased overall survival in patients with GBM aged 65 years or more, compared to radiotherapy alone, and significantly increased median time to disease progression compared with radiotherapy alone or radiotherapy plus procarbazine. The historical case series study by Glantz et al. (2003) of elderly patients with HGG concluded that chemotherapy with temozolomide was as effective as standard fractionated radiotherapy, with no significant difference in median survival between treatment groups. Initial Karnofsky performance score was the only significant variable predictive of survival.

Recurrent high grade glioma

There is some evidence from observational studies that tamoxifen, thalidomide and suramin may have potential as therapies, when used after standard chemotherapy for patients with recurrent HGG, although their benefit is not proven. The prospective case series study by Chamberlain & Kormanik (1999) found that of 24 young adults with recurrent anaplastic astrocytoma treated with oral tamoxifen, 4 patients (17%) demonstrated neuro-radiographic partial response, disease stabilised in 11 (46%) patients and 9 (38%) patients were found to have progressive disease, when evaluated after a median of 48 weeks of treatment. The case series study by Fine et al. (2003) examined the combination of thalidomide and BCNU to treat patients with recurrent BCNU. Median progression-free survival was 100 days and the objective radiographic response rate was 24%. These results compared favourably with historical data. The small case series study by Grossman et al. (2001) found that the use of suramin to treat patients with recurrent HGG was associated with no partial or complete tumour responses when evaluated after 12 weeks, but a later response was observed in 3 out of 12 patients treated.

Intra-arterial chemotherapy

Evidence from one RCT suggests that intra-arterially administered BCNU is neither safe nor effective in treating patients with malignant glioma; the treatment was associated with a significant reduction in survival compared to intravenously administered BCNU (Shapiro et al. 1992).

High dose chemotherapy with autologous bone marrow transplant

No evidence was identified to routinely support a role for high dose chemotherapy with autologous bone marrow transplant. The small, case series study by Mbidde et al. (1988) of high dose BCNU chemotherapy with autologous bone marrow transplantation in patients with high grade astrocytoma found a small prolongation of survival compared to historical experience and national studies, but there appeared to be no increase in the proportion of long term survivors. The authors concluded that the procedure should not be recommended routinely and did not warrant a RCT. The expert review by Fine & Antman (1992) concluded that there is little evidence to suggest that chemotherapy regimens administered at high dose with autologous bone marrow transplant improve survival for patients with recurrent, high grade astrocytoma, but that the treatment may have potential as an adjuvant therapy.

The use of chemotherapy implant wafers

Evidence from RCTs is suggestive of longer survival in patients treated with carmustine chemotherapy implants than in patients treated with placebo implants. The RCT by Brem et al. (1995) found that patients with recurrent malignant glioma treated with carmustine implants had a median survival of 31 weeks compared with 23 weeks for patients who received placebo implants (hazard ratio, adjusted for prognostic and treatment factors,0.67, 95% CI: 0.51 to 0.90, P = 0.006). There was no significant difference in survival rate between groups at 6 months. The RCT by Valtonen et al. (1997) found that median survival was significantly higher (58.1 weeks) for patients with HGG treated with carmustine implants than in patients treated with placebo implants (39.9 wks, p=0.012). The RCT by Westphal et al. (2003) comparing carmustine wafers versus placebo wafers in patients with malignant glioma (predominantly GBM) found median survival to be longer in the carmustine group compared to the placebo group (13.9 months versus 11.6 months respectively, p=0.03) with a 29% (95% CI 4%-48%) reduction in the risk of death in the carmustine group. This trial was examined by Whittle, Lyles, & Walker (2003), who concluded that patients who were enrolled onto the trial by Westphal et al. (2003), had better prognosis than patients who were not, as determined by a number of parameters, including age and performance status. The authors suggested that further patients may benefit from carmustine wafer therapy.

Table 5.3 In patients with high grade glioma, what is the evidence that chemotherapy improves outcome, in terms of survival, quality of life or functional status?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Stupp *et al.* 2005)	573 Patients aged 18 – 70 with newly diagnosed and histologically confirmed glioblastoma (WHO grade IV astrocytoma) International: Canada, Switzerland, Germany, Italy, Holland, Austria	RT Group: Fractionated focal RT of 2 Gy, 5 days / week for 6 weeks, for total of 60Gy RT + temozolomide Group: 75mg/m^2 body surface area, 7days / week during RT, plus 6 cycles 150 – 200mg/m^2 for 5 days during each 28 day cycle.	Overall survival. Progression free survival. Assessment of toxicity.	At a median follow-up of 28 months, the median survival was 14.6 months with RT plus temozolomide and 12.1 months with RT alone. The unadjusted hazard ratio for death in the RT-plus-temozolomide group was 0.63 (95 % CI, 0.52 to 0.75; P<0.001). The two-year survival rate was 26.5 % with RT plus temozolomide and 10.4 % with RT alone. Concomitant treatment with RT plus temozolomide resulted in grade 3 or 4 haematological toxic effects in 7 % of patients. Authors conclude that the addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity.	84 percent of patients had undergone debulking surgery. Median age 56 years. Median Follow up 28 months. Kaplan Meier survival analysis used.	RCT (85 centres).	1 ++
(Brandes & Fiorentino 1996)	Patients with high grade brain tumours Undertaken in Italy	Evaluation of published research	Survival	The author concludes that:- Currently patients with HGG are treated with resection followed by focal RT. Meta-analyses suggest that nitrosurea-based regimens provide a survival benefit in the adjuvant setting; no standard has emerged There is also no standard CT for patients with recurrent HGG. The safety superiority of temozolomide makes it the	*Not evidence based.*	Expert opinion	4 -

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				preferred agent at recurrence.			
(Brandes 2003)	Patients with malignant glioma (relapsing) receiving chemotherapy. Italy	Review of all phase II studies < 1994 of a single drug or combination of drugs, in relapsing patients following surgery and RT..	Survival	The review of the evidence indicates:- Single drug therapy with nitrosurea achieves an approximately 30% response rate accompanied by low toxicity- tauromustine warrants further testing In pre-treated patients response rate to cisplatin or carboplatin is approx. 10-15%. Polychemotherapy increases the response rate, but not significantly A 'standard' combination may be PCV, although data from studies with TPDC-5FUHU, together with BCNU + DDP and MOPP are encouraging. Alpha and beta interferon can be added to polychemotherapy without increasing toxicity.	*Insufficient details given for selection and inclusion of papers. No search details given*	Review	4
(Chang *et al.* 1983)	N = 626 randomised patients with malignant glioma grade III/IV (Kernohan) having had surgery (resection, biopsy) Recruited from multiple sites (exact number of sites not stated).	Radiotherapy alone vs. chemotherapy and radiotherapy Group 1 - Whole brain radiation (n = 167) 60Gy, 35 fractions, 7 weeks Group 2 Whole brain radiation	Median survival time and 18-month survival in relation to prognostic variables. Toxicity	Median survival time No significant difference in median or 18-month survival was seen between treatment groups. However, for patients in the 40-60 age groups, BCNU treated patients appeared to have significantly increased survival than patients in the control groups (P = 0.01, one-sided). Similarly, methyl-CCNU + DTIC was suggestively better than the control (P = 0.08, one-sided).	*Conducted between 1974 and 1979 (30 year old study)* *Intention to treat population not reported. Only 'evaluable' patient (n=535) analysis reported. Such analysis may*	Randomised controlled trial	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	US	(n = 114) 60Gy in 35 fractions over 7 weeks, followed by 10Gy to tumour volume plus margin delivered in 5 fractions over 5 days. *Group 3 – Radiotherapy plus Chemotherapy (n = 185) Whole brain radiation 60Gy, 35 fractions, 7 weeks plus BCNU 80mg/m2 x 3 intravenously every 6-8 weeks Group 4 – Radiotherapy plus chemotherapy (n=160) Whole brain radiation 60Gy, 35 fractions, 7 weeks plus methyl CCNU + DTIC. Methyl-CCNU 125 mg/m2 orally, every 8		Patients with anaplastic astrocytoma had a median survival of 27 months compared with 8 months for patients with glioblastoma. Age was the most significant prognostic factor in determining median survival time. <u>Patients with anaplastic astrocytoma</u> Patients ≤40 years – 39.2 months Patients 40-60 years – 23.9 months Patients ≥60 years – 5.2 months <u>Patients with glioblastoma</u> Patients ≤40 years – 16.7 months Patients 40-60 years – 9 months Patients ≥60 years - 6 months No significant increase in survival in group 2 (60Gy whole brain irradiation + 10Gy localised radiation) compared with 60Gy whole brain irradiation alone <u>Toxicity</u> *Methyl-CCNU + DTIC (group 4) had significantly more nausea (p=0.05), vomiting p=0.02) and thrombocytopenia than BCNU (p=0.005). Methyl-CCNU + DTIC produced severe or worse thrombocytopenia in 23% of patients compared with 6% on BCNU	*introduce bias in terms of excluding patients. Results should be interpreted with caution.* *12% of patients had major protocol deviations in delivery of chemotherapy; 37% had minor deviations. 19% of patients had protocol deviations in delivery of radiotherapy.* *Each institution randomised patients to treatments in two or three groups of their choice from the four treatment groups. Numbers of patients in treatment groups not equal.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		weeks DTIC 150mg/m2 x 5 intravenously every 4 weeks			*47% of group 3 (BCNU group) had tumour size <5cm compared with 22-26% in the other groups.* *There were 46% anaplastic astrocytoma in the <40 group compared with 14% in the 40-60 group and 7% in the >60 group. *important as GBM has worse prognosis and therefore proportion of both types could bias results.* *68% of patients diagnosed with glioblastoma multiforme (GBM) and 14% anaplastic*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					astrocytoma (AA). 18% of patients did not have reviewed diagnosis undertaken. Distribution of GBM and AA similar in all treatment groups.		
(Fine *et al.* 1993)	16 randomised trials involving more than 3000 patients with anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM). US	Radiation alone vs. radiation with chemotherapy	Survival rate. (Proportions of patients surviving at 6, 12, 18 and 24 months from start of therapy).	Median survival Median survival is significantly longer with radiation and chemotherapy combined compared with radiation therapy alone (p=0.002). Radiation therapy alone, median survival 7-34 months, median of 9.4 months. Radiation with chemotherapy; median survival 7-46 months, median 12 months. Estimated increase in survival For patients treated with combination radiation and chemotherapy was 10.1% at 1 year (95 CI, 6.8,	*Studies in meta-analysis were heterogeneous in terms of proportions of AA and GBM. This may introduce bias as GBM has worse prognosis than AA.* *Search strategy only conducted using Medline and in English language and only included published studies*	Meta-analysis.	1 -

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				13.3%) and 8.6% at 2 years (5.2, 12%) The authors concluded that 'chemotherapy is advantageous for patients with malignant gliomas and should be considered part of the standard therapeutic regimen'	*up to 1989.* *Only studies using drugs with ≥15% response rate against high-grade gliomas were evaluated* *Chemotherapy arm of studies included some studies with single agent and others with >1 agent (>10 different chemotherapy regimens were used).* *Studies used different radiation therapy regimens, 'some of which might be considered suboptimal by current standards'.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					Authors conducted subgroup analyses according to prognostic variables likely to influence survival. Analyses were undertaken both including and excluding apparently outlying studies.		
(Stewart 2002)	12 randomised controlled trials involving 3004 patients with high-grade glioma (anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) Trials considered eligible if they included patients with high-grade glioma who had undergone surgery and were then allocated radiotherapy alone or radiotherapy plus chemotherapy. Undertaken in the UK.	Radiation alone vs. radiation with chemotherapy	Median time to survival	Median Survival Significant prolongation of survival associated with chemotherapy, with a hazard ratio of 0.85 (95% CI 0.78-0.92, p<0.0001) or a 15% relative decrease in the risk of death. This effect is equivalent to an absolute increase in 1-year survival of 6% (95%CI 3-9) from 40% to 46% and a 2-month increase in median survival time. At two years it is equivalent to a five per cent (95%CI 2% to 8%) increase from 15% to 20%. No evidence that the effect of chemotherapy differed in any group of patients defined by age, sex, histology, performance status or extent of resection.	*Total radiotherapy doses ranged from 40Gy to 60Gy given in 25 to 35 fractions. In 4 trials whole brain irradiation was delivered, in eight trials localised tumour irradiation was delivered.* *Searches included published and unpublished studies up to November 2000*	Meta-analysis	1 ++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					using Cochrane methodology.. *Analysis was of individual data done by intention to treat. Data for 210 of 253 patients excluded from original published analyses were included in the meta-analysis..* *Stratified analyses of subgroups of patients were undertaken.* *Seven trials were not available for analysis.*		
(Huncharek *et al.* 1998)	9 randomised controlled trials involving 2179 patients . RCTs considered eligible if they included patients with high grade	Radiation plus single drug therapy vs. radiation plus combination chemotherapy	Survival rate at 1 year	<u>Median survival at 1 year</u> Single drug arm patients 55 months vs. multi-drug patients 50 months. Radiation plus combination chemotherapy is	*Only published studies included. Databases searched included Medline, CancerLit, Current Contents*	Meta-analysis	1 +

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	astrocytoma (AA and GBM) who had undergone post-operative radiation and were then allocated to single drug chemotherapy or multi-drug chemotherapy. US			associated with an approximately 22% decreased 1 year survival as compared with radiation plus single drug therapy (OR 1.22; 95% CI 0.99-1.36) Authors conclude that 'the data do not support the use of combination chemotherapy regimens in the treatment of high grade astrocytoma.	*and Embase (years not stated)* *In all except one study, radiation therapy mainly consisted of 60 Gy total dose, one fraction per day.* *No subgroup analysis according to prognostic variable likely to influence survival was undertaken.*		
(Shapiro *et al.* 1989)	N = 571 randomised patients with malignant gliomas having had maximum surgical resection (maximum delay between surgery and randomisation/treatment 3 weeks). Karnofsky performance status ≥40 at	<u>Chemotherapy (CT) and radiation therapy (RT) – comparison of different regimens</u> Group 1) (n = 185) CT (BCNU alone) (80mg/m2/day on 3 successive days for 8 weeks) and whole brain RT (6020 rads delivered in 35	Median survival time (months) in :- 1) Total randomised population (n=571) 2) VSG Valid Study Group (n=510)	<u>Whole brain RT and three different CT regimens</u> <u>Valid study group n = 510</u> No significant difference in median survival times between groups. Multiple drug chemotherapy conferred no significant advantage over BCNU alone. Group 1 BCNU + RT (n= 166) Median survival time = 13.1 months	*Intention to treat population not reported quantitatively. Only valid study group reported. Valid study group analysis may introduce bias in terms of excluding patients e.g. with short survival*	Randomised controlled trial	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	randomisation Patients recruited from seven institutions. US	fractions over 7 weeks) Group 2) (n =196) Alternating courses (every 8 weeks) of CT (BCNU (80mg/m2/day on 3 successive days for 8 weeks) and procarbazine (150mg/m^2 every day for 28 days) and whole brain RT (6020 rads delivered in 35 fractions over 7 weeks) Group 3) (n=190) CT (BCNU plus hydroxyurea (1000mg/m2/day every other day for total of 21 days) in combination for 8 weeks, alternating with procarbazine plus VM-26 (epipodophyllotixin)		Group 2 BCNU/PCZ + RT (n=176) Median survival time = 11.3 months Group 3 – BCNU + HU/PCZ + VM-26 + RT (n=168) Median survival time = 13.8 months Greater risk of haematotoxicity and higher incidence of abnormal liver function tests with use of multiple agents. Higher incidence of dermatological and gastrointestinal complaints reported for regimens containing procarbazine.	*times. Results should be interpreted with caution.* *Approximately 80% glioblastoma multiforme (GBM) and 20% anaplastic astrocytoma (AA) in each treatment group *important as GBM has worse prognosis and therefore proportion of both types could bias results.* Doses could be adjusted according to evidence of toxicity		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		(130mg/m^2/week for 6 weeks) in combination for 8 weeks and whole brain RT (6020 rads delivered in 35 fractions over 7 weeks)					
(Prados *et al.* 1999)	Patients > 18 yrs with anaplastic astrocytoma. US	Phase 3 trial comparing RT plus adjuvant procarbazine, CCNU and vincristine (PCV) chemotherapy with or without bromodeoxyuridine (BudR) given as 96 hr. infusion each week of RT. 1991-1996 trial period	Survival	As of 1996 281 patients had been randomised; 53 (20%) were ineligible and 39 cases were cancelled. The RTOG recommended suspension of enrolment based upon stochastic curtailment analysis which suggested that the addition of BudR would not be associated with increased survival. In 1997 study was closed prior to full enrolment. The 1 yr survival rate for RT,PVC and BudR was 68% versus 82% for RT plus PVC (p=0.96) The authors conclude that it is unlikely that a survival benefit will be seen. A final study will not be done for at least 3 years	*This study was closed prematurely when the initial 189 patients were analysed (see Laperriere 2003. Have checked Medline for further papers – none found*	Open label RCT	1 -
(Osoba *et al.* 2000)	Patients with recurrent glioblastoma multiforme enrolled in a Brain cancer Module (BCM20) that enrolled 366 patients. 138 and 225 patients with GBM	Determine whether chemotherapy with temozolomide (TMZ) versus procarbazine (PCB) for recurrent GBM is associated with improvement in	Role and social functioning, global QOL, visual disorders, motor dysfunction, communication deficit and	In the phase II study, of the 138 patients enrolled, 29 provided only baseline scores and 109 had a baseline score plus one or more HRQOL scores while on treatment. In the phase III study, of the 225 patients enrolled, 20 did not provide any HRQOL information, 26 provided only baseline data, and 179 (89 in the TMZ group and 90 in the PCB group)	*The 2 groups were similar apart from higher proportion of males.* *The reason for failing to collect baseline data was*	Questionnaire survey	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	at the time of their first recurrence were enrolled onto the phase II study and phase III study. Canada	health related QOL (HRQOL) The EORTC QOL C30 questionnaire was used.	drowsiness.	completed the questionnaires at baseline and while on treatment. Treatment with PCB was associated with toxicity. During both studies, attrition rates were high, and the numbers of patients remaining on study at 6 months were 29 in the phase II study, 28 in the phase III TMZ group, and 10 in the phase III PCB group. The authors conclude that treatment with TMZ was associated with improvement in HRQOL scores compared with treatment with PCB.	*administrative error. Serious problems with patient attrition and missing data* *Difficult study to interpret actual patient numbers..*		
(Dinnes *et al.* 2002)	Inclusion criteria: patients with recurrent malignant glioma (glioblastoma multiforme, anaplastic astrocytoma and mixed histology) 1 RCT (225 patients) 4 uncontrolled studies (138, 162, 116 and 48 patients).	1 RCT compared temozolomide (200 mg/m2/day for 5 days every 28 days) with procarbazine (150 mg/m2/day for 28 consecutive days in each 56 day cycle). Uncontrolled studies used same dose of temozolomide as the	Survival; progression free survival (PFS); and health related quality of life (HRQL)	Limited evidence from 1 RCT and one uncontrolled study suggests that temozolomide may improve progression free survival and quality of life but conclusions were tentative in view of limited evidence. There was no effect on overall survival. The authors concluded that the evidence is too weak for firm conclusions to be drawn	*Authors report the following limitations of the studies: uncontrolled studies with no control treatment; the one RCT compared temozolomide with procarbazine which is not commonly used in the UK, was not adequately*	Systematic review.	1 -

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	% previously treated with chemotherapy ranged from 10% to 68% among studies. UK	RCT. Aim: to compare quality of life and survival for temozolomide with standard alternative chemotherapy or best standard care.			*powered and reported insufficient details of the methods used; potential for bias from unblinded assessment of outcomes; and questionable generalisability of results.*		
(Brandes *et al.* 2003b)	79 elderly (> 65 years) patients with glioma enrolled over 3 consecutive time periods between 1993 and 2000. Patients had good prognostic features at baseline (minimal residual disease ≤ 2cm after surgery, Karnofsky performance status (KPS) ≥ 60). Had to have adequate bone marrow reserve and normal baseline	All patients underwent surgery. 1 radiotherapy alone (24 patients enrolled 1993 to 1995) v 2. radiotherapy plus PCV chemotherapy (procarbazine, lomustine and vincristine; (32 patients enrolled 1995 to 1997) v	Time to disease progression; overall survival, toxicity.	Radiotherapy plus temozolomide significantly increased median time to disease progression compared with radiotherapy alone or radiotherapy plus PCV (10.7 v 5.3 v 6.9 months, P = 0.0002). KPS (P < 0.001) and temozolomide (P < 0.001) were predictors of progression in multivariate analysis. Radiotherapy plus temozolomide significantly increased overall survival compared with radiotherapy alone (14.9 v 11.2 months, P = 0.002). There was no significant difference in overall survival between radiotherapy alone and radiotherapy plus PCV or between PCV and temozolomide (survival with PCV was 12.7 months). PCV increased Grade 3 and 4 haematological	*Not an RCT, Treatment groups were enrolled over consecutive time periods and other factors may have influenced results other than the specified treatment.* *Quality of life was not assessed. Article stated that there are concerns about cognitive impairment after radiotherapy but this was not*	Case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	liver and renal function. Treatment groups similar at baseline for age, KPS, residual disease, and co morbidity. Italy	3. radiotherapy plus temozolomide (23 patients enrolled 1997 to 2000). All groups received the same radiotherapy regimen. Aim: to compare surgery plus radiotherapy plus chemotherapy (2 different regimens) with surgery plus radiotherapy in elderly patients with glioblastoma		toxicity compared with temozolomide (10% v 1.7%, P not reported) The authors concluded that elderly patients with glioma who have a good performance status should receive definitive treatment with radiotherapy plus adjuvant temozolomide. They state that age alone should not determine treatment.	*assessed Treatment groups enrolled over different time periods.*		
(Glantz *et al.* 2003)	Mean age 73.8 (range 70-91); Malignant Gliomas (MG). Glioblastoma multiforme (GBM) n=84; anaplastic astrocytomas n=2; Male n=53 (62%)	Either Temozolomide (TMZ) n=32 (37%). Dosage 150mg/m^2 per day for 5 days every 28 days in 11 patients; dosage of 200 mg/m^2 for at least one cycle in 21 patients. Dose adjustments made in event of lowered blood counts. GBM	Survival; Adverse events; Karnofsky Performance Scores (KPS).	There were no significant differences between groups at baseline, in mean age; KPS and diagnosis. Survival: Median survival for entire cohort was 5mths and only 10.3% of patients survived 1 year. Median survival time was: TMZ = 6mths; RT = 4.1mths. However this difference was not	*Regular surveillance post RT imaging not performed. No data available regarding radiographic response.*	Historical case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Mean KPS 67.7 (range 40-70); TMZ:<50 (n=7); 60-70 (n=14); ≥80 (n=11) RT:<50 (n=9); 60-70 (n=30); ≥80 (n=15); Inclusion: Age: >70yrs; newly diagnosed MG Patients not treated with any postoperative therapy excluded. Patients referred from 3 centres1991 to 2002. US	n=30; anaplastic astrocytomas n=2, versus: Standard fractionated external beam radiation (180 cGy daily fraction, total tumour dose 60 Gy (n=54, 63%). All patients GBM (Patients chose treatment).		statistically significant.; 1yr survival rate: TMZ = 11.9%; RT=9.3%; The results did not appreciably change when two patients with anaplastic astrocytoma were excluded from analysis. KPS: Difference in survival among KPS subgroups was statistically significant (P<0.0001): Post operative KPS of 60-70 (hazard ration=0.329, P=0.01) and ≥80 (Hazards ration=0.119, p=0.0001) were protective factors compared with KPS ≤50. Age was not found to be a significantly predictive of survival. Adherence to treatment: TMZ: 32 patients received median of 3.5 cycles of TMZ (range 1-12 cycles); The only toxicity noted was occasional myelosuppression that required a delay in the next cycle or dose reduction in 5 (15.6%) patients. No patient required transfusions; none developed neutropenic fever. 2 patients (age 80 & 91yrs) at the time of diagnosis completed 12 cycles of TMZ.			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				RT: 15/54 (27.7%) did not complete irradiation, 10 due to tumour progression and 5 due to toxicity. Authors conclude that TMS is as effective as irradiation as a treatment of elderly patients with MG. It is an alternative and possibly a superior therapeutic option to irradiation base on its ease of administration and low morbidity.			
(Chamberlain & Kormanik 1999)	24 adults with recurrent anaplastic astrocytomas who had undergone previous surgery, radiotherapy (median dose 60gy; range 59-61Gy) 22 patients treated with adjuvant, nitrosurea-based chemotherapy (combined procarbazine hydrochloride, lomustine, vincristine sulphate in16; carmustine in 6); All patients were treated with salvage chemotherapy at first	Tamoxifen citrate administered orally at fixed dosage of 80mg/m2 as single or twice-daily dosage. Concurrent dexamethasone therapy permitted for control of neurological signs and symptoms; Tamoxifen administered regardless of white blood cell count, absolute granulocyte count or platelet	Survival; toxic effect	Survival median 13mths (range 3-27mths). Time to tumour progression Median 12mths (range 3-25mths); No tamoxifen-related toxic effects seen, nor were any treatment-related deaths. Median of 4 cycles of tamoxifen (range 1 – 8 cycles) administered. 4 patients (17%) demonstrated neuroradiographic partial response; 11 (46%) stable disease; 9 (38%) progressive disease following single cycle of tamoxifen. At end of study 5/24 (21%) patients alive with 3/5	*Generisability: Patients with favourable prognostic features only selected. Small sample size.* *(No attempt made to administer a loading dose of tamoxifen)* *Follow up of median 4 cycles equates to median 48 weeks of follow up.*	Prospective (phase 2) study.	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	recurrence, with 1 to 4 chemotherapy regimens (median 1regimen). Karnofsky performance score had median 90 (range 70-100); Inclusion criteria: ≥4wks since last dose of chemotherapy; ≥6wks for nitrosoureas. Patients must have recovered from adverse effects. Patients could not have received previous tamoxifen therapy. Karnofsky score ≥60; life expectancy ≥3mths. Adequate haematological, renal and hepatic functions. Excluded: pregnant/lactating women. Patients with meningeal gliomatosis;	count. Oral dexamethasone given concurrently in 17 patients; dosage increased in 8 patients with documented clinical and neuroradiographic progressions. Dexamethasone dosage decreased in 7 patients; therapy discontinued in 2 patients as clinical status permitted. Neurological & neuroradiographic evaluation performed every 12wks, operationally defined as a single cycle of tamoxifen.		receiving alternative chemotherapy regimens; 2/5 continuing tamoxifen. All deaths attributable to effects of progressive intracranial tumour. In group with responding & stable disease median survival was 15mths (range 8-27mths). Toxic effects: No treatment related complications; No evidence of myelosuppression, retinopathy, coagulopathy or cardiac arrhythmia. At end of therapy Karnofsky performance median 70 (range 50-70); Patients with no response to tamoxifen after initial stable disease were offered alternative therapy. Authors conclude that Tamoxifen demonstrated modest efficacy with no apparent toxic effects in this heavily treated cohort of young adults with recurrent anaplastic astrocytomas.			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	serious concurrent medical illness or active infection. Concomitant malignant disease except skin cancer (squamous cell or basal cell). Sex: Male 15; Female 9; Age: 19 to 45yrs (median age 31.5yrs); US						
(Fine *et al.* 2003)	40 patients aged ≥18 years with recurrent HGG and radiological evidence of tumour progression. Patients had to already have had standard surgery, radiation and chemotherapy and have baseline Karnofsky performance status ≥ 60.	Carmustine 200 mg/m2 on day 1 of a 6-week cycle plus thalidomide 1,200mg/day as tolerated. All patients received an aggressive prophylactic bowel regimen.	Adverse effects; progression free survival (PFS); percentage alive and progression free at 6 months; radiological response rates at 6 months.	Adverse effects: Treatment was generally well tolerated. Thromboembolic events in 12/40[30%] (8 DVTs and 7 PE); neutropenia in 3/40[8%]; thrombocytopenia in 1/40[3%]. Percentage alive and progression free at 6 months was greater than reported by Wang. 28% (95% CI: 17% to 46%) compared with Wang data 15% (95% CI: 10% to 19%). Median PFS was greater that Wang data. 100 days (95% CI: 58 to 172) compared with Wang 63 days	*No concurrent control group. Comparison of results with historical data with potential for bias and lack of accounting for confounding factors*. *Confidence intervals for the*	Case series study with historical control group	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	38 patient had glioblastoma, 2 patients had anaplastic astrocytoma. US	Aim: to compare progression free survival of thalidomide plus carmustine in patients with recurrent glioma, with historical data. Historical data cited from Wong (1999) (375 patients with recurrent glioblastoma from 2 major brain tumour centres who were enrolled in phase II trials)		(95% CI: 56 to 70). Radiological response (38 patients): complete: 1 (3%); partial: 8 (21%); stable disease: 9 (24%). The authors concluded that thalidomide plus BCNU was well tolerated and had activity against glioblastoma. Randomised controlled trials are required to reach definitive conclusions.	*PFS point estimates include the same values in this study and the historical data: the actual PFS may be identical.*		
(Grossman *et al.* 2001)	12 adults with recurrent HGG. US	Treatment with suramin	Percentage of patients with a complete or partial response, stable disease or disease progression	A response rate of 25% was considered to warrant further evaluation. Toxicity was mild in the 12 patients. No partial or complete responses were seen at 12 weeks. The authors state that as a result of the data patients with newly diagnosed HGG are now receiving concurrent suramin and RT.	*Preliminary results. Small numbers. Well designed and described study; apart from confounding effect of previous CT. No conclusions can be drawn from this study. The authors*	Case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					conclusions are not warranted from the evidence		
(Shapiro *et al.* 1992)	505 patients with newly resected malignant glioma were randomised. 190 patients were unable to receive intra-arterial drugs due to (severe arteriosclerosis. 315 patients analysed for intra-arterial versus intravenous drug. US	4 treatments compared 1. Intra-arterial 1,3-bis (2-chloroethyl)-l-nitrosurea (BCNU) alone 2. intra-arterial BCNU plus 5-fluorouracil (5FU) 3. Intra-venous BCNU alone 4. Intravenous BCNU plus 5FU BCNU dose: 200mg/m2 every 8 weeks 5FU dose: 1 gm/m2 three times daily 2 weeks after BCNU.	Survival; adverse effects	Serous toxicity (encephalopathy) developed in patients receiving intra-arterial BCNU and recruitment to that treatment arm was halted prematurely. Intra-arterial BCNU significantly reduced survival compared with intravenous BCNU (median survival: 11.2 v 14.0 months, P = 0.03). Life table estimates of survival at 2 years: 13% v 25%. Adverse effects: Most serious was encephalopathy with intra-arterial BCNU (11 patients had encephalopathy plus visual loss, 5 had encephalopathy alone, 15 others had visual loss). There was no significant difference in survival between groups given adjunctive 5FU and groups given no 5FU (P = 0.96). The authors concluded that intra-arterial BCNU is neither safe nor effective in prolonging survival in newly diagnosed patients with glioma.	*No quality of life assessment*.	RCT	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		Drugs administered within 72 hours of start of radiation therapy. All patients also received radiation therapy. Aim: to compare intra-arterial and intravenous BCNU and assess the effect of adjunctive fluorouracil					
(Fine & Antman 1992)	Patients with primary and recurrent HGG were included. US	High-dose chemotherapy with autologous bone marrow transplantation (ABMT). Chemotherapeutic agents included CCNU, BCNU (with and without 5 fluorouracil); ACNU; VP-16;	Severe or lethal toxicity (sepsis, lung, liver, CNS, mortality); response rate (complete and partial but not defined), survival. Results described separately for primary and recurrent tumours.	High dose chemotherapy plus ABMT for recurrent HGG (7 case series, 100 patients): where reported, sepsis rates ranged from 11% to 18%; lung toxicity rates from 9% to 14%; CNS toxicity from 9% to 17%; overall median survival 4.1 months (4 studies). Adjuvant high dose chemotherapy plus ABMT for HGG (5 case series, 161 patients): where reported, sepsis rates ranged from 8% to 14%; lung toxicity rates from 8% to 33%; CNS toxicity from 4% to 12%; overall median survival 15.4 months (4 studies).	*Non systematic review (no specified inclusion criteria, no stated search strategy, no assessment of validity of included studies, no details of methods used to conduct the review).* *Evidence was limited since from*	Expert review of generally small case series	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		Thiotepa; Aim: to review the rationale, laboratory data and clinical results on the effect of high-dose chemotherapy with autologous bone marrow transplantation.		The authors concluded that although studies suggest that high dose regimens do not improve survival for patients with relapse, ABMT may have the potential to help these patients.	*case series. Only one study had > 30 patients*		
(Mbidde *et al.* 1988)	Aim: To report on a series of 22 patients who received high dose BCNU (800-1,000mg m-2) with autologous bone marrow transplantation as the first post-surgical treatment for grade IV astrocytoma, followed by full dose radiotherapy. Median age 47yrs (range 32-58 yrs). 9 patients (41%) <45yrs; Males= 12 Females=10	Surgical exploration and debulking was the primary treatment. Median time from surgery to BCNU administration was 27 days (range 18-46); Bone marrow harvested according to standard techniques. Patients also received dexamethasone 8mg	Survival (measured from date of surgery) Time to progression determined clinically & by CT scan & measured from date of surgery. Toxicity; Anti-tumour effects; Comparison of results to radiation alone after	Survival: Median survival time was 17mths with actuarial probability of survival at 2yrs of 25%. When compared to historical experience and matched to control patients in national studies, there appeared to be a small prolongation of survival but no increase in the proportion of long survivors. Toxicity: Acute myelosuppression was mild but toxicity to lung and liver was substantial and limited further dose escalation. Mild nausea was common & lasted <24hrs from BCNU administration; All patients experienced flushing, often with transient tachycardia &	Small sample size. Study conducted 1983-1986. Patients consecutive recruitment	Case series.	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	World Health Organisation Performance Status <2 (PS); 13 patients PS =0; 8 patients PS =1; 1 patient initially PS 1 but deteriorated to PS 4 while awaiting marrow harvest. Histologically proven Grade IV astrocytoma. 19 patients had symptoms <6mths. 15 tumours showed presence of pre-treatment necrosis histologically; Pre-treatment blood counts within normal range in all patients.	intravenously. BCNU doses were as follows: 15 patients: BCNU 800mg/m^2; 7 patients 1g/m^2; 3 patients received 2 doses of BCNU 800mg/m^2 separated by 6wks; both injections given before radiotherapy. Separate marrow harvests performed before second BCNU treatment. Harvested bone marrow was returned after BCNU administration. After BCNU patients had full dose radiotherapy (55Gy in 33 fractions in 612	surgery with Medical Research Council trial (MRC;1983;). Minimum follow-up was one year for BCNU treatment at time of study.	hypotension at time of BCNU administration, possibly due to alcohol vehicle, but direct effect was not excluded. Short lived acute myelosuppression occurred in 17 (77%) patients; 2 patients developed septicaemia; 1 bronchopneumonia – successfully treated with antibiotics. Late bone marrow failure was seen in 4 patients. Pharmacokinetic studies were performed and suggested that the late marrow failure was due to persistence of BCNU at the time of marrow return. Failure occurred in 4 patients (median day of onset was day 58, range 48-111). 3 patients had marrow returned at 14hrs & 1 at 20hrs. No patient with marrow returned at 48hrs had late bone marrow failure. 3 patients developed interstitial pneumonia (fatal in one patient & contributed to death in another, 1 recovered). 13/20 had grade I WHO toxicity; only 2 had clinically significant liver syndromes including 1 with fatal hepatic failure and 1 with reversible severe hepatitis. Anti-tumour effect: Follow up scans showed improvements in all			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	UK	weeks).		patients but no scans were normal. Median time to Progression was 14mths; Patients who received two treatments BCNU before radiotherapy: 1 died with LMF at 5mths; 1 disease progression at 39mths; 1 was alive without disease at 42mths. Comparison of results to radiation alone after surgery based upon MRC trial: Survival (%) at 6mth MRC: 82 High dose BCNU: 68 Survival (%) at 12mth MRC 48 High dose BCNU: 59 Survival (%) at 18mth MRC: 21 High dose BCNU: 53 Survival (%) at 2yr MRC: 19 High dose BCNU: 25 Authors conclude that despite the suggestion of a			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				prolongation of survival this approach is not routinely recommended and a randomised trial is probably not justified			
(Westphal *et al.* 2003)	240 patients with unifocal malignant glioma (86% of whom had GBM). All patients received surgical resection and post operative radiotherapy according to standard practice. Patients were aged 21-72 years and had a Karnofsky performance score (KPS) of 60 or more at recruitment. Multinational, predominantly within European Union	carmustine wafer (n=120) versus placebo wafer (n=120) implanted at the time of primary surgical resection.	Overall survival by Kaplan Meier method. Time to clinical decline by KPS and neuroperformance score Time to disease progression	Median survival by intention to treat was 13.9 months for the carmustine wafer-treated group and 11.6 months for the placebo-treated group (p = 0.03), with a 29% (95% CI 4%-48%) reduction in the risk of death in the carmustine group. 29% of carmustine patients and 25% of placebo patients received a second operation after wafer implantation. Censoring patients at 2nd surgery, the survival advantage in the carmustine remained significant (median 14.8 months versus 11.4 months, p=0.02 with risk reduction of 36%, 95% CI 8%-55%). Factors considered in Cox model to potentially affect survival were baseline KPS, age, histological diagnosis and no. of wafers implanted. Age (p=0.001) and baseline KPS (p=0.0002) were found to be strong predictors of survival but adjusting for these, the survival advantage of carmustine wafer over placebo remained with reduction in risk of death of 28% (95% CI 2%-47%, p=0.03). Time to decline in KPS and in ten of eleven neuroperformance measures was statistically	The study was double blinded. The two groups were similar for age, sex, Karnofsky performance status (KPS), tumour histology and extent of tumour resection. Patients in the carmustine wafer group had significantly larger tumours than patients in the placebo group (66.8 vs. 50.8 cm^3, p=0.047). Two patients were lost to follow up and one patient withdrew consent.	Randomised controlled trial (phase three) undertaken in 38 centres in 14 countries (predominantly European).	1 +

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				significantly prolonged in the carmustine wafer-treated group ($p<0.05$). Adverse events were comparable for the 2 groups, except for CSF leak (5% in the carmustine wafer-treated group compared to 0.8% in the placebo-treated group) and intracranial hypertension (9.1% in the carmustine wafer-treated group compared to 1.7% in the placebo group). The authors conclude that local chemotherapy with carmustine wafers is well tolerated and offers a survival benefit to patients with newly diagnosed malignant glioma	Study excluded patients who had received prior radiotherapy or cytoreductive therapy.		
(Whittle *et al.* 2003)	56 patients with malignant glioma treated at Western General Hospital, Edinburgh between July 1998 and June 1999. UK	This study aimed to compare the characteristics of patients enrolled onto the carmustine wafer RCT by Westphal et al. (2003) at a single contributing centre with patients at the same centre who were not.	Parameters of interest were MRC prognostic indices compared between groups by retrospective ITT analysis i.e. age, Karnofsky score, type of surgery (resection vs. biopsy) and whether radiotherapy was received.	Only 25% of patients (14/56) were eligible for the RCT and all were recruited. The patients in the study group were younger (median 51 v. 59 years, $p = 0.085$); in better clinical condition (median Karnofsky score 85 v. 80, $p = 0.038$); more likely to have resective surgery (86% v. 38%, $p = 0.0001$); more likely to have postoperative radiotherapy (93% v. 55%, $p = 0.0001$) and more likely to survive longer (66 v. 19 weeks, $p = 0.06$) than those not eligible, even though one half of the carmustine cohort received placebo. Authors conclude that if the future use of carmustine is limited to the eligibility criteria used in the RCT by	The 14 patients in the recruited group had pathological diagnosis of malignant glioma. The 42 patients in the non recruited group had either pathological confirmation of malignant glioma, or diagnosis based upon MRI or CT.	Retrospective case series at a single centre	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Westphal et al. (2003) 21% (95% CI 13-34%) of patients with newly diagnosed malignant glioma will receive this therapy, at an estimated cost to the NHS of £3.65 million per year. Author suggests that further patients (not eligible for the RCT) may benefit from carmustine wafer therapy, considering their tumour characteristics.	*Retrospective ITT analysis applied since some patients in the recruited group did not receive the RCT intervention.* *Cost estimate is based upon £5000 per treatment.* *Study provides information on the prognostic characteristics of the non participants compared to participants. These were probably easy to demonstrate retrospectively since the RCT inclusion criteria were clear and explicit.*		
(Brem *et al.* 1995)	222 patients from 22 centres with recurrent	Aim: to assess the efficacy and safety of	Primary outcome was survival from	Median survival of the 110 patients who received carmustine polymers was 31 weeks compared with	*Study investigators and monitors*	RCT	1 +

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	malignant glioma requiring re-operation. Patients had to have Karnofsky performance status ≥ 60 and have previously received radiotherapy. 50% had previously received chemotherapy. 145 (65%) had glioblastoma. US	intra-operative placement of biodegradable polymers of carmustine in patients with recurrent glioma. Intervention: Intra-operative placement of wafers containing biodegradable polymers of chemotherapy (BIODEL polymer impregnated with carmustine). Control: As above, with placebo wafers. Patients had maximal resection of tumour and up to 8 wafers inserted into the resection cavity	the point of polymer implantation. Other outcomes were complications and toxicity.	23 weeks for the 112 patients who received only placebo polymers (hazard ratio, adjusted for prognostic and treatment factors was 0.67, 95% CI: 0.51 to 0.90, P = 0.006; The survival rate at 6 months did not differ significantly between groups: 60% with carmustine, versus 47% with placebo, P= 0.061). Carmustine significantly improved survival at 6 months in patients with glioblastoma (56% in the intervention group, versus 36% in the placebo group, P = 0.020). Adverse effects were similar between treatment groups (anaemia: 7% with carmustine versus 11% with placebo; thrombocytopenia: 2% in each group; postoperative seizures: 37% with carmustine versus 29% with placebo, P = 0.199). The authors concluded that intra-operative insertion of carmustine polymer wafers is a safe and effective treatment for recurrent malignant gliomas.	*blinded to treatment allocation.* *ITT analysis.* *Although the report stated that quality of life was assessed, results were not reported for this outcome*.		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Valtonen *et al.* 1997)	Multi-centre study. 32 patients included in study. Sex: Male 14; Female 18; Inclusion criteria: Unilateral, unifocal intrinsic brain tumour not crossing the mid-line, of ≤1.0cm diameter. Age: 18 to 65yrs. Karnofsky Performance Score (KPS) ≥60; Histopathological diagnosis of HGG (Grade III or IV); Exclusion criteria (any 1 of 5):	Intervention: Wafer implants containing 3.85% carmustine by weight (n=16). Control: Placebo wafer implants (n=16) 8 wafers available for each patient. Each carmustine wafer contained 7.7mg carmustine, maximal dose being 61.6mg of carmustine. All patients underwent resection of tumour mass; All patients underwent standard radiotherapy. Median cumulative dose was 54.03 Gy for placebo	Survival.	Survival: Median time from surgery to death was 58.1 weeks for intervention group versus 39.9 wks (95%CI: 37.6 to 45) for placebo group (P=0.012). Placebo group had no Grade III tumours. In 27 patients with Grade IV tumours, survival was 53.3wks (95%CI: 40.1 to 77.7%) for the intervention group and 39.9 wks (95%CI: 37.6 to 45) for the placebo group (P=0.008). At the end of the study 6/32 (19%) patients were still alive as follows: Intervention: 5/16 (31%) Placebo: 1/16 (6%). Survival at 3yrs after termination of study was as follows: Intervention: 4/16 Placebo 1/16 Both groups were well matched at baseline. There was a slight difference in KPS: Placebo group had median 90 (range 40-100) versus Intervention group median 75 (range 60-100). 2 patients in the intervention group received less than scheduled	Small sample size. Bias in Grade of tumour in each group. Bias due to lack of Grade IV tumours in placebo group (Discussion seems to contradict earlier results which specify Grade III). Infectious complications: in one centre instructions about sterility of wafer packages were misunderstood and nonsterile packages thought to be sterile.	Double-blind RCT	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Evidence of significant renal or hepatic disease Any other concomitant life-threatening disease <100x109 circulating platelets per litre or <4.0x109 leukocytes per litre Pregnancy Hyposensitivity to contrast media used. Norway & Finland	group; 54.92Gy for Intervention. 1 patient in intervention group received no radiation due to poor condition. All patients were treated with peri-operative corticosteroids to reduce brain swelling. Subsequent operations were performed if necessary. Follow-up: Before discharge and at 3mthly intervals to 2 yrs or death.		dose of drug. Covariates in addition to treatment: sex, age, KPS, tumour type, tumour size, total cumulative dose of radiotherapy. All significant for outcome as was mini-mental score (P=0.016) but do not explain risk ratio of 0.269 in favour of Intervention versus placebo. Adverse events & complications: No deaths occurred in the peri-operative period. 21 patients experienced adverse events during the study: placebo 9/16; Intervention 12/16. 15 serious and unexpected adverse events were reported by 9 patients, as follows: Intervention: 10 serious adverse events in 5 patients including wound infection, septic inflammation with meningismus; cerebrospinal fluid leukocytosis with hydrocephalus; deep venous thrombosis with pulmonary embolism; pneumonia with increase in aphasia; visual disturbances; hemiparesis. Placebo: 5 serious adverse events in 4 patients: pulmonary embolism; meningitis; wound infection;			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				deep venous thrombosis with pulmonary embolism. Treatment emergent adverse events: Intervention: Hemiparesis 38%; convulsion 19%; aphasia 13%; visual field defect 13%; Placebo: hemiparesis 25%; convulsions 13%. 1 patient in the intervention group underwent subsequent surgery. Authors conclude that carmustine, applied locally in biodegradable polymer at time of primary operation, seems to have a favourable effect on life span of patients with HGG.			

Chapter 6 Management of patients with meningioma

The question

What services are required for the management of patients with meningiomas?

The nature of the evidence

The evidence consisted of five observational studies, one RCT and five review articles. Studies included patients with:

- recurrent or refractory meningioma(Bendszus *et al.* 2003; Chamberlain *et al.* 2004; Ragel & Jensen 2003; Grunberg *et al.* 2005; Rosenthal *et al.* 2002)
- atypical or malignant meningioma (Hug *et al.* 2000)
- meningioma of any grade or stage (Whittle *et al.* 2004; DiBiase & Chin 2003; Drummond *et al.* 2004; Pollock 2003)

The studies considered the following treatments:

- hydroxyurea (Rosenthal *et al.* 2002), temozolomide (Chamberlain *et al.* 2004) and the antiprogesterone agent mifepristone (Grunberg *et al.* 2005)
- current active treatments (including surgery and radiotherapy) ((Whittle *et al.* 2004; DiBiase & Chin 2003; Ragel & Jensen 2003; Drummond *et al.* 2004)
- radiotherapy (Hug *et al.* 2000)stereotactic radiosurgery (Pollock 2003)
- embolisation (Bendszus *et al.* 2003)

One article reviewed current and future EORTC trials for patients with meningioma (Van Den Bent *et al.* 2004). None of the primary studies were from the UK so applicability to the UK setting is unclear.

Summary of the supporting evidence for the recommendations

Surgery is the primary therapy in patients who are not candidates for management by watch-and-wait (deferment of active therapy). Radiotherapy appears beneficial for incompletely excised tumours, high grade tumours or those in locations with high

surgical risk. Because of their shape and size, some meningiomas are good candidates for stereotactic radiosurgery. The EORTC is planning two RCTs to help define the role of radiotherapy in the treatment of recurrent or incompletely excised or recurrent meningioma (Van Den Bent *et al.* 2004), although given the indolent nature of most of these tumours, it may be a while before any findings are reported.

For recurrent or refractory meningiomas, in cases where surgery or radiotherapy are inappropriate, other therapies such as chemotherapy, embolisation and hormone therapy have been considered. The little evidence available suggests only modest effectiveness of such therapies.

Table 6.1 What services are required for the management of patients with meningiomas

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Bendszus *et al.* 2003)	7 patients with intracranial meningiomas treated at one institution. Mean age was 47 years (range 11 to 72 years). Inclusion criteria Patients whose intracranial meningioma was embolised without subsequent surgery. Patients were not candidates for surgery because of their age or severe comorbidity. GERMANY	Embolisation of meningioma, using a transfemoral approach under local anaesthesia. After diagnostic angiography a microcatheter system was placed in the feeding branches of the external carotid artery. Trisacryl gelatin microspheres were used as the embolic agent. The emboli were injected though the microcatheter, under fluroscopic control, until the investigators saw stagnation within the tumour.	Feasibility of embolisation, mortality and morbidity associated with the procedure. Tumour shrinkage (measured using MRI and MRS). Mean follow up was 20 months (range 16 to 27 months).	Embolisation was feasible in all patients, with no reported mortality or morbidity associated with the procedure. Five patients, whose tumour supply was entirely from the external carotid artery, complete angiographic devascularisation was achieved. In two patients there was a small contribution from the internal carotid artery which was not embolised. Tumour shrinkage Four patients showed only a thin rim of contrast enhancement on post embolisation MRI. Two patients had nodular contrast enhancement associated with areas of tumour supplied by the internal carotid artery. In all other patients, marked tumour shrinkage was noted. Post embolisation MRS was consistent with necrosis in the non-contrast enhancing areas of the tumour. In one patient complete devascularisation of the tumour did not cause any change in tumour size or contrast. The authors speculate that the occlusion was too proximal with recanalisation of the tumour vessels. They suggest this illustrates the limitations of the procedure.	*Very small series. Too small to analyse outcomes with respect to patient characteristics.*	Prospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Chamberlain *et al.* 2004)	16 patients with treatment resistant meningiomas were included. Median age was 62.5 years (range 48 to 70 years) Inclusion criteria Histologically proven WHO grade 1 recurrent meningioma. Patients must have progressed since radiotherapy, and must be at least 6 months post radiotherapy. No prior chemotherapy. KPS > 60. Life expectancy > 3 months. Adequate renal, haematologic and hepatic function. USA	Temozolomide was given at a dose of 75 mg/m^2 orally for 42 consecutive days, followed by a 28 day break. A treatment cycle was defined as 10 weeks, and cycles were repeated every 10 weeks if there was not significant toxicity. No dose escalation was allowed, but dose reductions were allowed.	6 month progression free survival, overall survival, toxicity.	Overall survival All patients died of disease progression with a median overall survival of 7 months (range 4 to 9 months). 6 month progression free survival The authors defined 40% progression free survival at 6 months as the threshold for success of the therapy. No patients achieved 6 month progression free survival and the authors terminated the trial after the first 16 patients. Toxicity Grade 3 or greater temozolomide related toxicity included anaemia (25%), neutropenia (37.5%), fatigue (19%), seizures (6%) and thrombocytopenia (19%). The authors concluded that temozolomide does not appear to have activity against recurrent meningioma.	*Small study, power calculations based on Simon Minimax 2 stage design.*	Prospective observational study (phase II trial)	3+
(DiBiase &	Patients with	Stereotactic	Tumour control and	The authors estimate, based on their review of case		Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
Chin 2003).	meningioma (patients with other benign brain tumours are also discussed).	radiosurgery	toxicity of stereotactic radiosurgery	series, that local tumour control rates after stereotactic radiosurgery average in the 90 to 100% range and treatment related toxicity is usually less than 10%. They conclude that the use of stereotactic radiosurgery in both the initial and recurrent setting should be strongly considered for patients with meningioma.			
(Drummond *et al.* 2004).	Patients with meningiomas	The presentation and diagnosis of meningioma are considered. The review discusses surgical excision, radiotherapy and chemotherapy for meningioma.	Tumour recurrence, morbidity associated with treatment	Clinical presentation Meningiomas typically present with 1 of 4 syndromes, determined by the size and site of the tumour: • Neurologic deficit due to neural compression • Symptoms of raised intracranial pressure • Seizures (more than 50% of patients) • Asymptomatic (approximately 10% of patients) Diagnosis Diagnosis is usually made by contrast enhanced CT or MRI scan. Angiography is performed when embolisation is considered. Surgery Safe complete surgical excision is the primary therapy. In some cases this is not possible: the tumour may be too large to remove completely without neurological deficit (e.g. large skull base or en plaque tumours), the tumour may be invading into or intimately associated with neural or vascular structures preventing complete		Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				excision. The use of image guided surgery and skull base techniques have reduced the number of inoperable meningiomas. Radiotherapy Conventional external beam radiotherapy may be effective in controlling incompletely resected or recurrent meningiomas. This must be balanced against the morbidity associated with radiotherapy. Stereotactic radiosurgery show similar control rates to conventional techniques but may have the benefit of fewer complications. Chemotherapy Cytotoxic agents have been disappointing so far in the treatment of meningiomas. Hydroxyurea has been shown to have some effect on tumour control.			
(Grunberg *et al.* 2005)	193 patients with unresectable meningioma, 180 patients were evaluable 80 in the treatment arm and 80 in the placebo arm. Median age was 57 years. 30% were male, 19% pre-	The treatment group received the antiprogesterone mifepristone (RU) the control group a placebo.	2 year progression free survival. Progression was defined as anatomic growth or neurologic deterioration. Toxicity.	Response to treatment There was no significant response to therapy between the treatment (RU) and placebo (P) arms. Progression free survival (PFS) Median PFS was 10 months for the treatment group and 12 months for the placebo group.	*Abstract only, limited details of the methodology.*	RCT	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	menopausal and 51% post menopausal women. 29% had received prior radiotherapy USA			Toxicity The most common toxicities were fatigue (72% RU vs 54% P), headache (44% RU vs 41% P), and hot flashes (38% RU vs 26% P). 9 RU pts (16% of female RU pts) also developed endometrial hyperplasia.			
(Hug *et al.* 2000)	31 patients with atypical (n=15) or high grade (n=16) intracranial meningioma. All patients received radiotherapy at a single institution between 1973 and 1995. Mean age at diagnosis was 49 years (range 6 to 79 years). USA	Radiotherapy, given using megavoltage photons in 15 patients and combined photons and 160MeV protons in 16 patients. All treatments were delivered as 5 fractions per week, 1.8 to 2 Gy/CGE per fraction, 1 fraction per day. CT or MRI scanning was done before radiotherapy in most patients (CT - 85%; MRI - 59%).	Local control, overall survival, toxicity of radiotherapy. Mean follow-up approximately 5 years (range 7 months to 155 months).	5 year local control rate 5 year local control rate was 38% for patients with atypical meningioma and 52% for those with malignant meningioma. These results were not significantly different on univariate analysis. 5 year overall survival 5 year overall survival was 89% for patients with atypical meningioma and 51% for those with malignant meningioma. Toxicity of radiotherapy Late radiation effects, due to radiation necrosis, were seen in 3/31 patients (9%).		Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Pollock 2003).	310 patients having stereotactic radiosurgery for meningioma, identified from the clinical database of a single institution between 1990 and 2002. Median age was 57 years (range 20 to 90 years). 42% had recurrent or residual tumours following surgery and 58% had radiosurgery as their primary treatment. 9.4% of patients had atypical or malignant tumours. The majority of tumours were at the skull base. USA	Stereotactic radiosurgery (single fraction high dose), performed using the Leskell Gamma Knife (using the model U before 1997 thereafter the model B). Dose planning was based on stereotactic MRI, or CT if MRI was contraindicated. Multishot dose plans were used, the median number of isocenters was 10 (range1 to 25). Dose prescription was based on tumour size, location and history of radiotherapy.	Tumour control, overall survival, complications of treatment. Follow-up evaluation and MRI were performed at 6, 12, 24 and 48 months thereafter biannually.	Tumour control Follow up data were available for 267 patients with benign tumours. 98% were either smaller or unchanged after radiosurgery. 2% showed disease progression Follow up data were available for 30 patients with atypical or malignant tumours. 60% were either smaller or unchanged after radiosurgery. 40% showed disease progression 5 year overall survival For the entire group 5 year overall survival was 82%. Disease specific 5 year overall survival was 94%. The disease specific 5 year overall survival rates for patients with benign, atypcial and malignant tumours were 100%, 76% and 0% respectively. Complications 8.4% of patients developed treatment related complications. These included cranial nerve deficits, parenchymal oedema, internal carotid artery stenosis and delayed cyst formation.		Retrospective case series	3+
(Ragel & Jensen 2003).	Patients with refractory meningioma	Current treatments for refractory meningioma: radiotherapy,	Tumour control.	Radiotherapy Radiotherapy is frequently used in this population, for high-grade meningiomas or those in high risk locations (such as the cavernous sinus). Evidence from case		Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		hydroxyurea and hormone therapy are discussed. Novel treatments: angiogenesis inhibitors, growth hormone inhibitors, somatostatin agonists, growth factor inhibitors and others are considered.		series suggests that conventional and stereotactic radiotherapy prolong the time to tumour recurrence. Hydroxyurea Evidence from a case series of patients with enlarging meningiomas is presented. 12/16 benign tumours stabilized at a median duration of therapy of 122 weeks. 4 patients with benign tumours showed disease progression as well as those with atypical or analplastic meningiomas. The authors suggest that complete tumour remission is not a realistic goal for this therapy. Hormone therapy Although there are theoretical reasons why hormone therapies could work for meningiomas, the few trials so far have been disappointing. Novel treatments Angiogenesis inhibitors, growth hormone inhibitors, somatostatin agonists, growth factor inhibitors and others are considered. The evidence is mostly lab based or translational; not yet full scale clinical trials.			
(Rosenthal *et al.* 2002).	15 patients with recurrent or high risk meningioma. Median age 39 years (range 24 to 79 years). 10 Median age 39 years (range 24 to 79 years). All patients had received surgery	20mg/kg hydroxyurea orally per day as a single morning dose.	Toxicity. Tumour response: complete response was complete disappearance of disease and partial response was a more than 50% recution in the size of the	Toxicity 2 patients stopped treatment because of skin rashes (grade II and grade III). One patient had grade III thombocytopenia and one patient grade I anemia/neutropenia. Tumour response 13 patients were evaluable for tumour response. No	*Small series, no control group or power calculation.* Authors conclude that hydroxyurea has only modest activity in this population.	Case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	and one had prior chemotherapy. AUSTRALIA		tumour. Response had to be sustained for at least one month. Disease progression was defined as a greater than 25% increase in the size of the tumour. Patients were reviewed monthly and underwent CT or MRI every 3 to 4 months.	complete or partial responses were seen. 11 patients achieved stable disease for a median of 11 months (range 3 to 24 months). The remaining 2 patients experienced disease progression.			
(Van Den Bent *et al.* 2004).	The review discusses the future meningioma trials of the EORTC brain tumour group.	Observation versus conventional fractionated radiotherapy or radiosurgery.	Tumour progression, quality of life and neurotoxicity of radiotherapy.	Two meningioma trials are in preparation. EORTC 26013: Phase III study on observation versus conventional fractionated radiotherapy or radiosurgery after non-radical therapy for benign intracranial meningioma EORTC 26014: Phase III study on observation versus adjuvant conventional radiotherapy or radiosurgery after recurrence of benign intracranial meningioma. Authors state that although there is a role for radiotherapy in the treatment of recurrent meningioma, the best timing for the therapy is unclear.	*No dates are mentioned, a long period of follow up is likely due to the benign nature of the tumours.*	Review	4
(Whittle *et*	The review addresses the	The presentation and diagnosis of	Tumour recurrence, morbidity associated	Presentation	*Comprehensive review. Evidence*	Review	4++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
al. 2004)	biology, diagnosis and treatment of meningioma. The review is based mainly on papers published between 1999 and 2004, although some classic articles are cited. Only papers with an English abstract were considered.	meningioma are considered. The review discusses endovascular treatment, surgical excision and radiotherapy for meningioma.	with treatment	Meningiomas may be discovered incidentally on CT or MRI. Symptomatic patients can present with a variety of symptoms resulting from the compression, invasion or obstruction of adjacent structures by the tumour. Patients with these tumours commonly present with seizure disorders. Diagnosis Brain or spinal CT or MRI are typically used, and many meningiomas have characteristic appearance. MRI is the investigation of choice as it can demonstrate the dural origin of the tumour. Catheter angiography may be used if MRI and CT appearances are ambiguous or in preparation for embolisation. Management The strategy will depend on the symptoms produced, the age of the patient and the site and size of the tumour. Many clinicians carry out MRI yearly for the initial 2 to 3 years and if there is no tumour growth the patient is followed clinically only. In other cases the active therapies may be used, including: Endovascular treatment Meningiomas can often be devascularised by embolisation, however the precise benefit and optimal timing of this procedure is unclear. Embolisation is a treatment option in patients who are not candidates for surgical excision of their tumour. Surgical excision This is the most common primary treatment for	*for the management of meningiomas is based on observational studies.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				meningiomas and most convexity and spinal meningiomas can be excised without significant morbidity. Many tumours, however, cannot be totally excised because they envelop vital neural or vascular strutures. The morbidity associated with attempted complete excision of such tumours is significant and many neurosurgeons favour subtotal resection with residual tumour followed by serial imaging or treated with radiotherapy. Radiotherapy Radiotherapy has been used: after incomplete resection, after recurrence and when the tumour histology reveals atypia or anaplasia. The evidence for the use of radiotherapy in this group is based on retrospective case series, and few had sufficiently long follow up to assess the efficacy of radiotherapy or the incidence of delayed complications. These studies have typically used radiological, rather than neurological, end points to define local control. Many meningiomas are candidates for stereotactic radiosurgery, because of their shape and size. The success of radiotherapy in controlling meningiomas has led some to question how extensive the primary surgery needs to be, and whether radiotherapy itself could be the primary treatment for some patients. The authors conclude that despite advances in imaging, interventional neuroradiology, neuropathology and radiotherapy, many meningiomas remain a challenging			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				clinical problem, and are increasingly being managed by a multidisciplinary team approach.			

Chapter 7 Management of patients with brain metastases

The question

In patients with brain metastases what is the evidence that active therapy improves outcome, in terms of survival, quality of life or functional status?

The nature of the evidence

For patients with a single brain metastasis:

- A systematic review (Hart *et al.* 2005) comparing surgical resection and WBRT with WBRT alone
- An American randomized trial of radiotherapy following surgical resection (Patchell *et al.* 1998)
- A systematic review (for an evidence based guideline) of diagnostic imaging and active treatment (Mintz *et al.* 2004)
- An American case series compared stereotactic radiosurgery with surgical resection (O'Neill *et al.* 2003)

For patients with more than one brain metastasis:

- A systematic review of the role of radiotherapy for the treatment of patients with brain metastases (Tsao *et al.* 2004)
- A North American RCT of stereotactic radiosurgery in addition to whole brain radiotherapy (WBRT) for patients with between one and three brain metastases (Andrews *et al.* 2004)
- A systematic review of the use of WBRT for the treatment of patients with brain metastases (Pease *et al.* 2005)

Most of the primary research was from North America: applicability to the UK setting is therefore unclear.

Summary of the supporting evidence for the recommendations

A systematic review (Hart *et al.* 2005) and an evidence-based guideline (Mintz *et al.* 2004) compared surgical resection and whole brain radiotherapy (WBRT) to WBRT alone in selected patients with a single brain metastasis. No significant difference in overall survival was noted in a meta-analysis of three RCTs. Improved functionally-independent survival was seen in patients receiving surgical resection and WBRT in the single RCT that included this outcome.

One of the reviews (Mintz *et al.* 2004) considered the issue of stereotactic biopsy of presumed solitary brain metastases before initiation of treatment and identified two primary studies. In one study of patients with a known systemic malignancy and a CT scan reported as being consistent with a single brain metastasis, 11% of cases were diagnosed as either primary brain tumours or non-neoplastic lesions following biopsy. The authors concluded that all patients should undergo biopsy. A second study, however, reported the rate of MRI misdiagnosis in patients undergoing surgical resection of presumed solitary brain metastases as 2%.

An RCT comparing WBRT plus stereotactic radiosurgery boost with WBRT alone in patients with one to three brain metastases (Andrews *et al.* 2004), found no significant difference in the median overall survival or performance status of the two treatment groups. In patients with a single metastasis however, a stereotactic radiosurgery boost was associated with improved median overall survival on univariate analysis, and this benefit approached significance on multivariate analysis.

Evidence comparing surgical resection with stereotactic radiosurgery for patients with a solitary brain metastasis was limited to a retrospective case series (O'Neill *et al.* 2003). The study did not observe an overall survival difference between the treatment groups, but noted improved local control in patients treated using stereotactic radiosurgery.

It remains uncertain whether WBRT is necessary after resection of a single brain metastasis. While this may reduce likelihood of further brain metastases, it may also be associated with radiation related CNS toxicity.

An evidence-based guideline (Tsao *et al.* 2004) comparing WBRT with supportive care alone in patients with multiple brain metastases identified a single RCT. Median survival was 14 weeks in the WBRT compared to 10 weeks in the supportive care group (p value not stated) with similar improvements in performance status seen in both groups. Patients in both groups received oral corticosteroids.

A systematic review (Pease *et al.* 2005) comparing palliative WBRT with supportive care for patients with brain metastases found limited evidence of a survival benefit following WBRT, but only for patients with good performance status.

Table 7.1 Active treatment for people with brain metastases

Abbreviations: FIS, functionally independent survival; WBRT, whole brain radiotherapy.

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Andrews *et al.* 2004)	331 patients enrolled by 55 North American institutions. Inclusion criteria: Patients with confirmed systemic disease and 1 to 3 brain metastases on contrast enhanced MRI. Exclusion criteria: Previous cranial radiotherapy, newly diagnosed cancer, lesions >4cm diameter, lesions in brain stem, deep grey matter, eloquent cortex or <1cm from optic apparatus.	Study aimed to assess whether stereotactic radiosurgery provided any therapeutic benefit in patients with brain metastases.	Primary outcome was overall survival. Secondary outcomes were: tumour response and local control rates, overall cranial recurrence rates, case of death and performance measurements (KPS).	Overall survival: Overall there was no significant difference between the median survival of the 2 groups, in both univariate and multivariate analysis. In patients with single metastasis the group with stereotactic boost had significantly better median survival (6.5 vs. 4.9 months, p<0.04, univariate analysis). The effect of treatment group approached significance on multivariate analysis (p=0.053), however, with only RPA class and type of tumour (squamous or non-small cell) being significant prognostic factors at the p<0.05 level. Local control Treatment group was the significant prognostic factor for local control, local recurrence being 43% greater in the WBRT alone group (p=0.0021). Performance measures A statistically significant improvement in KPS at 6 months post treatment was seen in the stereotactic boost group, but no difference between groups was noted. Authors conclusions		RCT	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	KPS<70			WBRT and stereotactic boost treatment improved functional autonomy (KPS) for all patients and survival for patients with a single metastasis. WBRT and stereotactic radiosurgery should be standard treatment for patients with a single unresectable brain metastasis and considered for those with 2 or 3 brain metastases.			
(Hart *et al.* 2005).	Inclusion criteria: studies of patients with single brain metastasis. Studies comparing WBRT versus WBRT plus surgical resection. 3 RCTs were included	Study aimed to assess the clinical effectiveness of surgical resection plus WBRT versus WBRT alone in the treatment of single brain metastases.	Survival, functionally independent survival (FIS: time taken for the KPS to fall below 70), neurological death, adverse effects.	Survival: A statistically significant effect of treatment group (WBRT+surgery versus WBRT) was not demonstrated, HR=0.74 (95% CI 0.39 to 1.40, p=0.35). FIS: A single trial included sufficient FIS data. Patients treated by WBRT and surgery had greater FIS, HR 0.42 (95% CI 0.22 to 0.80, p<0.008) Adverse effects: No significant effect of treatment group on adverse effect rate was seen. Neurologic cause of death: A trend towards reduced risk of death from neurological causes was seen in those treated by surgery, OR 0.57 (95% CI 0.29 to 1.10, p=0.09). Authors' conclusions Surgery and WBRT may improve FIS but not overall survival. There is a trend that is may reduce the proportion of deaths due to neurological cause. All	Small number of included studies.	Systematic review	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				these results were ina highly selected group of patients. Operating on metastases does not confer significantly more adverse effects.			
(Patchell *et al.* 1998)	95 patients were randomized, 49 to WBRT and 46 to observation. Investigators stratified patients according to extent of disease and site of primary tumour. Median follow-up was 48 weeks for the WBRT group and 43 weeks for the observation group. Inclusion criteria: Age >18 years, tissue proven diagnosis obtained from completely resected single brain metastasis and KPS>70 Exclusion criteria:	Study aimed to determine the effect of WBRT on the neurologic control of disease and survival in patients with a completed resected single brain metastasis.	Primary outcome was recurrence of brain tumour; secondary outcomes were survival, cause of death and preservation independent functioning.	Recurrence of brain tumour: Recurrence of tumour anywhere in the brain was less frequent in the WBRT group than the observation group (9/49 vs. 32/46, 18% vs. 70%; p<0.001). Recurrence at the original site in the brain was (5/49 vs. 21/46, 10% vs. 46%; p<0.001) and at other brain sites (7/49 vs. 17/46, 7% vs. 37%; p<0.01). Survival Median survival was 48 weeks in the WBRT group and 43 weeks in the observation group (not statistically significant). Cause of death Patients in the WBRT group were less likely to die of neurologic causes than those in the observational group (6/43 deaths vs. 17/39 deaths, 14% vs. 44%; p=0.003). Functional independence There was no significant difference in the length of time that the two groups remained functionally independent (KPS>70), median time was 37 weeks in the WBRT group and 35 weeks in the observation		RCT	1++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Incomplete resection of brain metastasis, leptomeningeal metastasis, those with certain radiosensitive primary tumours. USA			group, p=0.61. Authors' conclusions Patients with cancer and single metastases to the brain who receive treatment with surgical resection and postoperative WBRT have fewer recurrences of cancer and are less likely to die of neurologic causes than similar patients treated with surgery alone.			
(Pease *et al.* 2005).	Inclusion criteria: Studies where WBRT was used with palliative intent for patients diagnosed with brain metastases. Exclusion criteria: Studies where WBRT was used as adjuvant post-surgical therapy or for prophylaxis. Case reports, letters or reviews.	Study aimed to determine the effect of WBRT on the survival and QOL of people with brain metastases. To assess whether other factors modify the effect of WBRT.	Overall survival, radiological response, neurological status response, relief of symptoms, duration of response and toxicity.	Meta-analysis was not conducted due to heterogeneity, following a preliminary assessment of the studies. Qualitative data synthesis was undertaken. Overall survival: The studies suggested a median survival of 3.2 to 5.8 months in those treated with WBRT, compared to 2-3 months for those receiving supportive care only. Survival benefit was greater in studies were patients were selected by performance status, 3.75-7 months for patients with KPS>70. Patients with poor performance status did not appear to gain survival benefit from WBRT. Quality of life No studies reported QOL outcomes. Surrogate measures of QOL (such as neurological function or		Systematic review	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	40 papers from 32 primary studies were included. 8 were RCTs.			maintenance of KPS>70) produced response rates of 7-90% following WBRT. Authors' conclusions WBRT appears to be of benefit in patients with higher performance status but not in low performance status patients. This suggests a basis for current practice, but further research is needed.			
(Tsao *et al.* 2004)	Inclusion criteria: Published RCTs of external beam radiotherapy or radiosurgery in adult patients with brain metastases. Exclusion criteria: Studies of prophylactic radiotherapy, phase I or II studies, non-English language studies. The majority of patients in the included studies had	Study aimed to define the role of radiotherapy in the treatment of brain metastases, both alone and in combination with other therapies.	Survival, intracranial progression free duration, response of brain metastases to therapy, QOL, symptom control, neurological function and toxicity.	Single brain metastases: 2 RCTs of patients with KPS ≥ 70 compared WBRT+surgery versus WBRT. Sugery+WBRT was found to improve overall survival and duration of functional independence, compared to WBRT alone (6 month mortality 33% versus 61%, RR 0.54 (95% CI 0.31,0.93)). Multiple brain metastases: A single RCT compared WBRT with supportive care alone (oral prednisone). Median survival in the WBRT group was 14 weeks compared to 10 weeks in the supportive care group (p value not stated). The proportion of patients with improvement in performance status was similar in WBRT and supportive care groups (63% and 61% respectively). In 5 RCTs the addition of radiosensitizers did not add survival benefit to WBRT.		Systematic review	1++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	lung, breast or colorectal cancer primaries. Review undertaken in Canada			Authors' conclusions: Resection of a single brain metastasis in a patient with good performance status (KPS ≥ 70) may improve overall survival. The addition of WBRT following resection decreases recurrence rates. For multiple metastases the WBRT should be used, radiosensitizers should only be used in clinical trials. The optimal use of radiosurgery remains to be defined. In patients with 1-3 metastases (<3cm in size) and limited extra-cranial disease radiosurgery may be considered to improve local tumour control, either as boost therapy with WBRT or at the time of relapse after WBRT. The use of chemotherapy for brain metastases remains experimental, pending results from a number of RCTs.			
(Mintz *et al.* 2004).	Published English language studies of adults with confirmed cancer and a suspected brain metastasis. Studies had to address one of the 6 guideline questions and report at least one of the outcomes of interest.	Imaging for the identification of brain metastases; stereotactic biopsy and active treatment of single brain metastases.	Survival, quality of life, treatment associated morbidity and local control of disease.	1) What is the optimal imaging modality for the diagnosis of single brain metastases? The search identified 4 case series and 5 phase II trials. Evidence suggests that in patients with a single brain metastasis on CT, high-dose contrast enhanced MRI may identify additional brain metastases (greater sensitivity). The guideline recommends CT for patients with suspected brain metastasis, with further high contrast imaging studies if there appears to be a single metastasis (and the primary tumour is controlled or unknown). 2) Should stereotactic biopsy be used before the		Systematic review (for clinical guideline).	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				initiation of treatment? The search identified 2 RCTs. In one study of patients with a known systemic malignancy and a CT scan reported as being consistent with a single brain metastasis, 11% of cases were diagnosed as either primary brain tumours or non-neoplastic lesions following biopsy. The authors concluded that all patients should undergo biopsy. A second study, however, reported the rate of MRI misdiagnosis in patients undergoing surgical resection of presumed solitary brain metastases as 2%. The guideline recommends biopsy before treatment if a solitary lesion, suggestive of cancer, is seen with no known primary tumour. 3) Should patients with single brain metastasis have surgical resection prior to radiotherapy? The search identified 4 RCTs. A meta-analysis revealed no significant difference in overall survival between those having surgical resection plus radiotherapy and those having radiotherapy only (Cox regression, HR = 0.83, 95%CI 0.65 to 1.16). Improved functionally independent survival was seen in patients receiving surgical resection and WBRT, in the single RCT that included this outcome. 4) What is the role of chemotherapy? The search identified 2 cohort studies and 1 phase II			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				trial. There was insufficient evidence from studies using chemotherapy alone to extrapolate to patients with single brain metastases (where there are alternative treatments).			
(O'Neill *et al.* 2003)	97 patients, from a single institution 1991 to 1999, with a single brain metastasis. Patients had to have had both a neurosurgical and neurologic examination at the institution, and subsequent neurosurgery (n=74) or radiosurgery (n=23). Patients had to be candidates for both procedures: with a tumour less than 35mm in size; without a brain-stem or deep seated tumour and without ventricular obstruction. USA	Neurosurgery or stereotactic radiosurgery. 82% of patients having neurosurgery also had whole brain radiotherapy as did 96% of those receiving radiosurgery. Both groups typically received corticosteroids at the time of the procedure, subsequently tapered over 2 to 4 weeks.	Overall survival, complications and recurrence rate.	Overall survival Follow up ranged from 0 to 106 months (median 14 months). Median survival (from graphs) was approximately 14 months for the radiosurgery group and 17 months for the neurosurgery group. On univariate analysis there was no difference in the survival of the two groups (p=0.15, log rank test). When the analysis was restricted to patients with ECOG performance status 0 or 1, there was even less difference between the groups. The authors used multivariate analysis (Cox regression) to identify prognostic factors for survival. Age, ECOG performance status and systemic disease status were adverse prognostic factors for overall survival. Treatment type was not a significant prognostic factor. Cause of death was similar in the two treatment groups (p=0.22): 48% in the radiosurgery group and 59% in the neurosurgery group died of systemic tumour alone. 29% of patients in the radiosurgery group and 11% in the neurosurgery group died of cerebral tumour (p=0.36).	Small (underpowered) study. The decision to recommend neurosurgery or radiosurgery was not random, but the authors tried to account for selection bias using a propensity score for assignment to treatment. The radiosurgery group tended to have a greater proportion of right sided lesions, were less likely to be symptomatic at diagnosis but were more likely	Retrospective case series.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Complications The differences in short and long term complications between the two treatment groups were not statistically significant. Local recurrence None of the radiosurgery group experienced local recurrence compared to 58% of the neurosurgery group (p=0.020).	to have poor ECOG performance status. The diagnostic criteria for a single brain metastasis are not reported.		

Chapter 8 Specialization, hospital case volume and outcomes

The questions

a) Does treatment by a specialist neurosurgeon versus a general neurosurgeon decrease morbidity/increase survival?

b) What is the evidence for the association between specialist care and outcomes for patients with brain and CNS tumours?

c) Is there evidence for an association between volume of care for patients with brain and CNS tumours and outcome?

d) What is the evidence for the effect of centralisation and accessibility of cancer services for brain and CNS tumours patients?

The nature of the evidence

a) Does treatment by a specialist neurosurgeon versus a general neurosurgeon decrease morbidity/increase survival?

The evidence for this question was observational, consisting mainly of retrospective case series comparing specialist and general neurosurgeons.

Definitions of neurosurgeon's subspecialty

- Specialist neurosurgical oncologist, not further defined (Latif *et al.* 1998)
- Neurosurgeon with sole responsibility for the pituitary surgery in a neurosurgical unit (Lissett *et al.* 1998; Yamada *et al.* 1996; Gittoes *et al.* 1999)
- Specialist vascular neurosurgeon, not further defined, (Ashkan *et al.* 2003)
- Paediatric neurosurgeon, not further defined, (Albright *et al.* 2000)
- Members of the American Society of Pediatric Neurosurgeons (Albright *et al.* 2000)

The reported outcomes were:

- Survival (Latif *et al.* 1998; Ashkan *et al.* 2003)
- Performance status after surgery(Ashkan *et al.* 2003)
- Completeness of surgical resection (Albright *et al.* 2000)
- Complications of surgery (Latif *et al.* 1998; Ashkan *et al.* 2003; Albright *et al.* 2000; Gittoes *et al.* 1999)
- Cure rate of pituitary tumour surgery(Yamada *et al.* 1996; Lissett *et al.* 1998; Gittoes *et al.* 1999)

b) What is the evidence for the association between specialist care and outcomes for patients with brain and CNS tumours?

Evidence included:

- UK guidelines for the management of patients with pituitary tumours (Clayton & Wass 1998) and high grade glioma (Davies & Hopkins 1997b); and a French guideline for the management of patients with intracranial glioma (Frappaz *et al.* 2003)
- A UK observational study reporting outcomes in a diagnostic geriatric neurology referral service (Duncan & Caird 1991). A UK observational study comparing outcomes for patients with CNS tumours treated in neuroscience centres with those treated elsewhere (Northern and Yorkshire Cancer Registry and Information Service & University of Leeds 1998). An American observational study comparing outcomes for patients with high grade glioma treated at academic hospitals with those treated elsewhere (Chang *et al.* 2005).
- Systematic reviews (Grilli *et al.* 1998; Harding M *et al.* 2001) and reviews (Pheby & Bray 1998; Selby *et al.* 1996) of specialist care for people cancer in general

c) Is there evidence for an association between volume of care for patients with brain and CNS tumours and outcome?

Observational studies examined the relationship between case hospital and/or surgeon case volume and outcomes in the following populations:

- Patients undergoing resection of a primary intracranial tumour (Cowan, Jr. *et al.* 2003; Chernov *et al.* 2004; Barker *et al.* 2005)
- Patients undergoing craniotomy for brain tumour (Long *et al.* 2003), cerebral aneurysm (Solomon *et al.* 1996), paediatric brain tumour (Smith *et al.* 2004) or resection of metastatic brain tumour (Barker 2004)
- Patients undergoing clipping or coiling of cerebral aneurysm (Barker *et al.* 2003c)
- Patients undergoing transspheniodal surgery for pituitary tumour(Barker *et al.* 2003b; Ciric *et al.* 1997)
- Patients undergoing surgical excision of vestibular schwannoma (Barker *et al.* 2003a; Slattery *et al.* 2004)
- Healthcare in general (Halm *et al.* 2002) and cancer treatment in general(Hillner *et al.* 2000)

d) What is the evidence for the effect of centralisation and accessibility of cancer services for brain and CNS tumours patients?

There was no direct evidence from studies of patients with CNS tumours. The NICE guidance on *improving outcomes for people with sarcoma* considered this question and its evidence is included as follows:

- a systematic review on accessibility and centralization in cancer services
- four observational studies of good to poor quality surveyed people for their views on traveling for cancer treatment

- four observational studies of good to poor quality reported indirect estimates of patients' views on travel, such as the uptake of treatment options requiring more or less traveling.

Of the eight primary studies, patient travel was for radiotherapy in four cases, surgery in two cases and any treatment in three cases.

Summary of the supporting evidence for the recommendations

a) Does treatment by a specialist neurosurgeon versus a general neurosurgeon decrease morbidity/increase survival?

For pituitary tumour surgery, there was consistent evidence in favour of surgery performed by a specialist, rather than a general, neurosurgeon (Yamada *et al.* 1996; Lissett *et al.* 1998; Gittoes *et al.* 1999).

The UK study of Latif and co-workers (Latif *et al.* 1998) compared a series of 168 patients with high grade glioma treated by a specialist surgical neurooncologist with 68 treated by non-specialist neurosurgeons. No survival difference was seen in a case mix adjusted comparison.

A small retrospective audit of surgery for intracranial aneurysm in a UK neurosurgery department (Ashkan *et al.* 2003) noted that there was less morbidity and mortality and better patient performance status after neurovascular sub-specialisation was established in the unit.

An American observational study (Albright *et al.* 2000) analysed the correlation between neurosurgical subspecialisation and outcome using data from three clinical trials in 485 children with medulloblastomas/primitive neuro-ectodermal tumours and 247 children with malignant gliomas. Paediatric neurosurgeons were more likely than general neurosurgeons to resect more than 90% of the tumour. No difference in the complication rates of the paediatric and general neurosurgeons was observed; survival data were not reported.

b) What is the evidence for the association between specialist care and outcomes for patients with brain and CNS tumours?

Existing clinical guidelines recommend specialist care for patients with gliomas (Davies & Hopkins 1997a; Frappaz *et al.* 2003) and pituitary tumours(Clayton & Wass 1998).

In a case mix adjusted analysis (Chang *et al.* 2005), patients treated in academic institutions did not have improved survival compared to those treated elsewhere. In a univariate comparison, survival was better for those treated in academic centres and the authors concluded that the survival difference reflected the increased use of chemotherapy, radiotherapy at academic centres and the younger age of patients referred to such institutions.

A report by Northern and Yorkshire Cancer Registry (Northern and Yorkshire Cancer Registry and Information Service & University of Leeds 1998) compared the survival of patients with CNS tumours (high grade glioma, low grade glioma or meningioma) treated at 3 specialist neurosurgical centres with those managed elsewhere, in the period 1986 to 1994. Although in a simple comparison survival was better for those treated in neurosurgical units, patients with very poor prognosis tended not to be referred for neurosurgery. When patient age and treatment factors were adjusted for there was no significant difference in survival between those referred to the neurosurgical units and those treated elsewhere.

Indirect evidence, from systematic reviews (Grilli *et al.* 1998; Harding M *et al.* 2001) and a review(Pheby & Bray 1998) generally supports the role of specialist clinicians and units in the care of people with cancer, although the quality of the primary studies is low.

The evidence for the previous question about neurosurgical specialisation is relevant, because specialist neurosurgeons are an important component of specialist care. Similarly, the evidence for the following question is relevant, because specialist units are likely to treat a greater volume of patients.

c) Is there evidence for an association between volume of care for patients with brain and CNS tumours and outcome?

Consistent observational evidence suggests a positive relationship between hospital case volume and perioperative outcome following neurosurgery. However, there was no evidence about volume of care and outcome in the UK or about long term outcomes – many studies did not follow up patients after their discharge from hospital.

Most of the studies used data drawn from the American Nationwide Inpatient Sample (Barker *et al.* 2003b; Barker *et al.* 2003a; Barker *et al.* 2003c; Barker 2004; Barker *et al.* 2005; Cowan, Jr. *et al.* 2003; Smith *et al.* 2004) – this potentially limits the applicability of the evidence to the UK setting.

Indirect evidence (Halm *et al.* 2002; Hillner *et al.* 2000; Hannan 1999), reviewed for example in NICE Improving Outcomes in Colorectal Cancer, suggests that for complex or high risk cancer surgery outcomes are better in higher volume hospitals.

d) What is the evidence for the effect of centralisation and accessibility of cancer services for brain and CNS tumours patients?

Patients are likely to face an increased burden of travel if the recommendations for specialist treatment result in centralisation of services. A UK systematic review (Ferguson 1996) concluded that people with cancer would overcome such access difficulties in order to receive appropriate treatment. This view was supported by primary studies that surveyed patients for their views (Guidry *et al.* 1997; Barton *et al.* 2001; Fitch *et al.* 2003; Kearney 2003). In these studies, travelling for treatment was consistently seen as an inconvenience but people were prepared to travel if necessary.

There was less agreement, however, among studies of the uptake of treatment depending on travel time or distance. The UK study of Cosford and co-workers (Cosford *et al.* 1997) reported that the uptake of radiotherapy did not appear to be influenced by travel time. A US study (Meden *et al.* 2002) found that women with breast cancer who opted for more radical surgery, which required less travelling, tended to live further from the treatment centre. Two other US studies (Wright *et al.* 1994; Finlayson *et al.* 1999)presented patients and healthcare workers with

hypothetical treatment choices in order to estimate the additional risk of morbidity or mortality that would balance a reduction in travelling time or distance. A minority of people were prepared to accept increased risk of morbidity or mortality in order to reduce travel time. The evidence suggests that, when confronted with different treatment options, travel time is a consideration in a person's choice of treatment.

Table 8.1 Does treatment by a specialist neurosurgeon versus a general neurosurgeon decrease morbidity/increase survival?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Latif *et al.* 1998)	UK. 236 patients diagnosed with supratentorial glioma 1989–1995 and undergoing surgery. 158 had glioblastoma and 78 anaplastic astrocytoma.	Surgery was performed by the specialist in 168 cases (70 stereotactic biopsies and 99 craniotomy and resection) and by other surgeons in 68 (29 stereotactic biopsies and 38 craniotomy and resection).	Survival times. 30 day mortality and complication rates.	Initial assessment indicated that patients, operated upon by the specialist neurosurgeon had a median survival of 305 days (95% CI 243-377 days), whilst the median survival of those operated by other neurosurgeons was 190 days (95% CI 127-265). This difference was not however significant after correcting for case mix using multiple logistic regression and a hazards model. Surgical morbidity (8.9 versus 11.8%) was also not statistically significant. The extent of surgical resection was a highly significant independent prognostic variable (p=0,0004, log rank test). Adjusted for case mix since these are non-randomised results. After correcting for case mix there was no significant survival benefit from macroscopic resection versus partial resection or biopsy (p=0.121, HR 0.753, 95% CI 0.523-1.08). Patients receiving RT had a significantly better outcome than those that did not (p<0.0001, HR=0.1788, 95% CI 0.119-0.266). The authors suggest that future prospective studies in surgical neurooncology should use objective measurements of clinical neurological parameters and tumour volume before and after surgery so that potential merits of different surgical approaches in malignant glioma can be evaluated.	*Appropriate use of statistics. Insufficient details of patient characteristics.*	Retrospective cohort	2-
(Ashkan *et al.* 2003)	UK. 65 patients, median age 55 (29-	Comparison of results of	Use of Karnofsky scale to assess	There were fewer deaths, complications and better long-term patient performance status in the period	*No neurooncology patients. Small*	Retrospective audit	4-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	81 years) treated for intracranial aneurysms	neurosurgeons (period A) with specialist neurovascular neurosurgeons (period B)	outcomes. Mortality	where patients were operated upon by the specialist neurovascular surgeons. Median LOS for period A was 17 days (range 6-57 days) compared with 13 days (range 5-30 days) in period B	*numbers.* *Results could be an effect of learning curve of surgeons. Patient characteristics comparable in the two groups*		
(Albright *et al.* 2000).	732 children enrolled in 3 CCG studies, 1986-1992.Histology was 485 medulloblastoma/PNET and 247 malignant glioma. Operations were performed by 269 neurosurgeons: 213 general neurosurgeons, 29 designated paediatric neurosurgeons and 27 ASPN members. USA	Neurosurgery	Extent of residual tumour after surgery (determined from imaging). Transient and permanent operative complications. All outcomes were reported by the treating surgeons and not verified centrally.	Mean number of operations per surgeon was 1.8 for general neurosurgeons, 4.9 for paediatric neurosurgeons and 7.6 for ASPN members Controlling for tumour type (but not reported how this was done), paediatric neurosurgeons were more likely than general neurosurgeons to resect more than 90% of the tumour (58% versus 69% of cases, Chi2=5.04, p=0.025). Paediatric neurosurgeons were more likely than general neurosurgeons to leave <1.5 cc of residual tumour (65% versus 72% of cases, Chi2=4.4, p=0.04). Neurological complication rate was: 22% for general neurosurgeons, 32% for paediatric neurosurgeons and 18% for ASPN members. The difference between paediatric neurosurgeons and ASPN members was significant (p=0.03). There was no significant difference in non-neurological complication rates in the 3 groups.	*Indirect evidence (not an adult population)* *Neurosurgeons may not have enrolled all eligible patients in CCG trials. Overall, case volume is likely to be underestimated.* *Operations were carried out between 8 and 14 years before the study, practice likely to have changed in that time.*	Case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Clayton & Wass 1998)	Adult patients with pituitary tumours.	Consensus statement on recommendations for service provision		RECOMMENDATIONS RELATING TO SPECIALIST CARE: Once diagnosis is suspected patients should be referred to a specialist centre. The specialist centre may be located across several sites. Surgery should be performed by surgeons specialising in pituitary surgery. Additional super-specialisation expertise and operative experience, optimise outcome for patients with hormone-secreting adenoma. Outcome data are required to determine the minimum number of operations that should be performed annually by a single surgeon.	*Usual limitations of consensus produced guidelines. No supporting evidence provided. College advises that recommendations still patent. No data on outcomes.*	Guidelines	4+
(Lissett *et al.* 1998)	71 patients with acromegaly referred to one of 2 hospitals between 1974 and 1997. Mean age was 43 years (range 19 to 70). There were 51 macroadenomas (1cm or greater on CT or MRI scan) and 18 microadenomas. 4 patients did not have their tumour sized preoperatively.	Transspheniodal surgery (71 patients) or transfrontal surgery (2 patients).	Cure rate (post operative GH levels <5mU/l during an oral glucose tolerance test).	Cure rate Overall cure rate was 13/73 patients (18%). For microadenomas it was 7/18 (40%) and for macroadenomas it was 6/51 (12%). Comparison with other series The authors reviewed literature about cure rates following pituitary surgery for acromegaly. The cure rate for this series is significantly lower than other published series. The authors suggest that the lack of a specialist pituitary surgeon explains the discrepancy in cure rate. A single surgeon performed the surgery in the studies reviewed, compared to the 9 surgeons in this study.	Series covers 2 decades (during which MRI was introduced). Case mix not considered in detail.	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	9 surgeons operated during the course of the study: 3 between 1974 and 1979, 5 between 1980 and 1987 and 6 between 1988 and 1997. UK						
(Yamada *et al.* 1996).	61 patients with acromegaly treated surgically, at a single hospital 1969-1993. 22 other patients were excluded because follow up data were not available. Mean age was 42 years (range 22 to 65 years). 30 patients were operated in the period 1969 to 1986 and 31 from 1987 to 1993 (after MRI became available at	Transspheniodal surgery (58 patients) or surgery using a unilateral sub frontal approach (3 patients).	Early post operative and long term GH level. Cure was defined as mean basal GH level <6mU/l and normal GH dynamics (suppression of GH to <2mU/l during the OGTT).	Postoperative cure rate Postoperative cure rate was 36/61 (59%). Cure rate was 11/30 (37%) before 1987 and 25/31 (81%) after 1987. Long term cure rate Long term cure rate (mean follow up 6.8 years; range 1 to 14.5 years) was 31/61 (51%). Prognostic factors for cure Univariate analysis showed post operative GH level <6 mU/l and normal GH dynamics to be significant predictors of long term cure. The investigators did multivariate analysis of the influence of sex, age, tumour grade and stage, cavernous sinus invasion, GH level, period of operation	Relatively number of excluded patients because of insufficient clinical data. If all of those excluded were not cured (worst case scenario) then the long term cure rate would be 37%. There were important casemix differences between those treated pre and post specialization.	Retrospectiv e case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	the hospital). Median follow up was 6.4 years (range 0.8 to 18.6 years). Before 1987 operations were performed by a number of surgeons. After 1987 one surgeon performed all the operations. There were significant differences between the characteristics of the pre and post 1987 patients. Patients treated after 1987 were less likely to have suprasellar extension of the tumour, had lower preoperative GH levels and tended to be older than the pre 1987 patients. JAPAN			(pre or post 1987) on cure rate. The period of operation (RR 10.2; 95% CI, 1.9 to 54.0; p<0.01) and cavernous sinus invasion (RR 30.5; 95% CI, 5.0 to 183; p<0.001). Patients operated on in the period when a single surgeon was doing all the surgery had a significantly better outcome than those who were operated on when surgery was shared between a group of surgeons.	Also, those treated post 1987 had MRI scans.		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Gittoes *et al.* 1999).	66 patients with acromegaly. Mean age at diagnosis was 47 years (SE years) and 45% were female. Macroadenomas (1cm or greater) were identified in 44/66 (67%) of patients and microadenomas in the remaining 22/66 (33%). UK	Pituitary surgery for acromegaly. Surgery was performed either by one of a group of 8 surgeons (1986–1989) or by a single pituitary surgeon (1990–1998).	Cure rate (defined as basal growth hormone <5 mU/l or nadir growth hormone <2 mU/l across an oral glucose tolerance test). Post operative morbidity	Cure rates The cure rate during 1986–1989 (before sub-specialization) was 26/78 (33%). When one surgeon did all the operations (1990–1998) the cure rate was 42/66 (64%) ($p<0.001$, chi squared test). Post operative morbidity 8/66 (12%) patients were rendered hypopituitary after curative surgery. 4/66 (6%) patients experienced permanent diabetes insipidus. 4/66 (6%) patients experienced a CSF leak, requiring further surgery. There was no perioperative mortality. Morbidity was not analysed pre and post sub-specialisation.	Two possible confounders: the different time periods and the different surgical staff.	Case series	3+

Table 8.2 What is the evidence for the association between specialist care and outcomes for patients with brain and CNS tumours?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Clayton & Wass 1998)	Adult patients with pituitary tumours.	Production of consensus statement on recommendations for service provision		RECOMMENDATIONS RELATING TO SPECIALIST CARE: Once diagnosis is suspected patients should be referred to a specialist centre. The specialist centre may be located across several sites. Surgery should be performed by surgeons specialising in pituitary surgery. Additional super-specialisation expertise and operative experience, optimise outcome for patients with hormone-secreting adenoma. Outcome data are required to determine the minimum number of operations that should be performed annually by a single surgeon.	*Usual limitations of consensus produced guidelines. No supporting evidence provided. College advises that recommendations still patent. No data on outcomes.*	Guidelines	4+
(Davies & Higginson 2003)	Adults with malignant glioma	Development of clinical guidelines by a working group who considered the best evidence available.		RECOMMENDATIONS CONCERNING SPECIALISATION:- Neuro-oncology units with specialist nurse support should be developed	*No data on association of specialist treatment with outcome. Despite limitations in methodology, important with regard to service guidance.*	Guidelines	4+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Duncan & Caird 1991)	1446 cases (72% aged 65-80; 28% >80yrs.), referred between 1971-1989 to University Department of Geriatric Medicine for neurological diagnosis.	Referral to a specialist geriatric neurology centre	Length of stay. Confirmation of referring diagnosis. Change of management. Death in hospital.	635 patients had a referring diagnosis. Cerebrovascular disease was diagnosed in 637 cases (44%), subdural haematoma or hygroma in 59 (4%), and intracranial tumour in 228 (16%) of which 26 (11%) were benign. In 104 cases ((97%) no diagnosis was made. Of the 635 patients with a diagnosis on referral the diagnosis or management or both were changed in 511 (80%). Space occupying lesions were confirmed in 31% (81/262) and spinal cord lesions in 55 % (15/27). Length of stay was often prolonged in the specialist unit ranging from 3-28 days. The authors conclude that the high proportion of changes in diagnosis is the major numerical evidence of the value of the service.	*High risk of bias. Other methodological problems inherent in observational studies.. Study of interest for implications of protocol based care on outcomes.*	Retrospective case series	3+
(Frappaz *et al.* 2003)	Adult patients with intracranial glioma. FRANCE	Development of 'clinical guidelines' (standards, options and recommendations)		CONCLUSIONS CONCERNING SPECIALIST TREATMENT Grade 3-4 glioma:- Standard – transfer to specialist centre for surgery (No standard) Option - where optimal treatment is not possible (patients elderly, multiple pathologies etc.) transfer to specialist centre for expert evaluation.	*Methodology good and detailed in separate publication. Extensive bibliography available from FNCLCC. Standards are given where all the working group agree. Where the*	Guidelines	4++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					majority agree options are given. Recommendations provide additional information that provide ranking of options. *No data on outcomes*		
(Grilli *et al.* 1998)	Patients with cancer receiving specialist carer	Assess the impact of specialisation on processes & outcomes of care for cancer patients.	Mortality, morbidity. Process outcomes e.g. specialisation of treating clinician, numbers of patients treated.	47/189 potential studies met the inclusion criteria. 12/24 (50%) studies provided information on process and 17/32 (53%) information on outcomes. Overall results were in favour of specialised clinicians/centres and were generally statistically significant. The study quality was however low	*The authors discuss the possibility of publication bias, influence of methodological flaws, use of observational studies causing an over estimate of effect size. Note is taken of the need to adjust in comparisons for case mix. The aims and inclusion criteria were well defined.*	Systematic review	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					Care is required in concluding that there is good evidence for the apparent superiority of specialist versus non-specialist care.		
(Harding M *et al.* 2001)	Patients with cancer	Assessment of difference in outcome between treatment in specialist and non specialist centres	Survival	The authors conclude that there was insufficient high quality evidence to indicate that specialist care affected outcomes in cancer patients	*High quality study No studies in neurooncology met the inclusion criteria. Publication bias significant.*	Systematic review	1-
(Pheby & Bray 1998)	Patients with ICD9 diagnosis 140-208 of cancer, of any age	Review of studies on variations in cancer outcomes in relation to variations in patterns of practice.	Survival	1 paper (brain metastases secondary to lung cancer) dealing with neurooncology fulfilled inclusion criteria. The results indicated that physician related factors which may be associated with geographical variations in management practices are important in determining service provision.	*No data on effect of specialisation on neurooncology care.* *Comprehensive literature review and discussion of the literature and factors affecting cancer outcomes. There were data*	Review	4++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					problems but overall the studies indicated that survival was improved with treatment at specialist centres.		
(Selby *et al.* 1996)	All cancers	Specialised cancer care	-	The author concludes that there is some evidence to support the view that referral is not always necessary to a cancer centre.	*Low relevance to question. No neurooncology.y.*	Commentary	4-
PLACE OF CARE							
(Northern and Yorkshire Cancer Registry and Information Service & University of Leeds 1998)	Treatment practices in the former Yorkshire Region during 1986-1994. a total of 2948 patients were registered with tumours of the CNS during the study period.			85.1% of the patients were recorded as being managed at one of the 3 NS centres. There were differences in the proportion of patients managed outside of a specialist NS centre with the lowest rate seen in meningiomas and nerve sheath tumours and the highest in HGGs. Patients not actively managed at a NS centre were older with an average age of 69 years (median 72 yrs), whereas those managed at a specialist centre were younger , average age 54 (median age 58 yrs). Little variation in treatment between the specialist centres for the treatment of meningiomas and nerve (M & N) sheath tumours. There was considerable variation in the treatment of LGG. There was also some variation in treatment policies for HGG.	*The author emphasises that treatment practices may have altered over time. Very useful data within report for all aspects of treatment not only spec. Only limited casemix data available for relative risk calculations.*	Historical time series.	3++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Significant differences in survival were seen with patients managed at the NS centres compared with non specialist care for M & N tumours and LGG. Where relative risk for survival was calculated patient age was found to have the largest impact on survival. The observed lower survival of M & N patients managed at a non specialist centre was no longer significant when controlling for age and treatment factors reflecting that this group were generally older with more advanced disease. As with M & N tumours, for LGG s differences in survival could be attributed to age. For HGG patient age had the greatest effect on survival, although this was to a lesser degree than for LGG or M & N tumours			
(Chang *et al.* 2005).	788 patients were enrolled into the Glioma Outcomes Project between 1997 and 2000. 134 doctors from 52 institutions enrolled the patients. Inclusion criteria Age at least 18 years. People with	Any active treatment was recorded, as was data on patterns of care.	Morbidity and overall survival. Proportion of patients enrolled in clinical trials.	Place of care On univariate analysis (Chi square), patients treated at a university hospital was associated had better survival than those treated at community hospitals (54.6 weeks vs. 40.1 weeks; p=0.002). Patients treated at university hospitals were less likely to be discharged to supportive or hospice care than those treated at community hospitals (1% vs. 6.4%; p<0.001). In multivariate analysis (Cox proportional hazards model), however treatment at a university hospital was not an independent prognostic factor for survival – the	*Multiple statistical tests reported. The study was unlikely to be adequately powered for all the reported comparisons and putative prognostic factors.*	Prospective case series	3++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	high grade glioma (III or IV) undergoing a first or second operation for diagnosis or treatment. Exclusion criteria Patients admitted for their third or subsequent operation. Patients who could not read or understand English, or who could not give written consent to inclusion. CANADA and USA			authors speculate that this is due to the younger age of the patients treated at academic medical centres. Clinical trials In multivariate analysis there was no difference between the overall survival of patients enrolled in clinical trials when compared to those not enrolled in trials. Only 15.1% of patients were enrolled in clinical trials.			

Table 8.3 Is there evidence for an association between volume of care for patients with brain and CNS tumours and outcome?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Barker *et al.* 2003c)	3498 patients were identified from the US nationwide inpatient sample hospital database 1996-2000. This source contains information about inpatient admission and discharge from a stratified random sample of 2671 of non-federal hospitals in the US. 463 of these hospitals and 585 surgeons treated the patients. Inclusion criteria Patients coded with a primary diagnosis of unruptured cranial aneurysm and coded with a procedure of clipping of aneurysm.	Clipping or coiling of unruptured cranial aneurysm	Patient status at discharge (discharged home, discharged elsewhere or dead).	The authors defined high case volume as more than 20 aneurysm clippings per year; the low volume category was 1-2 clippings per year. They considered case volume a continuous variable in multivariate modelling. In a multivariate analysis there was a significant relationship between aneurysm clipping case volume (hospital or surgeon) and hospital discharge status (p=0.03 for hospital volume; p=0.007 for surgeon volume). Patients were more likely to be discharged home if they had been treated at a high volume hospital or by a high volume surgeon. When both hospital and surgeon case volume were included in the same model only hospital case volume predicted outcome (p=0.02). The relationship between hospital or surgeon case volume and in hospital mortality was not significant. Mortality at high volume hospitals was 1.6% compared to 2.2% at low volume hospitals.	*Only short term outcomes considered.* *The high/low hospital volume threshold was not defined beforehand but was chosen to optimise the statistical model.*	Cohort	2++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Exclusion criteria Patients with subarachnoid haemorrhage. USA						
(Barker *et al.* 2003a).	2643 admissions for vestibular schwannoma were identified from the US nationwide inpatient sample hospital database 1996-2000. This source contains information about inpatient admission and discharge from a stratified random sample of non-federal hospitals in the US. 265 of these hospitals and 352 surgeons treated the patients. Inclusion criteria Admission for excision of acoustic	Surgical excision of vestibular schwannoma.	In hospital mortality and discharge to institutions other than home.	In hospital mortality The investigators did a limited analysis of in hospital mortality, because there were only 13 deaths. In a multivariate analysis, they report trends toward lower mortality with larger hospital caseload (p=0.13) and surgeon caseload (p=0.06). Discharge status Higher volume hospitals were associated with better status at discharge (OR for a 5 fold higher case load 0.47; 95% CI, 0.37-0.58; p <0.001). This was also true for high case volume surgeons (OR for a 5 fold higher case load 0.46; 95% CI, 0.31-0.67; p <0.001).	*Sample was too small to use in-hospital mortality as a primary outcome.*	Cohort	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	neuroma in patients with a primary diagnosis of benign neoplasm of cranial nerve. The database did not record the surgical approaches for excision. USA						
(Barker *et al.* 2005)	32028 patients were identified from the US nationwide inpatient sample hospital database 1998-2000. This source contains information about inpatient admission and discharge from a stratified random sample of 2671 of non-federal hospitals in the US. 955 of these hospitals treated patients with primary brain tumours.	Needle biopsy, craniotomy for a primary supratentiorial brain tumour.	In hospital mortality, complications, length of hospital stay and whether living patients were discharged home	Hospital and surgeon caseload were strong predictors of in-hospital mortality after surgical procedures for primary brain tumours Hospital caseload Low and high case volume thresholds were defined as the 25th and 75th percentiles (approximately a 10 fold difference in caseload). Mortality was lower at high volume hospitals both for needle biopsies (OR, 0.54; 95% CI, 0.35-0.83; p=0.006) and for craniotomies (OR, 0.75; 95% CI 0.62-0.90; p=0.003). For low volume hospitals (1-2 admissions per year) mortality after needle biopsy was 3.6% compared to 1.7% at high volume hospitals (more than 12 admissions per year). The corresponding mortalities for craniotomy were 4.5% and 1.5%.	*It is unclear whether in-hospital mortality correlates with longer term outcomes in this group.* *Authors speculate that the greater frequency of neurological complications seen at high volume hospitals could reflect a more challenging case mix or more aggressive*	Cohort	2++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Inclusion criteria Age > 19 years. Diagnosis code of brain tumour (malignant, benign or uncertain behaviour). Procedure code of closed brain biopsy, open brain biopsy, lobectomy or other brain resection. Exclusion criteria Tumour of the cerebellum or brain stem. USA			Patients were more likely to be discharged home from high volume hospitals both after needle biopsy (OR, 0.67; 95% CI, 0.56-0.80; p<0.001) and craniotomy (OR, 0.77; 95% CI, 0.70-0.85; p<0.001). After adjusting for caseload in a multivariate analysis, urban location, teaching status and bed capacity of the hospital were not significant predictors of mortality or discharge disposition. Neurological complications were recorded more frequently at high volume hospitals (OR 1.67; 95%CI 1.13 - 2.45, p=0.009), patients with such complications were less likely to die at high volume hospitals than at low volume hospitals. Thromboembolic complications were also more likely at high volume hospitals (OR 1.46; 95%CI 1.11 - 1.91, p=0.007). Length of stay following needle biopsy was significantly shorter at high volume hospitals (19% shorter; p<0.001) but not significantly shorter for craniotomy (4% shorter; p=0.07). Surgeon caseload Mortality was lower for high volume surgeons for craniotomy (OR, 0.60; 95% CI, 0.45-0.79; p<0.001), but not significantly lower for needle biopsy (OR, 0.53; 95%	*resections at these centres.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				CI 0.24-1.12.; p=0.10). Patients were more likely to be discharged home from after craniotomy by a high volume surgeon (OR, 0.79; 95% CI, 0.70-0.89; p<0.001) but not significantly more likely after needle biopsy by a high volume surgeon (OR, 0.77; 95% CI, 0.56-1.06; p=0.10).			
(Barker *et al.* 2003b).	5497 patients were identified from the US nationwide inpatient sample hospital database 1996-2000. This source contains information about inpatient admission and discharge from a stratified random sample of non-federal hospitals in the US. 538 of these hospitals and 825 surgeons treated the patients. The patients represented approximately 20% of the national caseload of transspheniodal pituitary tumour surgery.	Biopsy or resection of the pituitary using a transspheniodal approach	In hospital mortality and discharge to institutions other than home.	In hospital mortality In a multivariate analysis, adjusting for case mix, mortality was lower at high case volume hospitals (OR for a 5 fold higher case load 0.54; 95% CI, 0.31-0.95; p = 0.03). There was a similar trend for high case volume surgeons (OR for a 5 fold higher case load 0.47; 95% CI, 0.20-1.1; p = 0.09). Discharge status Higher volume hospitals were associated with better status at discharge (OR for a 5 fold higher case load 0.74; 95% CI, 0.59-0.92; p = 0.007). This was also true for high case volume surgeons (OR for a 5 fold higher case load 0.62; 95% CI, 0.41-0.94; p = 0.02).	*In hospital mortality and discharge status are not independent outcomes.* *Short term outcomes only.*	Cohort	2++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Inclusion criteria Patients admitted for biopsy or resection of the pituitary gland using the transspheniodal approach. Diagnosis coded as: benign, uncertain or malignant neoplasm of the pituitary; endocrine neoplasm of uncertain nature; acromegaly (6% of cohort) or Cushing's syndrome (7% of the cohort). Exclusion criteria Any other intrasellar lesions (such as craniopharyngiomas or Rathke's cleft cysts). USA						
(Barker	13685 patients were	Craniotomy for	In-hospital mortality	In hospital mortality	*Only short term*	Cohort	2++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
2004)	identified from the US nationwide inpatient sample hospital database 1988-2000. This source contains information about inpatient admission and discharge from a stratified random sample of non-federal hospitals in the US. 821 of these hospitals and 1606 surgeons treated the patients. Inclusion criteria Adults admitted for craniotomy for a metastatic brain tumour. USA	metastatic brain tumour.	and whether the patient was discharged to their home.	The authors defined high volume surgeons as performing more than 7 craniotomies for metastases per year, low volume surgeons as performing a single craniotomy for metastasis per year. They considered case volume a continuous variable for multivariate analysis. Higher surgeon caseload was associated with lower in hospital mortality rates in a multivariate analysis adjusted for case mix (OR 0.49; 95% CI, 0.30-0.80;p=0.004). Mortality rate was 1.4% for high volume surgeons compared to 3.9% for low volume surgeons. An analysis of the influence of hospital caseload showed a similar pattern which approached statistical significance (OR 0.79; 95% CI, 0.59-1.03; p=0.09). Adverse disposition at discharge Averse disposition at discharge (patient not discharged home) was less likely for people treated by high volume surgeons (OR 0.51; 95% CI, 0.40-0.64; p<0.001) or in high volume hospitals (OR 0.75; 95% CI, 0.65-0.86; p<0.001).	*outcomes considered.*		
(Chernov *et al.* 2004).	307 patients identified from a population based source. All patients had surgical removal	Surgical removal of primary intracranial tumour	Post operative mortality and morbidity	The mean case volume was 23.6 per year (range 3 to 104 cases). Postoperative mortality	*Not a peer reviewed paper – but a letter in response to Cowan et al (2003).*	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	of a primary intracranial tumour at one of 13 neurosurgical departments. The most common histological diagnoses were 44% glioma, 28% meningioma, 13% pituitary adenoma and 5% vestibular schwannoma. RUSSIA			Mean mortality rate was 9.4% (range 0 to 33%). Univariate regression of mortality by case load suggested that high case volume hospitals (>41 cases per year) had lower mortality. Postoperative morbidity Mean morbidity rate was 19.5% (range 6 to 67%). Univariate regression of morbidity by case load suggested that high case volume hospitals (>41 cases per year) had lower morbidity.	*Presents data and figures from a 1999 Russian language paper.* *The author does not define postoperative mortality further (presumably, it is in hospital mortality). Short term outcomes.* *Analysis was not case-mix adjusted, statistical method not fully reported.*		
(Ciric *et al.* 1997).	Questionnaires were posted to 3172 neurosurgeons. 1162 replied of whom 958 performed transspheniodal surgery. 826 (86%) reported having performed	Transspheniodal pituitary surgery	Neurosurgeon reported complications. 14 possible complications were listed on the survey. The percentage of operations resulting in any of the listed complications.	Complications 98% of the surgeons reported having witnessed at least one of the 14 listed complications. The most frequently seen complications were diabetes insipidus (78% of respondents), CSF fistula (62%), anterior pituitary insufficiency (59%) and nasal septum perforation (34%). 0.9% of surgeons witnessed death as a complication of transspheniodal surgery. Effect of case volume	All the data are derived from surgeons' estimates. Unclear how the authors decided the case volume categories (beforehand or data driven?).	Cross sectional (survey)	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	less than 200 such operations. 88 (9%) reported performing between 200 and 500 operations and 27 (3%) reported performing more than 500 operations. USA			Surgeons with more extensive experience were more likely to have seen the complications listed in the survey ($p<0.05$, chi squared test). The proportion of operations resulting in complications was negatively correlated with case volume, for the 14 listed complications ($p<0.05$, Spearman correlation). The authors interpret the results as indicating greater surgical experience is associated with fewer complications in transspheniodal pituitary surgery.	No case mix adjustment		
(Cowan, Jr. *et al.* 2003)	US. 7547 patients, mean age 55.8 years (66.5% , 65yrs; 33.5% > 65yrs) with a diagnosis of malignant central nervous system neoplasm undergoing craniectomy or craniotomy in 379 hospitals	Hospital volume and surgeon volume were categorised by volume quartiles (very low.= 1-6 cases/annum; low = 7-11 cases; high 12-21 cases; or very high >21 cases)	Mortality	Hospital volume and surgeon were highly co-linear (R= 0.5; p= <0.001).) There was considerable variation in mortality depending on the location of the neoplasm. Mortality rates favoured highest volume hospitals for all tumour sites. Outcomes were significantly worse for parietal lobe lesions and metastatic lesions in the very low volume hospitals. *Small numbers in each tumour type. Not valid conclusion.* Using a logistic regression model significant predictors of mortality were emergent admission (OR 2.97;95% CI 2.02-4.38; p= <0.0001) and age > 65 years (OR 1.63; 95% CI 1.16-2.30; p= 0.005). Post operative mortality was reduced if the procedure was performed at a very high volume hospital (OR 0.58; 95% CI 0.35-0.97; p= 0.038) or by a very high volume surgeon (OR 0.42; 95% CI 0.22-0.84; p= 0.012. Metastatic disease did not significantly predict mortality when controlling for other	*Groups not equal, some patient characteristics (age, race, emergent/urgent admissions, presence of COPD and metastases) were significantly different between the volume quartiles.*	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				predictor variables (OR 1.24: 95% CI 0.88-1.74; p=0.808)			
(Halm *et al.* 2002)	All types of health care	Organisation. To review systematically the research evidence linking volume and outcome in health care	Health outcomes e.g. death, stroke or clinical complication	135 studies met the inclusion criteria. Overall 71% of all studies of hospital volume and 69% of studies of physician volume reported statistically significant associations between higher volumes and better outcomes. Differences in case mix and processes of care between high and low volume providers may explain part of the observed relationship between volume and outcome. The authors discuss the methodological problems with some of the primary studies and emphasise about making policy decisions based on the evidence. .	*No neurooncology papers were identified. Studies were too heterogenous to combine for metaanalysis but were combined according to procedure. Appropriate methods used for analysis of volume/outcome via pooling were used. Possibility of publication bias not formally tested*	Systematic review	1^{+}+
(Hannan 1999)	All types of health care			The author concludes that volume is a structural (although changeable) characteristic of hospitals that can be used to identify important variations in the outcomes of care. It should not however, be considered the final determinant of quality.	*Not specific for cancer*	Editorial	4+
(Hillner *et al.* 2000)	All types of cancer care	Evidence to support that hospital or physician volume or		A consistent literature was identified that support a volume-outcome relationship for cancers treated with technically complex surgical procedures. These studies	*Search limited to Medline 1988-1999*	Systematic review	1^{+}

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		specialty affects outcome of cancer care.		identified 30 day mortality. and used the hospital as the unit of analysis. For cancer treated with low-risk surgery there were fewer studies and there was only an association for colorectal and breast cancer. No neuro. papers			+
(Long *et al.* 2003)	US. All adult (4723) patients, undergoing craniotomy for tumour in 33 acute care hospitals between 1990-1996. 1740 with primary malignant neoplasms, 1071 with secondary malignancies and 1912 with benign tumours.	Analysis of effects of regionalisation by analysis of the cost and outcome of craniotomy for tumours and to compare the results in academic medical centres versus community based hospitals. Hospitals were categorised as high volume, >50 craniotomies/year or low volume , 50 craniotomies /yr.	Operative mortality, .length of hospital stay and costs	The mortality rate was 2.5% at high volume centres and 4.9% at low volume hospitals with an adjusted RR of 1.4 ($p<0.05$), assuming equivalence of disease severity. Adjusted LOS in high volume centres was 6.8 days compared with 8.8 days in low volume centres ($p=<0.001$). Hospital charges were significantly higher at high volume centres than at low volume hospitals. The mortality by diagnosis indicated that the adjusted relative risk for secondary malignancies was significantly lower at high volume centres.. The authors conclude that if all patients had been treated at centres with survival rates equal to those achieved by the high volume centres then 46 patients would have not have died of operation.	*Not enough details reported of statistical analyses.*	Retrospective case series	3 +
(Slattery *et al.* 2004)	1213 patients with acoustic neuroma (vestibular schwannoma) were identified from the Californian hospital discharge database	Surgery for acoustic neuroma.	Discharge status (home or not), surgical complications (indicated by certain medical procedures recorded in the	4 categories of hospital surgical case volume were defined: 1) 1 to 5 cases per year (49 hospitals), 2) 6 to 11 cases per year (7 hospitals), 3) 15 to 50 cases per year (4 hospitals) 4) 185 cases per year (1 hospital).	*Statistical method is inadquate: no adjustment for case mix. The authors suggest that patients at the lower volume*	Cohort	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	(1996 to 1998). 70% of the patients presented without a comorbid condition. Inclusion criteria Patients with acoustic neuroma (vestibular schwannoma) coded as their primary diagnosis and with (elective) acoustic neuroma surgery coded as their primary procedure. Exclusion criteria Patients admitted from a residential facitilty, long-term or acute care; newborn babies; emergency admissions and procedures not performed on the day of admission. USA		database), length of stay and costs of hospitalization.	On univariate analysis, the chance of a routine discharge home was significantly better in the group 4 (high volume) hospital (97%) than in group 1 to 3 hospitals (71%, 86% and 92% respectively). The average lengths of stay in hospital groups 1 to 4 were 5.5, 5.9, 4.4 and 6 days respectively (no significant difference). The average costs per day in hospital groups 1 to 4 were $7312, $8524, $6606 and $4332 respectively. The cost for the high volume hospital was significantly lower than for the other hospital groups (Mann Whitney test, $p<0.01$).	*hospitals tended to have more comorbidty, which confounds the results.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Smith *et al.* 2004)	4712 admissions for the resection of paediatric brain tumour were identified from the US nationwide inpatient sample hospital database 1988-2000. This source contains information about inpatient admission and discharge from a stratified random sample of non-federal hospitals in the US. 329 of these hospitals and at least 408 surgeons treated the patients. Inclusion criteria A hospital admission for the resection of a paediatric brain tumour, defined as: patient age <18 years; diagnosis of brain neoplasm (benign, malignant or	Surgical excision of paediatric brain tumour	In hospital mortality and discharge to institutions other than home.	In hospital mortality Mortality was significantly lower for patients treated at high case volume hospitals (OR for a 10 fold difference in case load 0.52; 95% CI, 0.28-0.94; p=0.03). The mortality rate for hospitals in the lowest caseload quartile was 2.3% compared to 1.4% for the highest quartile. There was a trend towards lower mortality for higher caseload surgeons (OR for a 10 fold difference in caseload 0.60; 95% CI, 0.29-1.24; p = 0.16). Discharge status Adverse discharge status was less likely for those treated at high case volume hospitals (OR for a 10 fold difference in case load 0.52; 95% CI, 0.39-0.71; p<0.001). The same was true for those treatedby high case volume surgeons (OR for a 10 fold difference in case load 0.70; 95% CI, 0.50-0.98; p=0.04).	*Primary outcome measures are not independent. Short term outcomes only. The surgeon was coded in only 45% of admissions.*	Cohort	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	uncertain behaviour); a primary procedure coded as lobectomy or excision/destruction of brain tissue/lesion. USA						
(Solomon *et al.* 1996)	5638 patients who had craniotomy for aneurysm, identified from health records in New York State 1987 - 1993. 4034 patients had ruptured and 1604 unruptured aneurysm. 110 hospitals performed the surgery USA	Craniotomy for aneurysm.	In hospital mortality, length of stay	In-hospital mortality rate for patients with ruptured cerebral aneurysm was: • 16% in hospitals performing <6 annual craniotomies for cerebral aneurysm • 16% in hospitals performing 6 to 10 annual operations • 15% in hospitals performing 11 to 20 annual operations • 15% in hospitals performing 21 to 30 annual operations • 10% in hospitals performing 31 to 100 annual operations • 7% in the hospital performing >100 annual operations. There was a 43% (95% confidence interval, 29% to 57%) reduction in operative mortality rate for hospitals performing >30 annual craniotomies for aneurysm compared with the rest of the state (8.8% versus 15.5%, P<.0001)		Cohort	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				In-hospital mortality for patients undergoing craniotomy for unruptured cerebral aneurysm was 12% in hospitals performing <6 annual craniotomies for cerebral aneurysm, 11% in hospitals performing 6 to 10 annual operations, 7% in hospitals performing 11 to 20 annual operations, 5% in hospitals performing 21 to 30 annual operations, 6% in hospitals performing 31 to 100 annual operations, and 3% in the hospital performing >100 annual operations. There was a 43% (95% confidence interval, 14% to 73%) reduction in operative mortality rate for hospitals performing >30 annual craniotomies for aneurysm compared with the rest of the state (4.6% versus 8.1%, P=.0087). There was no effect of case volume on length of stay, except for the single hospital that performed >100 craniotomies for cerebral aneurysm, where length of stay was significantly shorter than the rest of the state. Authors' conclusions Hospitals that frequently perform craniotomy for cerebral aneurysm have lower mortality rates than those performing fewer such operations.			

Table 8.4 What is the evidence for the effect of centralisation and accessibility of cancer services for brain and CNS tumours patients?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Barton *et al.* 2001)	74 patients with bone metastases treated with radiotherapy. AUSTRALIA	To identify and evaluate important patient-based outcomes that are specific to the palliative radiotherapy of bone metastases	Patients' priorities in radiotherapy	Although on average patients rated the travelling distance to the treatment centre as important, sustained pain relief and minimizing the risk of future complications were seen as the main priorities.	Some patients declined to participate because of deteriorating health, possible bias. Design of the questionnaire was based on a literature search and patient interviews. Inappropriate use of the mean with ordinal data.	Cross sectional study.	4-
(Cosford *et al.* 1997)	Residents of Bedfordshire and Hertfordshire registered by the	To examine whether longer travel times for radiotherapy are associated with	Radiotherapy uptake	There was no significant correlation between travel times for treatment and overall radiotherapy uptake (r = 0.40, p = 0.18), or with the ratio of palliative to radical radiotherapy at a single centre (r = –0.29, P = 0.34).	Individual patient travel time was not measured. An average travel time	Observational case series	4-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Cancer Registries as attending hospital with a diagnosis of cancer, and registered as receiving radiotherapy treatment. UK	reduced overall uptake of radiotherapy treatment, or with reduced uptake of palliative as opposed to radical radiotherapy.		Both measures of uptake showed considerable variability. Longest travel times were about one hour. Authors concluded “Travel times up to one hour do not appear to reduce radiotherapy uptake, and the variability observed is likely to be due to other factors. The recommendation of the Chief Medical Officer's expert advisory group on cancers, that radiotherapy should be provided in larger cancer centres, is unlikely to result in lower radiotherapy uptake with travel times of this order."	to the cancer centre was estimated for each of the 14 districts (n=14 for correlation analysis). Radiotherapy uptake was calculated using Cancer Registry data as the proportion of total number of cancer patients receiving radiotherapy. This approach cannot estimate the true uptake of radiotherapy.		
(Ferguson 1996)	57 studies relating to accessibility and patient utilisation of services (not restricted to cancer services).	To review the literature regarding accessibility and centralisation of cancer services in the light of the Calman-Hine report.	Distance and utilisation of: primary care, A&E, clinics & day cases, inpatients, visitors, and screening. Distance and: willingness to travel, mortality and	3000 articles were identified and approximately 300 were screened against inclusion criteria of relevance, outcome and design. 243/300 papers were rejected. The quality of the evidence was generally poor with a lack of properly controlled trials. Direct evidence of the relationship between distance and mortality or morbidity was rare, although 2 studies of cancer patients indicated that outcomes are not	Medline and 'other databases' searched, including those indexing unpublished studies. Researchers were also contacted for	Systematic review and cross sectional study.	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
			morbidity.	affected by distance. 2 studies reported that patients are willing to travel some distance to overcome delays in accessing hospital services. The author concludes that "Overall the research evidence on the accessibility and centralisation trade-off is of relatively poor quality. There is some evidence both from the literature and from discussions with local purchasers that patients – once diagnosed as having cancer – will overcome sometimes considerable access difficulties."	unpublished data. No language restriction. Studies relating to less developed countries or to mental health services were excluded. A wide range of studies are included across many countries, health care settings and patient groups.		
(Finlayson *et al.* 1999)	100 patients (95% male, median age 65) awaiting elective surgery. Patients tended to be from rural locations. Patients with high anxiety or poor cognitive functioning were excluded. USA	To determine the strength of patient preferences for local care.	Additional operative mortality risk that patients would accept to receive treatment locally.	Patients were presented with hypothetical clinical scenarios for surgical treatment of pancreatic cancer. Surgery could either be at the local hospital or at a regional centre (4 hours away by car), each option with known mortality risks. Risks were altered using a variation on the standard gamble technique. Patients preferred local surgery if the operative mortality risk at the local hospital were the same as the regional hospital (3%). If local operative mortality risk were 6% (twice the regional risk) 45 of 100 patients	The fact that 10% of patients would accept 100% mortality risk; suggests some patients either did not understand the concept of risk or did not answer the question truthfully.	Cross sectional study.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				would still prefer local surgery. If local risk were 12%, 23 of 100 patients would prefer local surgery. If local risk were 18%, 18 of 100 patients would prefer local surgery. 10% of patients said they would accept 100% local operative mortality rather than travel to the regional hospital for care. Authors' conclusions Many patients prefer to undergo surgery locally even when travel to a regional centre would result in lower operative mortality risk. Therefore, policy makers should consider patient preferences when assessing the expected value of regionalizing major surgery.			
(Fitch *et al.* 2003)	64 breast cancer and 35 prostate cancer patients. 3 groups were included: those travelling long distances (400–1400km) for radiotherapy following re-referral from their local centre, those receiving radiotherapy within	To gather the views of patients on travelling for radiotherapy.	Themes related to the travel experience were derived from patient interviews, using content and theme analysis.	Four travel related themes were reported: Waiting was the most difficult part of the experience The idea of travelling for treatment was distressing Travelling for treatment was tiring and posed difficulties for patients. Being away from home had both benefits and drawbacks.	Canadian study: travel was over greater distances than those required in the UK Some supportive strategies to ease the burden of travel and staying away from home were proposed by patients.	Cross sectional study.	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	local travelling distances (0.5–120km), and those who lived in remote areas who had to travel long distances to their local centre. CANADA			All patients reported a financial burden because of travel for radiotherapy. Authors' conclusions Given the inevitability of travelling for radiotherapy, and the issues that arise for patients, supportive strategies need to be designed and implemented.			
(Guidry *et al.* 1997)	Patients diagnosed with breast, colon, cervical or prostate cancer or lymphoma within a network of 20 cancer treatment facilities. Cases were diagnosed between 1989 and 1993. Patients were at least 17 years of age. USA	To estimate the effect of travelling distance to cancer treatment as a barrier to care.	Patients' perceptions of barriers to cancer treatment.	910 patients were identified as a systematic random sample drawn from more than 10000 patients with cancer. 593/910 (65%) surveys were returned. Perceived barriers to cancer treatment reported by patients: distance from treatment 46% access to car 48% access to a driver 48% Patient groups with lower household income tended to report greater problems with transportation.		Cross sectional study.	3+
(Kearney 2003)	Four focus-group interviews of a total of 22 parents (17 mothers and 5 fathers) of children with cancer.	To describe the experience of travelling to paediatric oncology centres.	Transcripts of focus group interviews	The transcripts were analyzed qualitatively. Several burdens of travel were identified: Travelling with a sick child, worry of car accidents, financial problems (cost of second car, accommodation near the centre and time lost from work).	Author argues for devolution of care in sparsely populated areas.	Qualitative interviews and focus groups	4+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	UK & EIRE						
(Meden *et al.* 2002)	66 patients treated for breast cancer (stage I or II) from 1999–2000. Patients were identified from the medical records of 3 community hospitals USA	To study the association between travel distance to radiotherapy and treatment for breast cancer.	Type of treatment (breast-conserving therapy (BCT) vs. modified radical mastectomy (MRM)).	Overall, BCT was utilised by 24% of patients. Patients who lived at greater distances from a radiation oncology unit were more likely to undergo MRM. Authors postulate that travel burdens include duration and expense of travel, and hazardous winter driving.	Association between travelling distance and the type of treatment could reflect differences between urban and rural populations (other than burden of travel).	Retrospective case series	3+
(Wright *et al.* 1994)	90 female hospital staff and 38 patients with carcinoma of the cervix, at a regional cancer centre. 18 of the patients had been previously treated and 20 were newly diagnosed. CANADA	To measure the strength of patient preference for high vs. low dose brachytherapy	The association between patient characteristics (including travelling distance) and preference or high vs. low dose brachytherapy.	A questionnaire assessed preference for high vs. low dose brachytherapy (initially assuming that the two were equally effective). When both methods were assumed to be equally effective, only 34% of the 38 patients preferred three fractions of high dose rate to one fraction of low dose rate. However, when high dose rate was assumed to be 20 more curative, or 6% less toxic, a simple majority of 50% then said they would prefer high dose rate. Both preference and strength of preference for low dose rate were significantly associated with a greater travelling distance for treatments. Age, marital status, family structure, education, employment, and family income were not associated. Patients who lived further away from the treatment centre were most reluctant to	In a hypothetical treatment scenario travelling distance was related to a patient's choice of treatment.	Case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				choose three or more high dose rate fractions as compared with one or two low dose rate fractions. In the theoretical situation that high dose therapy was 4% more curative and 12% less toxic than the low dosage, the patients preferring the lower dosage & fewer visits tended to live further away from the treatment centre. Authors' conclusions For our centre, for the comparison of three high dose rate fractions with one low dose rate fraction, and assuming both methods are equally effective, a majority of our patients would prefer to be treated with low dose brachytherapy. The high dose rate would have to be at least 2% more curative, or 6% less toxic, for at least 50% of the patients to prefer it over the low dose rate.			

Chapter 9 Management of patients with pituitary, spinal cord or skull base tumours

The questions

a) What services are required for the management of patients with pituitary tumours?

b) What services are required for the management of patients with spinal cord tumours?

c) What services are required for the management of patients with skull base tumours?

The nature of the evidence

a) What services are required for the management of patients with pituitary tumours?

The evidence for the management of pituitary tumours comprises six review papers, nine case series, one cohort study and a cross sectional survey. Papers were generated from many countries including Taiwan, Scandinavia, Australia, the USA and Europe.

b) What services are required for the management of patients with spinal cord tumours?

The searches identified a very limited volume of evidence. Three case series (Raco *et al.* 2005; Parker *et al.* 1996; Jellema *et al.* 2005) (one from the UK (Parker *et al.* 1996)) discussed the clinical presentation, diagnosis, treatment and outcomes of patients with intramedullary spinal cord tumours. Review articles discussed radiotherapy (Isaacson 2000) and chemotherapy (Balmaceda 2000) in this population.

c) What services are required for the management of patients with skull base tumours?

Eight studies were identified that provided evidence about the management of patients with skull base tumours (which included benign skull base meningiomas and skull base chordomas). A further six studies were identified

that provided evidence about the management of patients with vestibular schwannomas (acoustic neuroma).

For skull base meningiomas and skull base chordomas the evidence came from: one cross sectional study; one prospective non-randomised clinical trial; one retrospective study; two case series studies and two critical reviews. Studies were of good to of fair quality.

Summary of the supporting evidence for the recommendations

a) What services are required for the management of patients with pituitary tumours?

The treatment for pituitary tumours is dependent on tumour type. Microadenomas (<1mm diameter) or macroadenomas (>1mm diameter) may form from endocrine cells with hypersecretion of relevant hormones and subsequent hormonal problems. The hormones involved are commonly growth hormone, GH (acromegaly), prolactin, PRL (prolactinoma – amenorrhoea, galactorrhoea) and adrenocorticotrophic hormone, ACTH (Cushing's disease, Nelson's syndrome). Growth of non-secretory (non-functional) adenomas can still cause problems due to mass effects, optic tract compression and invasion of nearby structures.

Consensus based UK clinical guidelines recommend the referral of patients with pituitary tumours to specialist centres where management plans may be agreed jointly by endocrinologists, pituitary surgeons and radiotherapists.

Surgical treatment aims to debulk mass and reduce hormonal levels in order to restore normal pituitary function and hence quality of life for the patient. Transsphenoidal surgery with either microscope or endoscope has, in most cases replaced surgery via the frontal lobe, wherever possible. Evidence suggests that, in comparison to the sublabial approach, transnasal surgery, although no more effective, is less invasive, quicker, carries fewer surgical complications and hence for the patient has fewer side effects and leads to a shorter stay in hospital. However, several authors have pointed out that an important factor in outcome is the employment of a single dedicated pituitary surgeon.

Radiotherapy is rarely the first line treatment of pituitary adenoma but is used as an adjunct to surgery in cases of persistent hormonal hypersecretion, incomplete resection or as a first line treatment for patients who refuse surgery or have inoperable tumours.

Chemotherapy is first line treatment for prolactinoma, particularly dopamine agonists such as bromocriptine or cabergoline, and carries a higher success rate than surgery. For the treatment of acromegaly, chemotherapy is an adjunct to surgery and whilst not generally causing tumour shrinkage aims to control the symptoms of the disease.

Whilst there is little evidence to link treatments with delayed neurocognitive or carcinogenic effects these, and the risk of hypopituitarism, necessitate long-term follow-up by an endocrinologist.

b) What services are required for the management of patients with spinal cord tumours?

Surgical resection is the primary treatment for these patients (Raco *et al.* 2005; Parker *et al.* 1996; Jellema *et al.* 2005), but the eventual outcome may be compromised by the considerable diagnostic delay experienced by some. Evidence from case series (Isaacson 2000) suggests adjuvant radiotherapy is used in many cases (in patients with high grade or incompletely resected tumours). There is little direct evidence about the role of chemotherapy in this group (Balmaceda 2000), although indirect evidence from intracranial neoplasms of similar histological type suggests a potential role for chemotherapy (see chapters 4 and 5, the management of patients with low and high grade gliomas).

c) What services are required for the management of patients with skull base tumours?

The cross sectional study aimed to develop a disease-specific, multidimensional quality of life (QOL) assessment instrument for patients undergoing surgical extirpation of anterior skull base tumours. It found that patients older than 60 years of age had significantly poorer scores in the domains of performance and physical function than younger patients. Patients with malignant tumours had significantly poorer scores in the domains of specific symptoms, influence on emotions, physical function, and performance

compared with patients with benign tumours. Radiotherapy was associated with poorer scores in the domains of specific symptoms and influence on emotions. Co-morbidity was associated with poor physical function scores. Using the final questionnaire, we prospectively evaluated the QOL of 12 additional patients before they underwent surgery and again between 5 and 6 months postoperatively to test the utility and validity of the instrument further. Again, significantly poorer QOL scores were recorded for patients with malignancy.

The non-randomised clinical trial evaluated the use of intra-operative electron beam radiotherapy (IORT) as an adjuvant modality in the treatment of advanced head and neck and skull base cancer. Findings of this study showed at 2 years overall and disease-free survival was 32% and 21%, respectively, for the SCCA patients and 50% and 40%, respectively, for the non-SCCA patients. Tumour control rates at 2 years in the IORT field were 46% for the SCCA patients and 52% for the non-SCCA patients. For squamous cell histology, survival in patients with microscopic residual tumour did not differ from those with no residual tumour, but they both had significantly longer disease-free survival than those patients with gross residual at the time of IORT ($p = .03$), with a trend toward longer overall survival ($p = .09$). The only complication directly attributable to IORT was a neuropathy in a patient who received an IORT dose of 22.5 Gy (cumulative dose 130.1 Gy).

The retrospective study aimed to investigate the use of linear accelerator (LINAC) -based stereostatic radiosurgery (SRS) as a treatment for patients with skull base meningiomas. Patients who received SRS-only were compared to patients who had received SRS and undergone a prior resection Results of this study showed a 7 year overall survival rate = 80.2% and 7 year disease free survival = 78.9%. The 7 year local tumour control rate for SRS group was 100% and for the SRS + resection it was 84%. There was no statistical significance in local control for the two groups of the study. No prognostic factor (such as age, sex, history or prior resection, time-interval between diagnosis and SRS, SRS target volume and SRS target dose), was statistically significant with respect to local control. With respect to adverse events; for the group that received surgery and SRS, a number of cranial neuropathies were observed after surgery and after SRS. In this group, most

neuropathies were unchanged with treatments. Some improvements were recorded without deterioration in 11 of 29 patients. For the group that received SRS only, most patients remained stable or had improved neurological status without deterioration.

A case series study evaluated the efficacy and safety of stereotactic radiosurgery for patients with skull base meningiomas. In this study all patients underwent CT and MRI to locate and measure tumour size and position. High speed computer imaging integrated dose plans were performed to determine appropriate 3D isodose configurations and aided dose selection. Mean dose delivered to the tumour margin was 15 Gys; dose range was 9 - 18.5Gy. Multiple iso-centers were used when required to increase conformality of dose. Follow-up was done using gadolinium -enhanced CT or MRI for post-op radiological evaluation in all patients. The actuarial freedom from progression rate (defined as further tumour growth) for all patients was 95% with a median follow up interval of 26 months. 44% of these patients had decreased tumour volumes and 56% had tumour volumes which were unchanged in size. Immediate and long term clinical status of patients was reported. 49% had unchanged symptoms after 24 hours after surgery. Long term effects showed improvement for 34% of patients and 57% had unchanged clinical symptoms. Early adverse effects such as transient nausea, vomiting or headaches were reported in 9% of patients. 49% of patients had unchanged early adverse effects. With respect to long term complications; no deaths were directly related to radiosurgery and 57% of patients were unchanged by clinical exam and 34% had improved.

The critical review reported the optimum treatment options for patients with benign and meningiomas of the skull base. The treatment options refer to; surgery, radiosurgery and radiotherapy. Efficacy of treatment was measured by local control, survival and the types of complications experienced. After surgery, the progression free survival decreases with longer follow up. (Where local control implies complete removal of the tumour without evidence of recurrence on follow up). Local control after radiosurgery (gamma-knife radiosurgery or LINAC radiosurgery) was greater than or equal to 90%. Local control rate after radiotherapy for 5 or 10 year progression free survival ranged from 70-98%. Doses range from 50-55Gy, median dose per fraction1.7-1.8Gy. Local control rate after radiotherapy for 5 or 10 year

progression free survival ranged from 70-98%. Doses range from 50-55Gy, median dose per fraction1.7-1.8Gy. (Where local control for both radiosurgery and radiotherapy implies stabilisation of the tumour with no evidence or progression on follow up evaluations). With respect to survival; for 315 patients treated surgically the 10 year survival rate was approximately 79%. Survival rates after surgery alone compared to surgery and radiotherapy at 10 years was 42% compared to 77% ($p \leq 0.05$) respectively and for 20years it was 18% compared to 38% (not statistically significant). For 262 patients (60% skull base) treated with surgery alone or surgery and post operative radiotherapy or radiotherapy alone and radiosurgery the 15 year cause specific survival rates was 88% subtotal resection, 86% radiotherapy, 51% subtotal resection alone ($p=0.0003$). With respect to radiosurgery, survival data is rare. For 178 patients treated at Mayo Clinic, the 5 year cause specific survival rate was 100%. For radiotherapy: 180 patients (WHO grade 1 meningiomas) treated with stereotactic-radiotherapy, the 5 year overall survival rate was 97%, the 10 year overall survival rate was 96%. For benign skull base tumours the overall survival rate was 71%. Complications range from severe to moderate neurological deficits. Probability of complete resection depends on the location and extent of tumour. All treatments (surgical, radiosurgery and radiotherapy) offer some complications.

For skull base chordomas, two studies were identified. One was a case series study that reported clinical results about the effects of carbon ion radiotherapy for the treatment of patients with skull base tumours and spinal/sacral chordomas and chondrosarcomas. In this study eighty-seven patients with chordomas and low-grade chondrosarcomas of the skull base received carbon ion radiotherapy alone (median dose 60 GyE); 21 patients with unfavourable adenoid cystic carcinomas and 17 patients with spinal and sacrococcygeal chordomas and chondrosarcomas were treated with combined photon and carbon ion radiotherapy. Twelve patients received re-irradiation with carbon ions with or without photon radiotherapy for recurrent tumours. Furthermore, 15 patients with skull base tumours other than chordomas and low-grade chondrosarcomas were treated with carbon ions. Actuarial 3-year local control was 81% for chordomas, 100% for chondrosarcomas, and 62% for adenoid cystic carcinomas. Local control was obtained in 15/17 patients with spinal (8/9) and sacral (7/8) chordomas or

chondrosarcomas and in 11/15 patients with skull base tumours other than chordomas and low-grade chondrosarcomas, respectively. Six of 12 patients who received re-irradiation are still alive without signs of tumour progression. Common Toxicity Criteria Grade 4 or Grade 5 toxicity was not observed.

The critical review about skull base chordomas provides an overview of treatment options and patient outcomes. The following management options were reviewed: surgical approaches and radiation therapy (conventional RT, proton beam RT, radiosurgery and interstitual brachytherapy). Patient outcomes were also reported. Cranial base chordomas are locally invasive tumours that, from a midline, clival location, extend in different directions and display various patterns of skull base invasion. Although histologically benign, their invasive nature makes true "oncological" resection virtually impossible to achieve in most cases, despite modern skull base surgical techniques. Moreover, because of the tumour's location and proximity to critical neural and vascular structure, surgery related morbidity can be significant when an aggressive resection is undertaken. Cytroreductive surgery assumes a critical role in the management of these lesions. The choice of surgical approach and the extent of resection are dependent on several factors: location and extension of the tumour, the surgeon's philosophy and familiarity with a specific approach, and the patient's pre-existing clinical status. Proton-beam radiotherapy seems to be effective as an adjunct to surgery in achieving local tumour control. The timing of radiation therapy, however, remains controversial. Gamma knife surgery has been proposed as an adjunctive therapy, but the limited experience and short follow-up periods do not permit formulation of meaningful conclusions at this time. Recurrences are common, although in a subset of patients prolonged disease-free survival is demonstrated.

The management of acoustic nueromas was described in six identified studies. These studies included: two meta-analyses, two systematic reviews, one retrospective study and one cohort study. Overall quality of these studies was fair.

The first meta-analysis compared outcomes for surgery and gamma knife radiosurgery for acoustic neuroma. The other meta–analysis defined the role of conservative management of acoustic neuromas.

The meta-analysis comparing surgery and gamma knife radiosurgery included 2579 patients who underwent surgery; mean age 48.8 years; 56% of tumours were small (<2 cm), 33% were medium sized (between 2 and 4 cm) and 11% were large (> 4cm). The review also included 875 patients who underwent gamma knife radiosurgery; mean age 56 years; mean tumour size was 1.61 cm. Mean follow up was 24 months for surgery and 25 months for gamma knife radiosurgery. The 2 different treatments (using data from case series) were as follows: surgery (sub occipital/ retro sigmoid approach in 58%; Tran labyrinthine used in 34%; middle fossa in 7%; combined in 1%) compared with gamma knife radiosurgery. Average total radiation dose was 37.4 Gy with and an average peripheral dose of 17.27 Gy and central dose of 37.6 Gy. Outcomes of interest were hearing loss, facial function, complications and tumour control after surgery (defined as no tumour recurrence after complete resection and no growth after partial resection) and tumour control after gamma knife radiosurgery (defined as no tumour growth). Findings were as follows: Facial nerve outcomes: There was no significant difference between treatments in the proportion of patients with a good outcome (967/1192[81.1%] with surgery v 582/717[81.2%] with radiosurgery, P = 0.23). Radiosurgery results included patients with NF2 and those who had previous treatment. Hearing outcomes: There was no significant difference between treatments in the rate of serviceable hearing preservation (599/1420[42%] had pre-operative serviceable hearing and 256/599[44%] retained service with surgery versus 219/552[40%] with 96/219[44%] retained service with radiosurgery. Complications: none of the studies reported results by tumour size. Complications were significantly lower after surgery than radiosurgery (22% v 38%. Tumour control was significantly better after surgery than radiosurgery (uncontrolled tumour rates were 2% with surgery v 9% with radiosurgery. The authors concluded that surgery had a lower complication rate than gamma knife radiosurgery but results reflect historical data. Results from more recent studies are required to assess the current complication rate.

The meta-analysis about conservative management of acoustic neuromas reported a total of 21 studies comprising 1,345 patients. The average length of follow-up for these studies was 3.2 years. The average initial tumour size was 11.8 mm; 43% of 1,244 acoustic neuromas showed growth, whereas 57% showed either no growth or tumour regression. The average growth rate was

1.9 mm/year in 793 individuals. Hearing loss occurred in 51% of 347 individuals. In 15 studies, 20.0% of 1,001 individuals eventually failed conservative management. The analysis supports the role of conservative management of acoustic neuromas in properly selected patients on the basis of a slow overall rate of growth and a substantial incidence of no growth. However, the lack of predictive factors, the relatively short duration of follow-up, and the variability of inclusion criteria underscore the need for continued collection of long-term data. This analysis does not provide any statistics for predictive factors and tests of significance. As the authors point out, predictive factors are difficult to identify especially when not all studies reported include this in the analysis. A high attrition rate was reported in this study with respect to conservative management. Lost to follow-up was not consistently reported for the other cited literature. Non-compliance with conservative management will be ineffective without regular clinical and radiological follow-up.

A retrospective study analysed the relationship between the number of acoustic neuroma surgeries performed at California hospitals with surgical outcome and hospital stay cost. For surgical outcomes (discharge, outcome, complications), the study shows that there is an increased chance of routine discharge with increasing hospital volume (14.8 times more likely than low volume hospitals). And that the risk for non-routine discharge is smaller for high volume hospitals. (Where routine discharge is the arrangement or event ending a hospital stay after surgery with no additional procedure such as craniotomy, ventriculostomy, etc see reference). With respect to complications, significantly fewer additional surgical procedures were performed for higher volume hospitals than for low volume hospitals. More than one third of patients in low volume hospitals had a non routine discharge compared to 4 % in high volume hospital. For hospital stay the average length was 4.4-6 days. Low volume hospitals were 5.7 days compared to moderately high hospital which was 4.4 days. When considering cost; higher volume hospitals are on average less expensive than lower volume hospitals. The high volume hospital had lower charges and cost per day than any other hospital groups, though it may be useful to have included physician fees into the costing.

The aim of the systematic review was to compare neurotological complications resulting from two treatment alternatives to microsurgery:

radiosurgery and observation. The review included uncontrolled cohort studies and was compared to a study conducted by the authors who used clinical results obtained in a cohort of consecutive patients suffering from acoustic neuromas who were followed up using conservative management. The review reported complications such as facial hypoesthesia, hearing loss and hydrocephalus, were more frequently encountered after radiosurgery than with conservative management. In comparison, the risk of growth of acoustic neuromas is significantly higher with conservative management and the rate of stability of the tumour did not differ significantly between the two treatments. It is important to highlight the lack of consistency in reporting tumour growth. A high level of non-compliance was reported and will influence results with some patients not attending follow-up sessions which report the effects of conservative management.

The systematic review by Yamakami et al reviewed conservative management, gamma-knife (GK) radiosurgery, and microsurgery as therapeutic options for acoustic neuromas. Conservative management over 3.1 years showed that 51% of acoustic neuromas showed a tumour growth, at a rate of 1.87 mm (in year-1). Also, 20% of acoustic neuromas ultimately required surgical intervention, and a third of the patients lost useful hearing. The majority of acoustic neuromas grow slowly, but ultimately require intervention. Carrying the risk of hearing loss, conservative management should be supplemented with close follow-up. For gamma-knife radiosurgery a significant reduction in enlargement of acoustic neuromas was reported. A reduction in the percentage that underwent microsurgery to 4.6% over a 3.8-year period was also reported. With a low rate of morbidity, gamma-knife radiosurgery suppresses tumour growth and provides good tumour control. Microsurgery removed 96% of acoustic neuromas totally, with tumour recurrence, mortality, and major disability rates of 1.8%, 0.63%, and 2.9%, respectively. Microsurgery provides the best tumour control, although mortality and morbidity are not completely eliminated. Surgeon's operative experience was important in microsurgery. It was reported that surgeon's experience has some affect on postoperative facial function outcome in the first 20-60 patients, however, no significant relationship was found between size of population and the surgical outcome.

The surgical excision of acoustic neuroma reporting patient outcome and provider caseload was evaluated in a cohort study. The investigators did a limited analysis of in hospital mortality, because there were only 13 deaths. In a multivariate analysis, they report trends toward lower mortality with larger hospital caseload and surgeon caseload. Higher volume hospitals were associated with better status at discharge and this was also true for high case volume surgeons.

Table 9.1 Management of patients with pituitary tumours

Abbreviations: CI, confidence interval; GH(R), growth hormone (receptor); GKR, gamma knife radiosurgery; OGTT, oral glucose tolerance test; PRL, prolactin; SS, Somatostatin, DA, dopamine; IGF-1, insulin growth factor-1; ACTH, adrenocorticotrophic hormone; RT, radiotherapy; GKR, gamma knife radiosurgery.

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Burt & Ho 2003)	Australia	To review and compare three drug regimes in the treatment of acromegaly.	Three main drug therapies are discussed in chronological order: dopamine (DA) agonists e.g. bromocriptine, somatostatin (SS) analogues e.g. Octreotide, Lanreotide and growth hormone receptor (GHR-) antagonists e.g. Pegvisomant. Remission: Normalisation of GH and reduction in IGF-1 levels. Cure: Resumption of hypothalamic control over GH levels. SS analogues: If a single dose suppressed GH release a successful outcome to treatment was predicted. Many groups had pre-selected patients in this way and found that both drugs acted equally well, particularly as depot preparations. They were well tolerated & normalised IGF-1 in > 50% patients. Symptoms were reduced in 90% patients according to one large multi-centre trial. There was poor evidence for tumour shrinkage and therefore these drugs could never replace surgical resection. DA agonists: Inhibit GH release in hormone secreting adenomas. Pills are cheap to produce and can be taken orally. Bromocriptine had disappointing results according to meta-analysis: IGF-1 was normalised in only 10% patients, except for those patients who also experienced co-hypersecretion of prolactin with GH. Cabergoline or Quinagolide improved IGF-1 normalisation to 39%. Overall these drugs provided a good therapy to only a minority of patients and had side effects that were not well tolerated. D2 receptor specific drugs were better than non-selective DA agonists but are usually given for hyperprolactinaemia not		Authors conclude that SS analogues are superior to DA agonists because of availability of depot preparations, tolerability and efficacy. However, GH receptor antagonists may be more effective than SS analogues even though the primary effect is not tumour shrinkage but disease control as an adjuvant to surgery.	Review paper. 51 references.	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
			acromegaly. Trials comparing SS analogues and DA agonists were few and suggested the former to be more efficacious. Opinions on combination therapy were divided. GHR antagonists: Pegvisomant was proposed as the drug of choice. It prevents GH receptor dimerisation, and hence inhibits function but does not reduce GH levels, hence cannot replace surgery as a first line treatment. A dose related response in IGF-1 reduction up to 89% was observed compared with 10% placebo. 6% patients withdrew due to side effects and 3% from lack of effect.				
(Chon & Loeffler 2002).	USA	To review the advantages and disadvantages of radiotherapy and radiosurgery in the treatment of all types of pituitary adenoma.	For hormone secreting tumours radiotherapy may be used for post-operative persistent hypersecretion or, for non-secreting tumours, as adjuvant treatment in case of incomplete surgical removal, recurrence or invasion of sinuses or base of skull. As a primary treatment radiotherapy may be indicated for those patients who refuse surgery or for inoperable tumours. A potential side effect of radiotherapy is hypopituitarism, which can occur years after treatment and the likelihood of which appears to be related to total dosage and dosage per fraction. A threshold is suggested of 50Gy beyond which there is a significant risk of hypopituitarism occurring. Similarly, exposure of the optic tract to doses below 10Gy may reduce risk of neuropathy. There is little evidence to link radiotherapy alone with the neurocognitive deficit seen in patients treated for pituitary adenoma. Such patients are likely to have confounding factors such as underlying hormonal imbalance, hormonal therapy and/or repeated surgery.		Authors conclude that radiation therapy is a safe & effective treatment for adenoma and effects control of tumour growth and restoration of hormonal balance in the majority of patients. They recommend that the time lag before normalisation may be many months so evaluation and follow-up by an endocrinologist is essential. Long term follow-up is	Review paper. 31 references.	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					required to asses the neurocognitive and carcinogenic effects in long term survivors.		
(Ciric *et al.* 2000).		To review the current (2000) knowledge of the origin and standards in the diagnosis and management of pituitary tumours.	Prolactinoma: DA agonists Bromocriptine and Cabergoline are of equal efficacy but the latter is associated with less side effects. TS surgery carries minimal morbidity if conducted by dedicated pituitary surgeon. Success is rated by reduction of PRL to ≤5ng ml-1 whereas higher levels are associated with a greater chance of recurrence. Pharmacotherapy is superior to surgery for macroadenomas both for controlling mass effect and endocrine abnormality. Acromegaly: Surgery is the main treatment modality with post-operative GH levels ≤2.5ng ml-1 defining 'cure'. Invasive tumours are less likely to be resolved by surgery alone. SS analogues can lower or normalise GH levels in 65% patients and reduce tumour size by half in up to 50% of patients. These drugs may be used with DA agonists. IGF levels were normalised in the majority of patients using a novel drug Trovert (1 trial). RT will reduce but will not normalise either GH or IGF and hence, over time, will not control the symptoms of acromegaly. Gamma knife surgery is effective at normalising GH levels in up to 60% patients. Cushing's Disease: ACTH secreting tumours are usually microadenomas which respond well to surgery by an experienced and dedicated pituitary surgeon. Unlike GH secreting tumours these tend not to be invasive and hence use of radiosurgery is not usually necessary. A 'cure' is effected with ACTH levels ≤2.5µg dl-1. Post surgery, ACTH levels can be controlled by endocrine therapy.	*This is a review of current (2000) knowledge of pituitary tumours, including elements of molecular biology and treatment.* The authors compare surgical techniques in some detail and conclude that TS surgery and, more recently, endoscopic surgery were the most promising avenues of treatment but stress the importance of having a dedicated	Book chapter - review paper. 55 references.	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
			Non-secreting tumours: Surgery is more effective than radiotherapy.		pituitary surgeon.		
(Laws, Jr. *et al.* 2003).	10 patients (8 males and 2 females). Median age 51yrs (range 20 - 65yrs). All had previous transsphenoidal surgery (TS) and a range of other treatments at various times prior to this study. Inclusion: the presence of an aggressively recurrent pituitary adenoma or craniopharyngioma that was refractory to all standard forms of treatment incl. chemotherapy, radiotherapy and surgery. Exclusion: Patients	To determine the effectiveness of Gliadel wafers in the treatment of patients with recurrent pituitary adenoma or craniopharyngioma. Insertion of between 2 and 8 Gliadel wafers, impregnated with bischloroethyl-nitrosourea (BCNU), into the sella turcica following surgical tumour resection.	Retardation of relapse.	Mean follow-up was 19/12 (range 5/12 - 27/12) excluding 3 patients that died at 11/12, 13/12 and 14/12. Six patients were reported to have good tumour control. Two patients died, having had large invasive tumours which may have been inadequately covered with the chemotherapeutic agent. One patient died from a stroke following cranial recurrence. One patient had tumour recurrence but was alive at the time of writing. There were no reported adverse side effects from this treatment.	Authors stated that the low numbers of patients that qualify for this treatment are such that a RCT will never be feasible and also left this particular study under powered to draw significant conclusions. *This is an experimental procedure which included the breaking of chemotherapy wafers to conform to the required size/shape of the treatment area.* *The authors agreed that this may have*	A 'phase I feasibility study' with the features of a prospective case series. No measurable data. No statistical analysis. Patients were followed up with 'periodic imaging studies and visual evaluations'.	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	<16yrs, pregnant women, patients that could benefit from additional 'conventional' treatment. Active CSF leakage. USA				*changed the applied dose against the manufacturer's recommendations.* *Lack of data, and statistical analyses, render the findings anecdotal. Nonetheless, this group of patients who had a poor prognosis may have received benefit from this novel procedure.*		
(Thoren *et al.* 2001)	Sweden.	To review the role of the gamma knife in the treatment of all forms of pituitary adenomas.	Somatotrope tumours: When gamma knife RS was used as a primary treatment of acromegaly, improvement was seen in ~50% of a very small number of patients. More recently, RS was used as an adjunct to surgery - GH levels fell and continued to fall for more than 10yrs whether or not patients had also received conventional radiotherapy. IGF-1 was normalised in about half of patients. Lactotrope tumours: These tumours usually respond well to medical therapy and so gamma knife RS is rarely used but may be a suitable adjunct for those who cannot tolerate DA agonist treatment or who have tumour extension beyond the sella region. Prolactinomas appear to be resistant to RS but PRL levels decrease		The authors conclude that gamma knife radiosurgery is a good adjunct if primary treatment is unsuccessful, is contraindicated or refused by the patient.	Review paper. 34 references.	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
			in up to 50% in the majority of patients. Corticotrope tumours: Before the availability of MRI, gamma knife RS was used as a first therapy with about 80% success in normalising cortisol hypersecretion & reducing symptoms of Cushing's disease in adults. With limited visualisation, treatment often had to be repeated and remission could take a long time. Control of Cushing's disease and Nelson's syndrome is similar with no recurrence after mean follow-up of 17yrs. Gamma knife RS could be primary treatment when open surgery is contraindicated or refused or as a secondary treatment if surgery is unsuccessful or in cases of tumour extension. Non-functioning tumours: Only ten patients have been evaluated of which six showed no change in tumour growth after treatment. Side-effects may include hypopituitarism, which can be delayed. PRL hypersecretion has been observed. There is a very low morbidity and mortality rate associated with gamma knife RS.			
(Wowra & Stummer 2002)	30 patients with non-functioning pituitary adenomas (NPA) with complete clinical and hormonal follow-up information and a quantitative tumour volumetric analysis (out of a total of 45 patients with NPA).	Treatment with outpatient gamma knife radiosurgery (GKR) Median dose to tumour margin was 16 Gy (range 11 to 20 Gy). Mean prescription isodose was 55% (range 45% to 75%).	Follow-up was with stereotactic MRI to measure NPA volume. The effect of GKR was measured by comparing sequential tumour volumes after GKR with initial	No new ophthalmic or other focal neurological deficits were recorded. One patient developed a small asymptomatic tumour haemorrhage on MRI. Three patients developed partial pituitary insufficiency. The actuarial risk of radiosurgery induced pituitary damage was calculated as 14% after 6 year. The actuarial long-term recurrence free survival was calculated as 93% for a single GKR and 100% for a repeated GKR.	The authors concluded that postoperative gamma knife radiosurgery for residual or recurrent small fragments of non-functioning pituitary adenomas is effective and safe.	Case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Characteristics: Median age 55 years (range 21 to 77); 53% female; 37% had neurological deficit; 27% had visual field cuts; 70% had hypopituitarism (50% partial and 20% global). Germany	29 patients had had undergone prior resection of NPA (1 to 3 operations per patient) Aim: to assess the efficacy of gamma knife radiosurgery (GKS) for non-functioning pituitary adenomas (NPAs)	tumour volumes. Median follow-up was 55 months (range 28 to 86 months).	In 4 patients transient swelling of the NPA was detected.	Follow-up of NPAs should include tumour volumetric analysis. *Small sample size.*		
(Hill & Mathias 2000)	UK	To give an overview of current (2000) approaches in the treatment of pituitary adenoma with emphasis on the role of surgery.	For hormone secreting tumours surgery is used to remove microadenomas with ~80% success rate. Macroadenomas may respond to chemotherapy but surgery and radiotherapy are indicated in some tumours including those refractory to drug treatment. The aim of surgery is to restore normal hormonal function and to debulk masses that may compress the pituitary stalk or optic nerves. Various approaches are discussed, surgery may be achieved using instrumentation, both single and double handed, through the nose, orbit or cranium. Each method has its advantages and disadvantages in relation to		The authors recommend that treatment of pituitary adenomas requires a MDT comprising endocrinologists, pituitary surgeons & radiotherapists.	Very concise journal article. No referenced papers.	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
			access and patient morbidity. These factors are briefly discussed.				
(Jane, Jr. & Laws, Jr. 2003)	USA	To review the current and future treatment of non-functioning pituitary adenomas.	Recommends careful neurological and endocrinological history taking, biochemical diagnosis and screening of the pituitary axis to identify pituitary insufficiency, including MRI with gadolinium enhancement. Aims of treatment should include improved quality of life, relief of mass effects, normalisation of endocrine hypersecretion and recovery of normal pituitary function. Treatment regime is generally TS surgery, more recently with endoscopy, although there are no studies to confirm the efficacy or otherwise of this new approach. Some patients experience post-surgical hormonal deficit, although this appears to be a rare event. In the authors' experience the recurrence rate was 16% over 10 years and such patients could be treated successfully with medical, surgical or RT intervention. Generally, RT is reserved for incomplete resection since it is inconvenient, may lead to pituitary dysfunction, late cognitive deficit and invokes only a slow regression response. Gamma knife radiosurgery has been reported to have between 90% - 100% control of tumour growth in macro- and micro-adenomas respectively. A tumour volume reduction of 50% is reported in nearly 30% of patients and new hormone deficit has not been identified thus far because of the short term follow-up of this relatively new treatment.		Authors conclude that gene therapy may in future play a greater role in the treatment of pituitary adenomas and that an understanding of the molecular pathenogenesis should lead a more effective treatment. The MDT should comprise endocrinologists, neurosurgeons, neuro-ophthalmologists, radiation therapists and neuroradiologists.	Review paper. 79 references.	4
(Swords *et al.* 2003)	21 patients (8 males and 13 females). Mean age at time of radiosurgery = 42yrs (range 18yrs - 67yrs).	To report the use of stereotactic radiosurgery delivered through an adapted linear	Comparison of measurements of pre-and post-RT biochemical parameters to	Somatotrope tumours: Follow-up data available for 12/13 patients over med time of 25/12 (range 3/12 - 48/12). 7/13 achieved mean serum GH < 5mU l-1 and 6 of these patients were able to stop other therapy. For the group, mean GH before SMART was 21.1mU l-1	Authors conclude that, following SMART, 50% of acromegalic patients normalised	Retrospective case series.	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	All patients had macroadenomas, 13 with acromegaly, 4 with Cushing's Disease (or Nelson's syndrome), 1 with hyperprolactinaemia and 3 with non-secretory tumours. All but 3 patients (acromegalics) had had at least one surgical intervention and all patients had received radiotherapy of between 45Gy - 50Gy in between 25 - 40 fractions. All patients had signs of clinical disease dependant on cell type. All tumours were > 5mm from the OC (< 3mm precludes RT). UK	accelerator (SMART) for pituitary adenomas not cured by conventional therapy. Pre- and post-treatment serum hormone levels were compared using paired Student's t-test. SMART was given to 21 patients between 1989 and 1999. Up to five 140-degree noncoplanar arcs of X-rays were given. The SMART dose for each patient was calculated using computer software taking various parameters into consideration and ranged between 8Gy and 15Gy. Patients were given pre and	indicate 'cure'.	(range 5.4 - 60.7) and after SMART 7.85mU l-1 (range 1.9 - 26.4) P<0.01. IGF-1 mean levels (available for 11/13 patients) before SMART were 623.5 ng ml-1 (range 220 - 1281) and after SMART 383.9 ng ml-1 (range 99 - 965) P<0.001. There was no change in tumour size in the majority of patients. Regular scanning was ongoing at the time of publication. Corticotrope tumours: Follow-up was available for all patients for 6/12. Plasma ACTH, but not cortisol, was reduced in both patients with Cushing's disease. 1/2 patients with Nelson's syndrome had improvement in symptoms. Tumour size did not change for any patients. Lactotrope tumours: The single patient obtained temporary pain relief from SMART treatment but later died of cardio-respiratory arrest despite further chemotherapy and SMART. Non-functioning tumours: 1/2 patients experienced disease progression but neither have required further surgery.	both GH and IGF-1 levels without significant adverse effect. SMART provided a highly effective complementary therapy in treating cases refractory to surgery or conventional radiotherapy. No objective benefits were illustrated in other tumour types. *There was no formal testing of neurocognitive function following treatment although no adverse effects have been reported. No visual side-effects have been reported. Patient surveillance is ongoing. Very low patient numbers in all but*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		post-radiation DEX to reduce any risk of oedema.			*the acromegaly patient group.*		
(Marquardt *et al.* 2004).	104 consecutive patients (from 1999 to unknown) with 'pituitary lesions' had details collected prospectively concerning duration of (direct transnasal) surgery and major & minor complications. These data were compared with those collected retrospectively from 52 patients operated on from 1997 - 1999 using the sub-labial transsphenoidal approach. No patient data. Comparison of data was made using Student's t-test and chi square test for independent	To evaluate the benefits and efficacy of a minimally invasive direct transnasal approach to the sella turcica. Direct transnasal or sublabial transsphenoidal surgery to remove pituitary tumour.	Incidence of minor complications (nosebleed, facial swelling, bruised cheeks, raccoon eyes). Operative time.	Mean operative time of direct transnasal surgery was 62.9min compared with 113.1min (P<0.001) for sublabial approach. There were no major complications with either approach. Minor complications for sublabial cf transnasal surgery were respectively, nosebleed 6/52 cf 1/104 (P<0.01), facial swelling 5/52 cf 1/104 (P<0.05) and bruising 8/52 cf 1/104 (P<0.001). There was nsd in the occurrence of raccoon eyes.	The authors state that the transnasal and sublabial approaches are equally effective at exposing the pituitary fossa for successful tumour resection. They feel that that transnasal surgery is less disruptive to healthy tissue and so carries less likelihood of side-effects, is quicker and so reduces in-patients duration. Endoscopy is a useful adjunct to the operating microscope but has no advantages	Review/ retrospective case series.	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	samples. Germany				when used alone requiring as much manual dexterity, giving less depth of field and more likely to require cleaning whilst in situ. *This paper is more of a technical review than a case series containing little data with underpowered statistical analysis.*		
(Cho & Liau 2002)	Group A: 22 patients (all female) mean age 45.3yrs (range 22yrs - 60yrs). Group B: 22 patients (1 male and 21 female) mean age 46.7yrs (range 18yrs - 56yrs). No significant difference in the	To compare endoscopic surgery with microsurgery and evaluate both for safety & effectiveness using the treatment of prolactinoma for the study. Surgical removal of prolactinoma by	Comparison of pre- and post-operative PRL levels, relief of symptoms (restoration of menstrual cycle, relief of galactorrhoea), operative time and hospital stay and surgical complications between groups A	Mean follow-up was 3.5yrs (range 6/12 - 5yrs). Reduction of serum PRL (nsd between group A and B.) Group A: from 273ng dl-1 to 89ng dl-1 (P<0.001) 66% patients were returned to normal PRL values. Group B: from 256ng dl-1 to 75ng dl-1 (P,0.001) 75% patients were returned to normal PRL values. There was nsd between groups A and B in respect of relief of symptoms. Group A experienced a shorter mean operative time	Authors conclude that the use of the endoscope reduced the operative time by as much an hour and the in-patient stay by as much as 2 days. This was due to the less invasive nature of the procedure	Retrospective case series.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	number of microadenoma, macroadenoma frequency or degree of cavernous sinus, suprasellar or sphenoidal invasiveness between A and B. Statistics included Wilcoxon signed rank tests (symptom comparison), Student t-test (duration of stay in hospital and operation time) and Mann Whitney rank sum test (surgical complication). Taiwan	either endonasal endoscopic (Group A) or sublabial transsphenoidal microsurgery (Group B).	and B.	1.7h (range 1h - 3h) cf 2.7h (range 1.5h - 4h) and a shorter mean hospital stay 3.2days (range 2days - 5days) cf 5.3days (range 4days - 8days).Group A suffered significantly less surgical complications than Group B: 4.5% cf 27% patients.	requiring less post-surgical care e.g. wound packing. The procedures were equally effective at tumour removal and relief of symptoms but by reason of less side-effects and surgical complications, endoscopy would be a better experience for the patient.		
(Clayton & Wass 1998)	Adult patients with pituitary tumours.	Production of consensus statement on recommendations for service provision		RECOMMENDATIONS RELATING TO SPECIALIST CARE: Once diagnosis is suspected patients should be referred to a specialist centre. The specialist centre may be located across several sites.	*Usual limitations of consensus produced guidelines. No supporting evidence provided.*	Guidelines	4+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Surgery should be performed by surgeons specialising in pituitary surgery. Additional super-specialisation expertise and operative experience optimise outcome for patients with hormone-secreting adenoma. Outcome data are required to determine the minimum number of operations that should be performed annually by a single surgeon.	*College advises that recommendations still patent. No data on outcomes.*		
(Barker *et al.* 2003b)	5497 patients were identified from the US nationwide inpatient sample hospital database 1996-2000. This source contains information about inpatient admission and discharge from a stratified random sample of non-federal hospitals in the US. 538 of these hospitals and 825 surgeons treated the patients. The patients represented approximately 20% of the national caseload of transspheniodal pituitary tumour	Biopsy or resection of the pituitary using a transsphenoidal approach	In hospital mortality and discharge to institutions other than home.	In hospital mortality In a multivariate analysis, adjusting for case mix, mortality was lower at high case volume hospitals (OR for a 5 fold higher case load 0.54; 95% CI, 0.31-0.95; p = 0.03). There was a similar trend for high case volume surgeons (OR for a 5 fold higher case load 0.47; 95% CI, 0.20-1.1; p = 0.09). Discharge status Higher volume hospitals were associated with better status at discharge (OR for a 5 fold higher case load 0.74; 95% CI, 0.59-0.92; p = 0.007). This was also true for high case volume surgeons (OR for a 5 fold higher case load 0.62; 95% CI, 0.41-0.94; p = 0.02).	*In hospital mortality and discharge status are not independent outcomes.* *Short term outcomes only.*	Cohort	2++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	surgery. Inclusion criteria Patients admitted for biopsy or resection of the pituitary gland using the transspheniodal approach. Diagnosis coded as: benign, uncertain or malignant neoplasm of the pituitary; endocrine neoplasm of uncertain nature; acromegaly (6% of cohort) or Cushing's syndrome (7% of the cohort). Exclusion criteria Any other intrasellar lesions (such as craniopharyngiomas or Rathe's cleft cysts). USA						

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Ciric *et al.* 1997)	Questionnaires were posted to 3172 neurosurgeons. 1162 replied of whom 958 performed transsphenoidal surgery. 826 (86%) reported having performed less than 200 such operations. 88 (9%) reported performing between 200 and 500 operations and 27 (3%) reported performing more than 500 operations. USA	Transsphenoidal pituitary surgery	Neurosurgeon reported complications. 14 possible complications were listed on the survey. The percentage of operations resulting in any of the listed complications.	Complications 98% of the surgeons reported having witnessed at least one of the 14 listed complications. The most frequently seen complications were diabetes insipidus (78% of respondents), CSF fistula (62%), anterior pituitary insufficiency (59%) and nasal septum perforation (34%). 0.9% of surgeons witnessed death as a complication of transsphenoidal surgery. Effect of case volume Surgeons with more extensive experience were more likely to have seen the complications listed in the survey ($p<0.05$, chi squared test). The proportion of operations reported as resulting in complications was negatively correlated with case volume, for the 14 listed complications ($p<0.05$, Spearman correlation). The authors interpret the results as indicating greater surgical experience is associated with fewer complications in transsphenoidal pituitary surgery.	All the data are derived from surgeons' estimates. *Unclear how the authors decided the case volume categories (beforehand or data driven?).* *No casemix adjustment*	Cross sectional (survey)	3-
(Gittoes *et al.* 1999).	66 patients with acromegaly. Mean age at diagnosis was 47 years (SE years) and 45% were female. Macroadenomas (1cm or greater) were	Pituitary surgery for acromegaly. Surgery was performed either by one of a group of 8 surgeons (before 1990) or by a single pituitary surgeon (after 1990).	Cure rate (defined as basal growth hormone <5 mU/l or nadir growth hormone <2 mU/l across an oral glucose tolerance test). Post operative morbidity	Cure rates The cure rate during 1986-1989 (before sub-specialization) was 26/78 (33%). When one surgeon did all the operations (1990-1998) the cure rate was 42/66 (64%) ($p<0.001$, chi squared test). Post operative morbidity	*Possible confounders: the different time periods and the different surgical staff.*	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	identified in 44/66 (67%) of patients and microadenomas in the remaining 22/66 (33%). UK			8/66 (12%) patients were rendered hypopituitary as a result of curative surgery. 4/66 (6%) patients experienced permanent diabetes insipidus. 4/66 (6%) patients experienced a CSF leak, requiring further surgery. There was no perioperative mortality. Morbidity was not analysed pre and post sub-specialisation.			
(Lissett *et al.* 1998)	71 patients with acromegaly referred to one of 2 hospitals between 1974 and 1997. Mean age was 43 years (range 19 to 70). There were 51 macroadenomas (1cm or greater on CT or MRI scan) and 18 microadenomas. 4 patients did not have their tumour sized preoperatively. 9 surgeons operated during the course of the study: 3 between 1974 and 1979, 5 between 1980 and 1987 and 6 between	ITranssphenoidal surgery (71 patients) or transfrontal surgery (2 patients).	Cure rate (post operative GH levels <5mU/l during an oral glucose tolerance test).	Cure rate Overall cure rate was 13/73 patients (18%). For microadenomas it was 7/18 (40%) and for macroadenomas it was 6/51 (12%). Comparison with other series The authors reviewed literature about cure rates following pituitary surgery for acromegaly. The cure rate for this series is significantly lower than other published series. The authors suggest that the lack of a specialist pituitary surgeon explains the discrepancy in cure rate. A single surgeon performed the surgery in the studies reviewed, compared to the 9 surgeons in this study.	Series covers 2 decades. *Casemix not considered in detail.*	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	1988 and 1997. UK						
(Yamada *et al.* 1996)	61 patients with acromegaly treated surgically, at a single hospital 1969-1993. 22 other patients were excluded because follow up data were not available. Mean age was 42 years (range 22 to 65 years). 30 patients were operated in the period 1969 to 1986 and 31 from 1987 to 1993 (after MRI became available at the hospital). Median follow up was 6.4 years (range 0.8 to 18.6 years). Before 1987 operations were performed by a number of surgeons.	Transsphenoidal surgery (58 patients) or surgery using a unilateral sub frontal approach (3 patients).	Early post operative and long term GH level. Cure was defined as mean basal GH level <6mU/l and normal GH dynamics (suppression of GH to <2mU/l during the OGTT).	Postoperative cure rate Postoperative cure rate was 36/61 (59%). Cure rate was 11/30 (37%) before 1987 and 25/31 (81%) after 1987. Long term cure rate Long term cure rate (mean follow up 6.8 years; range 1 to 14.5 years) was 31/61 (51%). Prognostic factors for cure Univariate analysis showed post operative GH level <6 mU/l and normal GH dynamics to be significant predictors of long term cure. The investigators did multivariate analysis of the influence of sex, age, tumour grade and stage, cavernous sinus invasion, GH level, period of operation (pre or post 1987) on cure rate. The period of operation (RR 10.2; 95% CI, 1.9 to 54.0; p<0.01) and cavernous sinus invasion (RR 30.5; 95% CI, 5.0 to 183; p<0.001) were independent predictors of cure. Patients operated on in the period when a single surgeon was doing all the surgery had a significantly	Relatively number of excluded patients because of insufficient clinical data. If all of those excluded were not cured (worst case scenario) then the long term cure rate would be 37%. *There were important casemix differences between those treated pre and post specialization. Also, those treated post 1987 had MRI scans.*	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	After 1987 one surgeon performed all the operations. There were significant differences between the characteristics of the pre and post 1987 patients. Patients treated after 1987 were less likely to have suprasellar extension of the tumour, had lower preoperative GH levels and tended to be older than the pre 1987 patients. JAPAN			better outcome than those who were operated on when surgery was shared between a group of surgeons.			

Table 9.2 Management of patients with spinal cord tumours

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Raco *et al.* 2005).	202 patients who had surgical removal of intramedullary spinal cord tumour at a single neurosurgical centre between 1972 and 2003. Mean age was 42 years (range 8 to 72 years). Tumour types were astrocytoma (42%), ependymomas (34%), epidermiod tumours (5%), hemangioblastomas (4%), oligodendrogliomas (2%) and others (13%). Mean follow-up was 7.1 years (range 13 months to 15 years). ITALY	Surgical removal of intramedullary tumour through posterior median approach with a laminectomy (or laminotomy in children) or discontinuous myelotomy (20 patients). One patient was operated on via a transthoracic anterior approach.	Preoperative symptoms and their duration. Progression free survival, analysed by histological type and extent of resection. Adverse post operative outcomes: pain; impaired sensitivity; sphincter and sexual dysfunction; motor disorders and cord tethering	Presenting symptoms The duration of clinical symptoms ranged from 2 months to 20 years (mean 3 years). Presenting symptoms were: hyperaesthesia/paraesthesia (70%) motor disorders (20%) sphincter dysfunction (10%) 10 year progression free survival for patients with: Grade I astrocytomas: 87% Grade II astrocytomas: 30% Grade III or IV astrocytomas: 0% Ependymomas 72% Completeness of resection and outcome by tumour type Ependymomas: 55 (81%) were completely removed and 13 (19%) incompletely removed. In 66% of the patients (42 patients), the presenting signs and symptoms remained unchanged at long-term follow-up; in 25% (16 patients), they improved; and in 9% (6 patients), the clinical status worsened. Of the 27 Grade I astrocytomas, 22 (81%) were completely removed and 5 (19%) incompletely	Series spans 3 decades, patients after 1986 underwent MRI. Strong influence of grade on the outcome of patients with intramedullary astrocytoma.	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				removed. Functional assessment of the 23 patients available at "late" follow-up showed that 26% (6 of 23 patients) had improved, 9% (2 of 23 patients) had worsened, and 66% (15 of 23 patients) remained unchanged from preoperative status. Of the 41 Grade II astrocytomas, only 5 (12%) were completely removed, and 10% had improved. None of the 18 Grade III to IV astrocytomas could be completely removed. In 61% (11 of 18 patients), the postoperative functional status worsened. Adverse post operative outcomes: pain 80% impaired sensitivity 85% sphincter dysfunction 25% sexual dysfunction in male patients 5% cord tethering 17% motor disorders, post operative motor function was predicted by pre operative motor function. Patients with good preoperative function were more likely to have reasonable post operative motor functioning.			
(Parker *et al.* 1996).	13 children with intrinsic spinal cord tumour, were identified from the medical and	Diagnosis of intrinsic spinal tumour (on MRI). .	Referral delay (from presentation to district paediatric service to diagnosis at the regional	Referral delay The average delay was 12 months (range 1 week to 6 years). In only 3 out 13 cases was spinal tumour mentioned as a possibility on the referral letter.	Small study. Indirectly relevant - paediatric population.	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	radiological records of 2 neurosurgical units (1984 to 1995). Mean age was 5.4 years (8 months to 11 years). 6 had astrocytomas, 3 ependymomas and one each with PNET, harmartoma, neuroenteric cyst and ganglioglioma. UK		paediatric neurology unit). Presenting symptoms	Symptoms 77% had chronic back pain, 70% torticollis and 54% a change in gait. Outcomes 10/13 children were still alive at the time of analysis. 8 had a static neurological deficit; 6 of these could walk but with abnormal gait and 2 had spinal curvature but normal gait. Method of diagnosis MRI revealed the tumour in all 13 case. Spinal x-rays were taken in 6 cases in referring hospitals but only 1 was reported as abormal.			
(Jellema *et al.* 2005)	108 patients were identified from the records of a neurosurgical centre (1986 to 2000). Tumour types were: schwannoma (30%), ependymoma (23%), meningioma (14%), astrocytoma (11%), cyst (7%) and others (36%).	Diagnosis of primary spinal tumour. Diagnostic technique was: MRI (n=61), CT-myelography (n=36) or caudography(n=11).	Time to diagnosis (from the onset of symptoms to the date at which the tumour was detected on imaging). Presenting symptoms and symptoms at the time of diagnosis.	Time to diagnosis The median time to diagnosis was 12.3 months. Time to diagnosis was greater than 2 years in 33% of patients Initial symptoms Symptom frequency: back pain 42% pain in legs 35% paresis 15% walking disturbance 14%	Authors comment that the delay in diagnosis is probably due to the initially non-specific signs and symptoms and the slow progression of the neurologic deficits. There is no	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Inclusion criteria Histologically proven primary intraspinal tumour. Exclusion criteria Extraspinal malignancy or neurofibromatosis; insufficient clinical data (9 patients) NETHERLANDS			sensory disturbances 5% Symptoms at diagnosis Symptom frequency: back pain 36% pain in legs 30% paresis 26% walking disturbance 14% sensory disturbances 23% sphincter dysfunction 20% paraparesis 12% erectile dysfunction 3% The range of symptoms increased during the diagnostic delay, some patients deteriorated considerably. Misdaignoses given included: disc herniation (12%); multiple sclerosis (3%); polyneuropathy (3%) and orthopaedic diagnoses (5%).	comparison between the symptom progression in delayed patients and non-delayed patients.		
(Isaacson 2000)	Studies of patients with intramedullary spinal cord tumours who received post operative radiotherapy (1980 to 1998). 11 studies	Post operative radiotherapy intramedullary spinal cord tumours	Local control, 5 and 10 year overall survival (2 year survival for high grade astrocytoma).	Ependymoma 5 year survival ranged from 60 to 100% 10 year survival ranged from 60 to 100% Local failure rate ranged from 0 to 38% Author comments that there does not appear to be a dose response relationship with local failure in the 40 to	Review of non comparative studies. Little evidence to support the author's conclusions.	Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	reported outcomes in patients with ependymoma, 6 in those with low grade astrocytoma and 7 in those with high grade astrocytoma. Individual studies tended to be small ranging from 1 to 59 cases; most included less than 20 cases.			54 Gy range. Low grade astrocytoma 5 year survival ranged from 60 to 90% 10 year survival ranged from 50 to 100% Local failure rate ranged from 1 to 56% Author comments that there does not appear to be better local control or survival in doses higher than 50.4 Gy. High grade astrocytoma Very few patients survived more than 2 years. Author comments that CSF dissemination appears to occur despite radiation of the primary site. Author concludes that there is a role for post operative radiotherapy in patients with low grade incompletely resected astrocytomas, or piecemeal resected low grade ependymomas. Also in all high grade astrocytomas and ependymomas, and in multi-focal low grade ependymoma.			
(Balmaceda 2000)	Studies of patients with intramedullary spinal cord tumours who received post operative chemotherapy (1976	Chemotherapy for intramedullary spinal cord tumours.	Response to chemotherapy.	Case series reported responses to chemotherapy (diverse protocols) in astrocytomas and ependymomas, but there was insufficient evidence to draw any overall conclusions. The author concludes that given the rarity of these	Review of small non comparative studies. Mostly paediatric patients (limited relevance).	Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	to 1998). 2 studies reported outcomes in patients with ependymoma, 7 in those with astrocytoma, 4 in those with intramedullary metastases and 2 in those with germ cell tumours. Individual studies tended to be very small ranging from 1 to 13 cases; many were individual case reports. The majority of studies were of children with spinal cord tumours.			tumours it is unlikely that a case series from a single institution will have sufficient power to draw any meaningful conclusions. Multi-centre trials needed.			

Table 9.3 Management of patients with skull base tumours

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Pollock 2003).	310 patients having stereotactic radiosurgery for meningioma, identified from the clinical database of a single institution between 1990 and 2002. Median age was 57 years (range 20 to 90 years). 42% had recurrent or residual tumours following surgery and 58% had radiosurgery as their primary treatment. 9.4% of patients had atypical or malignant tumours. The majority of tumours were at the skull base. USA	Stereotactic radiosurgery (single fraction high dose), performed using the Leskell Gamma Knife (using the model U before 1997 thereafter the model B). Dose planning was based on stereotactic MRI, or CT if MRI was contraindicated. Multishot dose plans were used, the median number of isocenters was 10 (range1 to 25). Dose prescription was based on tumour size, location and history of radiotherapy.	Tumour control, overall survival, complications of treatment. Follow-up evaluation and MRI were performed at 6, 12, 24 and 48 months thereafter biannually.	Tumour control Follow up data were available for 267 patients with benign tumours. 98% were either smaller or unchanged after radiosurgery. 2% showed disease progression Follow up data were available for 30 patients with atypical or malignant tumours. 60% were either smaller or unchanged after radiosurgery. 40% showed disease progression 5 year overall survival For the entire group 5 year overall survival was 82%. Disease specific 5 year overall survival was 94%. The disease specific 5 year overall survival rates for patients with benign, atypcial and malignant tumours were 100%, 76% and 0% respectively. Complications 8.4% of patients developed treatment related complications. These included cranial nerve deficits, parenchymal oedema, internal carotid artery stenosis and delayed cyst formation.	*The majority of patients had skull base tumours.*	Retrospectiv e case series	3+
(Barker *et al.* 2003a)	2643 admissions for acoustic neuroma (vestibular	Surgical excision of acoustic neuroma.	In hospital mortality and discharge to institutions other than	In hospital mortality The investigators did a limited analysis of in hospital	*Sample was too small to use in-hospital mortality*	Cohort	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	schwannoma) were identified from the US nationwide inpatient sample hospital database 1996-2000. This source contains information about inpatient admission and discharge from a stratified random sample of non-federal hospitals in the US. 265 of these hospitals and 352 surgeons treated the patients. Inclusion criteria Admission for excision of acoustic neuroma in patients with a primary diagnosis of benign neoplasm of cranial nerve. The database did not record the surgical approaches for excision.		home.	mortality, because there were only 13 deaths. In a multivariate analysis, they report trends toward lower mortality with larger hospital caseload (p=0.13) and surgeon caseload (p=0.06). Discharge status Higher volume hospitals were associated with better status at discharge (OR for a 5 fold higher case load 0.47; 95% CI, 0.37-0.58; p <0.001). This was also true for high case volume surgeons (OR for a 5 fold higher case load 0.46; 95% CI, 0.31-0.67; p <0.001).	*as a primary outcome.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	USA						
(Chuang *et al.* 2004)	43 patients with Skull Base meningiomas, 14 patients received SRS only and 29 patients had surgery and SRS	29 pateints had surgery and SRS received a target dose of16Gy, median number of isocenter of 4, median target volume of 5.2cc. 14 patients who received SRS only received a target dose of18Gy, median number of isocenter of 3, median target volume of 9.8cc.	7 year overall and disease free survival rate and local tumor control.	As a complete group (n=43), the 7 year overall survival rate = 80.2% and 7 year disease free survival = 78.9% The 7 year local tumor control rate for SRS group was 100% and for the SRS+surgery it was 84% (p=0.21). There was no statistical siginificance in local control for the two groups of the study. Clinical and treatment variables were determined by univariate analysis (incl: age, sex, history or prior resection, timeinterval b/n diagnosis and SRS, SRS target volume and SRS target dose), no prognostic factor was stat sig wrtlocal control. WRT Adverse events: For the group that received surgery and SRS, a number of cranial neuropathies were observed after surgery and after SRS. In this group, most neuropathies were unchanged with treatments. Some improvements were recorded without deterioration in 11 of 29 patients. For the group that received SRS only, 11 out 14 remained stable or had improved neurological status without deterioration.	The nature of the study design was questionable. The prospective design claimed by the researcher was not clearly described. From the paper, patients were recruited as they required treatment. Therefore some patients had already received surgery and some had not. They were not randomly allocated to surgery + SRS or SRS only. The prospective followup occurred once patients received SRS treatment. A true propective study would have admintered both	2-	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					surgery+SRS or SRS only to patients at the same time. No comparable surgery only group was included.		
(Gil *et al.* 2004)	The study included 35 patients who had been surgically treated for more than 3 months before the study was begun.	Relevant QOL questions were generated from a review of the literature and interviews with health professionals, patients, and their caregivers. Six relevant domains were identified using factor analysis: performance, physical function, vitality, pain, specific symptoms, and influence on emotions. The internal consistency of the instrument had a correlation coefficient of 0.8 and	The validity of the construct was assessed by testing whether the clinical variable of the patient influenced his QOL domain score as hypothesized.	Patients older than 60 years of age had significantly poorer scores in the domains of performance and physical function than younger patients. Patients with malignant tumors had significantly poorer scores in the domains of specific symptoms, influence on emotions, physical function, and performance compared with patients with benign tumors. Radiotherapy was associated with poorer scores in the domains of specific symptoms and influence on emotions. Comorbidity was associated with poor physical function scores. Using the final questionnaire, we prospectively evaluated the QOL of 12 additional patients before they underwent surgery and again between 5 and 6 months postoperatively to test the utility and validity of the instrument further. Again, significantly poorer QOL scores were recorded for patients with malignancy.	Author's Conclusions. The proposed questionnaire appears to be sufficiently reliable and valid in estimating a patient's QOL after extirpation of anterior skull base tumours. The instrument can be used in face-to-face interviews and via electronic or regular mail. Reviewer's comment: Because no comparison groups or comparison	cross sectional survey	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		a reliability coefficient (test-retest reliability) of 0.9.			questionnaires were measured it is difficult to judge whether this questionnaire accurately measures QOL for these patients.		
(Pinheiro *et al.* 2003)	34 patients with squamous cell carcinoma (SCCA) and 10 patients with non-SCCA	Most patients had been previously treated with combinations of surgery, external beam radiotherapy, and chemotherapy. The most frequent sites treated were the skull base (56%) and the neck (44%). IORT was delivered in a dedicated operating room suite with energies of 6 to 15 MeV (6 MeV most commonly used) at doses of 12.5 to 22.5 Gy.	overall and disease-free survival, tumour control rates	At 2 years overall and disease-free survival was 32% and 21%, respectively, for the SCCA patients and 50% and 40%, respectively, for the non-SCCA patients. Tumor control rates at 2 years in the IORT field were 46% for the SCCA patients and 52% for the non-SCCA patients. For squamous cell histology, survival in patients with microscopic residual tumor did not differ from those with no residual tumor, but they both had significantly longer disease-free survival than those patients with gross residual at the time of IORT (p =.03), with a trend toward longer overall survival (p =.09). The only complication directly attributable to IORT was a neuropathy in a patient who received an IORT dose of 22.5 Gy (cumulative dose 130.1 Gy).	Author's comments: IORT at a dose of 12.5 Gy is safe and produces tumor control and survival for patients likely to have microscopic residual disease in sites difficult to resect such as the skull base. Reviewer's comment: due to the study design this study is unable to make comparisons with a well designed control group (patients who did	a prospective non-randomised clinical trial	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					not receive IORT)		
(Kaylie *et al.* 2000)	The review included 2579 patients who underwent surgery between 1970 and 1998; mean age 48.8 years; 56% of tumours were small (<2 cm), 33% were medium sized (between 2 and 4 cm) and 11% were large (> 4cm). The review also included 875 patients who underwent gamma knife radiosurgery between 1969 and 1997; mean age 56 years; mean tumour size was 1.61 cm. Mean follow up was 24 months for surgery and 25 months for gamma knife radiosurgery.	Comparison of 2 different treatments using data from case series. Surgery (sub occipital/ retro sigmoid approach in 58%; Tran labyrinthine used in 34%; middle fossa in 7%; combined in 1%) compared with gamma knife radiosurgery. Average total radiation dose was 37.4 Gy with and an average peripheral dose of 17.27 Gy and central dose of 37.6 Gy	Hearing outcomes, Facial function, Complications, Tumour control after surgery.	Hearing outcomes assessed using Gardener-Robertson scale Facial function assessed using the House-Brackman scale (grade I or II was classified as good outcome) Complications Tumour control after surgery (defined as no tumour recurrence after complete resection and no growth after partial resection) and tumour control after gamma knife radiosurgery (defined as no tumour growth). Facial nerve outcomes: There was no significant difference between treatments in the proportion of patients with a good outcome (967/1192[81.1%] with surgery v 582/717[81.2%] with radiosurgery, P = 0.23). Radiosurgery results included patients with NF2 and those who had previous treatment. Hearing outcomes: There was no significant difference between treatments in the rate of serviceable hearing preservation (599/1420[42%] had pre-operative serviceable hearing and 256/599[44%] retained service with surgery versus 219/552[40%] with 96/219[44%] retained service with radiosurgery, p = 0.82).	The authors concluded that surgery had a lower complication rate than gamma knife radiosurgery but results reflect historical data. Results from more recent studies are required to assess the current complication rate. No details were reported of the methods used to select studies or extract data. Search limited to one database. Heterogeneity among studies was not assessed or discussed. Patients from 1960s onwards were included and may	Meta-analysis	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Complications: none of the studies reported results by tumour size. Complications were significantly lower after surgery than radiosurgery (22% v 38%, p < 0.0001) Tumour control: Tumour control was significantly better after surgery than radiosurgery (uncontrolled tumour rates were 2% with surgery v 9% with radiosurgery, p < 0001)	not be representative of the current situation as acknowledged by the authors. There was no exploration of the effect of year of surgery on outcomes. Comparisons were made between case series and so any conclusions are suggestive and not definitive. Some exploration of the effect of publication date or date of surgery on outcomes would have been helpful		
Management of benign skull base meningiomas: a review. Mendenhall	Patients with skull base meningiomas	Surgery, radio-surgery and radiotherapy in terms of Local control, survival and complications.	Efficacy of treatment is measured by local control and complications. Survival is of interest but it must be noted that death due to	**<u>Local control</u>:** **Surgery:** 338 patients (98% benign) with skull base meningiomas followed for ≥10yrs. No patient with Simpson grade IV or V resection who had follow up for more that 20yrs was free of symptomatic disease free progression. Local recurrence was highest in patients with central	No details about the literature search are reported.	Narrative review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
,W.M.; Friedman, W.A.; Amdur,R.J.; Foote,K.D. Skull Base 2004 Feb;14(1):53-60			benign tumours is secondary.	skull base tumours. In 119 patients with skull base tumours, mean follow-up of 34months, gross total resection was achieved in 61% (72% for tumour diameter ≤ 3cm and 58% for tumour size ≥3cm). No relationship was found b/n likelihood of gross total resection and whether the patient had received prior treatment. 5yr local control rate = 81% after complete resection Vs 62% after subtotal resection. For petroclival meningiomas studies have shown, a diversity of results ranging from post-op death, low level of disease progression and generally improvement in in karnofsky score. Numbers in these studies are very low. **Summary**: After surgery, the progression free survival decreases with longer follow up. **Radiosurgery**: 206 menengiomas were treated with gamma-knife radiosurgery. 5 year local control rate for benign tumours was 93% 62 patients with petro-clivival meningiomas who had gamma-knife radiosurgery, local control rate at 96 months was 92% for of 54 patients with benign tumours who has received prior radiotherapy. 176 patients with cavernous sinus meningiomas treated with gamma-knife radiosurgery, followed for a mean of 35 months, 10 year control rate for benign tumours = 93%.			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Out of 155 meningiomas treated with LINAC radio surgery who were followed for 1.2 - 79.8 months, approx 50% were skull base and 68% were benign. 5 year local control rate for benign tumours = 89%. Out of 76 benign tumours (45% skull base) treated with LINAC radiosurgery, mean follow-up of 23 months, local control rate for benign tumours = 100%. **Summary**: local control after radiosurgery (gamma-knife radiosurgery or LINAC radiosurgery) was greater than or equal to 90%. **Radiotherapy**: 189 patients (82% skull base) treated with stereotactic radiotherapy (SRS), followed for median of 35 months, average dose = 56.8Gy, median fraction size = 1.8GY. 45% of patients experienced neurological improvement. Local control obtained in 98% of 180 patients with WHO grade 1 tumours. 82 patients with skull base meningiomas, treated with radiotherapy. Doses = 55-60Gy in 33 fractions. 10 progression free survival rate = 83%. 31 patients with skull base meningiomas, treated with radiotherapy. Doses = 50-65 Gy at median dose per fraction of 1.9 GY. Median follow-up = 6.1 yrs, 10 progression free survival rate =93%. 46 patients (92% with skull base meningiomas), treated with proton and photon radiotherapy, dose range 53.1-74.1 cobalt gray equivalent (CGE) delivered at 1.8-1.9 CGE per fraction. 10 year progression free survival rate			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				= 88%. 40 patients with benign (80% skull base) meningiomas treated with intensity modulated radiotherapy (IMRT). Median follow up= 30 months, median dose = 50.5Gy at 1.7-2 Gy per fraction. 5 year local control rate=93%. 54 patients with benign skull base meningiomas treated with radiotherapy, median follow up= 55 month, 5 year progression free survival rate =93% (tumours smaller than 5cm compared to 40% for tumours 5cm or larger ($p < 0.0001$). Overall, 5 year progression free survival rate = 76%. 117 patients with benign skull base meningiomas treated with radiotherapy, median dose 54Gy. 5 and 10 yr progression free survival rate = 89% and 77% respectively. Progression free survival rate was found not to be related to tumour size. Progression free survival rate was better when CT or MRI was available to define the extent of the tumour and for patients who received doses > 52Gy (p=0.04). **Summary**: local control rate after radiotherapy for 5 or 10 year progression free survival ranged from 70-98%. Doses range from 50-55Gy, median dose per fraction1.7-1.8Gy. **Survival:** **Surgery**: 315 patients, 10 year survival rate = 79% approx. Survival rates after surgery alone compared to surgery+radiotherapy: 10 yrs= 42% VS 77% ($p \leq 0.05$)			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				and 20yrs = 18% VS 38%(not statistically sig.) 262 patients (60% skull base), surgery alone, surgery+post op radiotherapy, radiotherapy alone and radiosurgery: 15 yr cause specific survival rates: 88% subtotal resection, 86% radiotherapy, 51% subtotal resection alone (p=0.0003) **Radiosurgery**: Survival data is rare. 178 patients treated at Mayo Clinic, 5 yr cause specific survival rate= 100%. **Radiotherapy**: 180 patients (WHO grade 1 meningiomas) treated with SR-radiotherapy, 5 yr overall survival rate=97%, 10 yr overall survival rate = 96%. For benign skull base tumours 71% overall survival rate. **<u>Complications:</u>** **Surgery**: 29 patients with cavernous sinus meningiomas. 17% complete resection. 14% Oculometer nerve function deteriorated. New cranial nerve deficits included: trochlear, ophthalmic, maxillary, mandibular and abducens. No death during surgery. 39 patients with cavernous sinus meningiomas.20% complete resection. cranial nerve deficits assessed after 6 months, New cranial nerve deficits observed, Oculomotor nerve function deteriorated. No post op			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				deaths. 119 skull base meningiomas patients, 61% complete resection. Complications: 21% cerebrospinal fluid leakage, 14% pituitary dysfunction, cerebrvascular accident, infection, brain haematoma. 69% Petroclival meningiomas, 69% complete resection, 4 post-op deaths due to complications. 33% with permanent cranial neuropathies. 41 patients with benign meningiomas of the cavernous sinus. 76% complete resection. 18% with new cranial nerve deficits. 7% died post op. 33 petroclival meningiomas, 79% complete resection76% with new cranial nerve deficits, 6% worsening pre-existing deficits. 9% died post-op. **Radiosurgery**: Reported complications include severe symptoms, new or persistent cranial nerve deficits. Severe symptoms include death, unilateral blindness and deafness, hemiparesis and leg weakness. Other new or persistent cranial nerve deficits include symptomatic parenchymal changes, internal carotid artery stenosis, symptomatic cyst formation, decreased functional status, visual deteriation, trigeminal nerve dysfunction, medically controlled partial complex seizures and cognitive deterioration. **Radiotherapy**: Reported complications include severe and moderate symptoms. These included diminished vision,			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				decreased short term memory, development of hypopituitarism. Patients treated with IMRT experienced significant toxicity including memory loss, personality changes and fatal brainstem necrosis. SR-radiotherapy initiated significant late toxicity. **Summary**: Probability of complete resection depends on the location and extent of tumour. All treatment offers some complications. Complications range from severe to moderate neurological deficits.			
(Nikolopoulos & O'Donoghue 2002).	Literature review (1977-2000) of papers reporting outcomes after vestibular schwannoma management.	Evidence for optimum method of management to improve outconmes.	Management methods producing improved outcomes.	111 articles were identified, 78 concerned surgery, 20 radiosurgery, 9 radiological surveillance and 4 different methods of management.. The evidence supporting the various management strategies was low (Type III or Type IV). Well designed comparisons (RCTs) between treatment methods do not exist and therefore definite conclusions cannot be made.	*Good description of methods. Well designed study. The outcomes measured were varied.*	Literature review	4
(Schulz-Ertner *et al.* 2004)	152 patients with skull base tumors and spinal/sacral chordomas and chondrosarcomas	Eighty-seven patients with chordomas and low-grade chondrosarcomas of the skull base received carbon ion RT alone (median dose 60 GyE); 21 patients with unfavorable adenoid cystic carcinomas	Actuarial 3-year local control rate, toxicity effects.	Actuarial 3-year local control was 81% for chordomas, 100% for chondrosarcomas, and 62% for adenoid cystic carcinomas. Local control was obtained in 15/17 patients with spinal (8/9) and sacral (7/8) chordomas or chondrosarcomas and in 11/15 patients with skull base tumors other than chordomas and low-grade chondrosarcomas, respectively. Six of 12 patients who received re-irradiation are still alive without signs of tumor progression. Common Toxicity Criteria Grade 4 or Grade 5 toxicity was not observed.	Author's conclusion: Carbon ion therapy is safe with respect to toxicity and offers high local control rates for skull base tumors such as chordomas, low-grade chondrosarcomas,	Case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		and 17 patients with spinal (n = 9) and sacrococcygeal (n = 8) chordomas and chondrosarcomas were treated with combined photon and carbon ion RT. Twelve patients received reirradiation with carbon ions with or without photon RT for recurrent tumors. Furthermore, 15 patients with skull base tumors other than chordoma and low-grade chondrosarcoma were treated with carbon ions			and unfavorable adenoid cystic carcinomas. Reviewers' remarks: This study of Raster Scanned carbon ion radiation therapy indicated high local control rates with relatively low toxicity compared with photon and proton RT. The study results offer a possible alternative treatment to the current stanard care of proton RT for patients with chordaomas and chrondrosarcomas of the skull base. The study showed optimal prescription dose wrt effectiveness and avoidance of radioation-induced		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					side-effects could be acheived by using a total target dose of 60GyE delivered within 20 days. Reviewer comments: There are no 95% CIs for these estimates. They report the median follow up which reflects the early reporting at 3 years. Since they plot graphs for locoregional control and survival, each of these have 'events' of interest i.e. recurrence/progression and death, respectively. They do not compare survival between tumour types, nor between treatments, so		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					there was no log rank test (for example) nor any p values. Although the sample size overall is 152, the sub groups are much smaller and maybe this prevented meaningful hypothesis testing. The authors use a lot of narrative to describe findings.		
(Shin *et al.* 2003)	Conservative management: Patients with acoustic neuroma treated at the author's institution. Gamma knife surgery: Studies included had to report gamma-knife surgery for the treatment of acoustic neuroma (and fit other specified inclusion criteria)	A review of the literature dealing with radiosurgery for acoustic neuromas and compared the rate of neurotological complications in this population with that in a cohort of patients managed conservatively.	Neurotological complications: • facial hypoesthesia • hearing loss • hydrocephalus • rate of stability of the tumour.	The review reported that neurotological complications, namely facial hypoesthesia ($p = 0.002$), hearing loss ($p < 0.05$) and hydrocephalus ($p = 0.02$), were more frequently encountered after radiosurgery than with conservative management. In comparison, the risk of growth of AN is significantly higher with conservative management and that the rate of stability of the tumour did not differ significantly between the two treatments.	Author's comments: We prefer a conservative management regimen for patients who cannot be operated on for their AN. However, there are some difficulties inherent in this conservative management	Systematic review	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					policy, namely non-compliance and difficulties in establishing the evolution of the tumour. Reviewer's comment: It is important to highlight the lack of consistency in reporting tumour growth. Authors point out that because of the lack of standardisation in the criteria that reports tumour growth several valuable publications were not included in the review. It has been shown that 3D measurement indicates more accurate measurements; unfortunately this has not been		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					conducted in studies included in the review. Therefore there maybe discrepancies in the assessment of the two interventions wrt effects on tumour growth. Non-compliance will also influence results with some patients not attending follow-up sessions which report the effects of conservative management. In order to accurately measure treatment effects a prospective study design is required.		
(Lanzino *et al.* 2001)	Patients with skull base chordomas	The following management options were reviewed:	To provide an overview of characteristics of	Cranial base chordomas are locally invasive tumours that, from a midline, clival location, extend in different directions and display various patterns of skull base	This paper presents a review of management	Narrative review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		surgical approaches and radiation therapy (conventional RT, proton beam RT, radiosurgery and interstitual brachytherapy). Patient outcomes was considered	skull base chordomas, including imaging characteristics. As well as to summarise characteristics of surgical procedures such as radical or conservative resection, radiation therapy, and patient outcomes.	invasion. Although histologically benign, their invasive nature makes true "oncological" resection virtually impossible to achieve in most cases, despite modern skull base surgical techniques. Moreover, because of the tumour's location and proximity to critical neural and vascular structure, surgery related morbidity can be significant when an aggressive resection is undertaken. Cytro-reductive surgery assumes a critical role in the management of these lesions. The choice of surgical approach and the extent of resection are dependent on several factors: location and extension of the tumour, the surgeon's philosophy and familiarity with a specific approach, and the patient's pre-existing clinical status. Proton-beam radiotherapy seems to be effective as an adjunct to surgery in achieving local tumour control. The timing of radiation therapy, however, remains controversial. Gamma knife surgery has been proposed as an adjunctive therapy, but the limited experience and short follow-up periods do not permit formulation of meaningful conclusions at this time. Recurrences are common, although in a subset of patients prolonged disease-free survival is demonstrated.	issues for skull base chordomas and considers patient outcomes. No intervention is evaluated in an empirical method, only expert opinion is presented. The review did not follow a systematic approach and no search strategy is reported for the identification of evidence.		
(Slattery *et al.* 2004)	1213 patients with acoustic neuroma (vestibular schwannoma) were identified from the Californian hospital	Surgery for acoustic neuroma.	Discharge status (home or not), surgical complications (indicated by certain medical procedures	4 categories of hospital surgical case volume were defined: 1) 1 to 5 cases per year (49 hospitals), 2) 6 to 11 cases per year (7 hospitals), 3) 15 to 50 cases per year (4 hospitals)	*Statistical method is inadquate: no adjustment for case mix. The authors suggest that patients at the*	Cohort	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	discharge database (1996 to 1998). 70% of the patients presented without a comorbid condition. Inclusion criteria Patients with acoustic neuroma (vestibular schwannoma) coded as their primary diagnosis and with (elective) acoustic neuroma surgery coded as their primary procedure. Exclusion criteria Patients admitted from a residential facitilty, long-term or acute care; newborn babies; emergency admissions and procedures not performed on the day of admission.		recorded in the database), length of stay and costs of hospitalization.	4) 185 cases per year (1 hospital). On univariate analysis, the chance of a routine discharge home was significantly better in the group 4 (high volume) hospital (97%) than in group 1 to 3 hospitals (71%, 86% and 92% respectively). The average lengths of stay in hospital groups 1 to 4 were 5.5, 5.9, 4.4 and 6 days respectively (no significant difference). The average costs per day in hospital groups 1 to 4 were $7312, $8524, $6606 and $4332 respectively. The cost for the high volume hospital was significantly lower than for the other hospital groups (Mann Whitney test, $p<0.01$).	*lower volume hospitals tended to have more comorbidty, which confounds the results.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	USA						
(Smouha *et al.* 2005).	Any relevant study that reported the conservative treatment of patients with acoustic neuromas.	Selection criteria for conservative management, duration and frequency of follow-up, patient demographics, initial tumour size and rate of growth, change in hearing status, and the need for definitive treatment was used.	Long term results of conservative management, with respect to tumour growth, hearing preservation and the need for definitive treatment. A set of predicitive factors for tumour growth to better define those patients best suited to conservative management.	A total of 21 studies comprising 1,345 patients were included in our meta-analysis. The average length of follow-up these studies was 3.2 years. The average initial tumor size was 11.8 mm (n = 900); 43% of 1,244 acoustic neuromas showed growth, whereas 57% showed either no growth or tumor regression. The average growth rate was 1.9 mm/year in 793 individuals. Hearing loss occurred in 51% of 347 individuals. In 15 studies, 20.0% of 1,001 individuals eventually failed conservative management.	Author's comments: Our meta-analysis supports the role of conservative management of acoustic neuromas in properly selected patients on the basis of a slow overall rate of growth and a substantial incidence of no growth. However, the lack of predictive factors, the relatively short duration of follow-up, and the variability of inclusion criteria underscore the need for continued collection of long-term data. Reviewer's comments:	Meta-analysis	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					This meta-analysis presented important evidence about the factors that affect patients who are managed with conservative management for acoustic neuromas. It does not provide any statistics for predictive factors and tests of significance. As the authors point out, predictive factors are difficult to identify especially when not all studies reported include this in the analysis. A high attrition rate was reported in this study wrt conservative management. Lost to follow-up was not consistently		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
					reported for the other cited literature. Non-compliance with conservative management will be ineffective without regular clinical and radiological follow-up.		
(Villavicencio *et al.* 2001)	56 patients with sypmtomatic, growing or recurrent skull base meningiomas. Age: 20-86 years, median 58 years. 36 patients had at least one prior surgical procedure, 7 patients had received 40 to 60 Gy of fractionated EBRT prior to radiosurgery. 4 of these patients had received RT for thesame tumor. The most common site of the tumor was	All patients underwent CT and MRI to locate and measure tumour size and position. High speed computer imaging integrated dose plans were performed to determine appropriate 3D isodose configurations and aided dose selection. Mean dose delivered to the tumour margin was 15Gys, dose range was 9 -18.5Gy.	Follow-up data (actuarial freedom from progression rate - defined as further tumour growth. Immediate and long term clinical responses. Acute complications. Early adverse effects Long term complications	Follow-up: The actuarial freedom from progression rate (defined as further tumour growth) was 95% 27% had follow-up (f/u) imaging 6-12 months after radiosurgery, all had decreased or stable tumour volumes. 21% had 12-24 months f/u, 33% had decreased tumour volume, 67% had unchanged tumour volume. 52% had imaging f/u greater than 24mnths. 90% had decreased or unchanged tumour vol. 3 patients had tumours which were increased in size. Clinical Response: Immediate and long term clinical status of patients was reported (median length=28months). 49% had unchanged symptoms after 24hours after surgery. Long term effects showed improvements for 34% of patients and 57% had unchanged clinical symptoms.		Case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	the cavernous sinus (20%), tentorial (18%), Meckel's cave (18%). 50% of patients had tumor size of 2-3cm, 60.4mm3	Multiple isocenters were used when required to increase conformality of dose. Follow-up was done using gadolinium - enhanced CT or MRI for post-op radiological evaluation in all patients. the median follow-up interval for patients was 26 months (range 6-66 months)		Acute complications: Early adverse effects = transient nausea, vomiting or headaches. Long term complications: no deaths were directly related to radiosurgery. 5% of patients experienced long term complications.			
(Yamakami *et al.* 2003)	Data from 903 patients with conservative management, 1475 with GK radiosurgery, and 5005 with microsurgery from 38 studies	Treatments that were reviewed included conservative management, gamma-knife (GK) radiosurgery, and microsurgery. Inclusion criteria for literature: population of patients ≥ 20 with unilateral acoustic neuroma who underwent conservative	Outcomes of interest included: facial function, hearing and speech effects	Conservative management over a 3.1-year period showed that 51% of acoustic neuromas showed a tumour growth, an average tumour growth rate was 1.87 mm year-1, 20% of acoustic neuromas ultimately required surgical intervention, and a third of the patients lost useful hearing. The majority of acoustic neuromas grow slowly, but ultimately require intervention. Carrying the risk of hearing loss, conservative management should be supplemented with close follow-up. Gamma knife radiosurgery significantly reduced the percentage of acoustic neuromas that enlarged, to 8%, and reduced the percentage that underwent	Reviewer's comments: Only Medline was used to search for literature, limiting the retrieval of relevant studies. Negative results are less commonly reported or published. Follow-up period for conservative management and	Systematic review	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		management with radiological follow-up, a mean follow-up period ≥2 years and a study not including recurrent tumours or tumours treated previously. 13 studies were selected.		microsurgery to 4.6% over a 3.8-year period. With a low rate of morbidity, GK radiosurgery suppresses tumour growth and provides good tumour control. Microsurgery removed 96% of acoustic neuromas totally, with tumour recurrence, mortality, and major disability rates of 1.8%, 0.63%, and 2.9%, respectively. Microsurgery provides the best tumour control, although mortality and morbidity are not completely eliminated. Surgeon's operative experience was important in micro-surgery. It was reported that surgeon's experience has some affect on postoperative facial function outcome in the first 20-60 patients, however, no significant relationship was found between size of population and the surgical outcome.	gamma knife may need to be longer for acoustic neuroma, but it is consistent with the follow-up time reported in other reviews of conservative management. Author's comments: Only MEDLINE was searched.		

Chapter 10 Management of patients with primary CNS lymphoma, medulloblastoma, pineal tumours or optic glioma

The questions

What services are required for the management of patients with:

a) primary CNS lymphoma

b) medulloblastoma

c) pineal tumours

d) optic glioma

The nature of the evidence

a) Patients with primary CNS lymphoma

The reference database comprises one systematic review (2003), one RCT (2000), one retrospective cohort study (2004), eight prospective case series (1996-2003), two retrospective case series (2004-2005) and three reviews (2000-2003).

b) Patients with medulloblastoma

There was limited evidence from adult populations: most studies were concerned with paediatric medulloblastoma. Evidence included three institutional case series of adults with medulloblastoma (from Italy, Turkey and the USA), one population based case series of children with medulloblastoma and one observational study of children enrolled in medulloblastoma clinical trials (both from the USA).

c) Patients with pineal tumours

Evidence was limited to retrospective case series discussing clinical presentation, diagnosis and surgical procedures.

d) Patients with optic tract glioma

Evidence was limited to case series and a literature review of high grade adult optic glioma. Most of the literature identified in the search related to the more

benign form of the disease associated with childhood onset and neurofibromatosis.

Summary of the supporting evidence for the recommendations

a) Patients with primary CNS lymphoma

Authors agree that high dose methotrexate is the chemotherapy drug of choice, although the dose is yet to be optimized, and it appears to be no more effective when combined with other drugs than when given alone, prior to radiotherapy and/or cytarabine. Since WBRT proves so toxic in older patients it has been suggested that it be withheld in cases where a patient responds well to chemotherapy or is reserved for treatment of relapse. Again, the effective dose of WBRT is yet to be determined and in elderly patients may represent a trade-off between the risk of relapse and the strong probability of disabling delayed neurotoxicity.

Evidence in support of the recommendations

- **Rituximab and temozolamide**. Wong *et al* (2004) anticipated that treatment with the anti-CD20 monoclonal antibody rituximab predisposed activated B-cells to be sensitive to the cytotoxic effects of the alkylating agent temozolomide. Both drugs are able to penetrate the BBB and are non-toxic to the kidneys. Nonetheless, in the small sample group (n=7), general myelosuppression or reduction in white blood cells or platelets caused problems in three patients. The overall survival in this elderly and heavily pre-treated group was eight months.

- **CHOD (cyclophosphamide, doxorubicin, vincristine, & dexamethasone) and BVAM (carmustine, vincristine, cytarabine, & methotrexate).** Bessell *et al* (1996, 2001, 2002) detailed schemes of treatment with two multi-drug chemotherapy regimes administered together or separately and with or without subsequent WBRT. CHOD comprises an alkylating agent, antibiotic, mitotic inhibitor and synthetic steroid. BVAM comprises anti-metabolites and an alkylating agent. There is no strong evidence to show that these drugs penetrate the BBB efficiently, except when the barrier is weakened by tumor infiltration. Five year survival rates were in a range between 30 - 36%.

Corn *et al* (2000) attempted to optimize the CHOD plus WBRT regime by varying the radiotherapy dose but, although the patients achieved a high response rate, the majority of them did not survive beyond four years. The earliest study identified that elderly patients (≥70yrs) did not survive this chemotherapy regime and hence were subsequently excluded from later trials. Patients ≥60yrs suffered significantly from dementia or died as a result of treatment. Mead *et al* (2000) attempted to conduct a controlled trial on the administration of WBRT with or without modified CHOD chemotherapy (prednisone replacing dexamethasone) but found no overall or disease free survival advantages to either, having a three year survival rate of less than 30%. The trial was terminated due to poor accrual.

- **MTX (methotrexate), vincristine, procarbazine, WBRT and cytarabine.** DeAngelis *et al* (2002) and Abrey *et al* (2000) reported case series on patients who had received multi-chemotherapy regimes incorporating either 2.5gm^2 or 3.5gm^2 methotrexate prior to radiotherapy and cytarabine. The 5yr survival rate was between 32 - 40% and the response rate was good in all patients. However, it was apparent that younger patients tolerated this therapy far better than those >60yrs who experienced considerably more delayed neurotoxicity, although this was reduced by deferment of radiotherapy. Watanabe *et al* (2003) increased the dose of MTX from 3.5gm^2 to 8gm^2 and then administered radiotherapy (stereotaxic rather than whole brain in the case of patients >60yrs) and observed a five year overall survival rate of 51%. The use of SRT reduced the observed neurotoxicity amongst elderly patients. Hodson *et al* (2005) reported a similar treatment regime on patients, half of whom were deemed unfit to receive high dose methotrexate. The median survival was dramatically reduced in comparison with those people who were young enough and fit enough to undergo the complete treatment regime.

- **High dose methotrexate - neuropsychological impact.** Two groups tested the neuropsychological impact of treatment with high dose methotrexate as part of a multi-chemotherapy regime, together with radiotherapy. Harder *et al* (2004) compared two groups of patients, one with systemic and one with CNS lymphoma. PCNSL patients were by

comparison considerably more cognitively impaired but this was ascribed to treatment rather than to the tumor location. Fliessbach *et al* (2003) reviewed cases of patients that had received high dose methotrexate together with vinca alkaloids vincristine and vindesine or alkylating agents cyclophosphamide or ifosamide. They reported that there was no significant deteriorations in cognitive function over time but rather that there were measurable improvements, both in the young and older (>60yrs) patient groups.

- **Review papers –** The reviews, Robins *et al* (2003), Batara *et al* (2003), Ferreri *et al* (2000) and Gustavson *et al* (2003), highlight similar key issues. Firstly, that PCNSL is, whilst rare, on the increase, not only in immunocompromised patients. Perversely, patient numbers are not sufficient to adequately inform clinical trials and hence the best available evidence is from small case series often across multiple treatment centres worldwide.

b) Patients with medulloblastoma

Most of the studies identified concerned paediatric medulloblastoma. The few adult studies consisted of case series describing clinical presentation, diagnosis, treatment and outcomes. Of note is the high risk of spread along the neuraxis which means that patients routinely received craniospinal radiotherapy. Patients perceived as high risk also received chemotherapy: cisplatin, ectoposide and cyclophosphamide in two series (Brandes *et al.* 2003a; Greenberg *et al.* 2001), and some combination of lomustine, vincristine and procarbazine in two other series (Greenberg *et al.* 2001; Abacioglu *et al.* 2002). One study suggested that the first protocol was associated with less toxicity (Greenberg *et al.* 2001).

The evidence about specialist care for people with medulloblastoma was limited to paediatric studies. An American observational study (Albright et al. 2000) using data from clinical trials in 485 children with medulloblastomas/primitive neuro-ectodermal tumours and 247 children with malignant gliomas, observed that paediatric neurosurgeons were more likely than general neurosurgeons to resect more than 90% of the tumour. An American population based observational study (Kramer et al. 1984) noted

that the survival of children with medulloblastoma, between 1970 and 1979, was better if they had been treated at a cancer centre than if they had been treated elsewhere.

c) Patients with pineal tumours

There was little adult evidence beyond case series spanning decades which usually combined adult and paediatric cases. Treatment varied according to the tumour's histological type, emphasising the importance of biopsy, intraoperative neuropathology and the investigation of CSF for markers of germ cell tumours(Czirjak *et al.* 1992; Tamaki & Yin 2000). Evidence from a case series suggested that stereotactic biopsy of the pineal region can be as safe and accurate as elsewhere (Regis *et al.* 1996). Case series suggest that stereotactic or endoscopic biopsy, cerebrospinal fluid diversion or surgical resection of the tumour are frequently required in this group (Czirjak *et al.* 1992; Tamaki & Yin 2000). The anatomic location of these tumours means that patients may experience opthalmological symptoms or complications following treatment.

d) Patients with optic nerve or tract glioma

Searches identified very little evidence about optic nerve gliomas in adults. Much of the literature relates to the more common benign optic gliomas typically found in children. A case report and literature review noted the rarity and high grade nature of optic nerve gliomas presenting in adulthood.

Table 10.1 The management of patients with rare brain and other CNS tumours (primary CNS lymphoma, medulloblastoma, pineal tumours and optic nerve or tract glioma)

Abbreviations: BBB, Blood brain barrier; BVAM, Carmustine, Vincristine, Cytarabine, Methotrexate; CHOD, Cyclophosphamide, Doxorubicin, Vincristine, & Dexamethasone; CHOP, Cyclophosphamide, Doxorubicin, Vincristine, & Prednisone; CR, Complete response; CT, Computerised tomography; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Treatment & Research of Cancer; HADS, Hospital Anxiety & Depression Scale; HD, High dose; IF-RT, Involved-Field Radiotherapy; KPS, Karnofsky performance scale; MBVP, Methylprednisolone, Methotrexate, Teniposide, Carmustine; MMSE, Mini Mental State Examination; MTX, Methotrexate ; NCI, National Cancer Institute; NE, Not evaluated; NHL, Non-Hodgkin Lymphoma; OS, Overall survival ; PCNSL, Primary Central Nervous System Lymphoma; PD, Progressive disease; PFS, Progression free survival; PR, Partial response; QOL, Quality of life; RTOG, Radiation Therapy Oncology Group; RCT, Random controlled trial; SD, Stable disease; SRT, Stereotaxic radiotherapy; WBRT, Whole brain radiotherapy; WHO, World Health Organisation.

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
Primary central nervous system lymphoma							
(Wong *et al.* 2004)	7 patients (gender not stated, median age = 64yrs (range 41-76yrs) were selected from a single centre database from 1997 - 2003. 3 patients had recurrent primary central nervous system lymphoma (PCNSL), 3 had	To determine if rituximab & temozolomide work synergistically to treat PCNSL with less associated toxicity. Patients received 4 cycles of rituximab and temozolomide, where each cycle was given monthly, followed by 8 monthly cycles of temozolomide alone.	Comparison of pre- and post-treatment with respect to CSF cytology, leukopenia thrombocytopenia, myelosuppression, and toxicity. Complete response (CR) or	All patients received rituximab without toxicity. High dose (375mg m2) temozolomide treatment caused 2 patients to experience grade II leukopenia & thrombocytopenia. One patient suffered myelosuppression. Median duration of response = 6/12 (3/12 - 12/12+) and median survival = 8/12 (range 3/12+ - 12/12+). CR = 5, PR = 2.	Authors suggest Temozolomide alone is less efficient at removing CNS lymphoma but pre-treatment with Rituximab sensitizes CD20+ lymphoma cells to cytotoxic effects of the second drug. Both drugs penetrate the BBB	Retrospective case series.	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	systemic non-Hodgkin's lymphoma (NHL) and 1 had newly diagnosed PCNSL. All but one of the patients had received prior chemotherapy (different regimes). All patients had received both drugs in 'uniform fashion'. JAPAN		partial response (PR).		and are non-toxic to the kidney. *This study looks at 7 patients that have been selected from a single centre database - the patients fall into three groups with respect for tumour type.* *Small sample size. No statistical analysis.*		
(Watanabe *et al.* 2003)	20 patients with newly diagnosed PCNSL. 11 males and 9 females. Median age = 62yrs (range 37-74yrs). Patients admitted to a single centre from 1994-2000 & chosen consecutively for this study if immunocompetent and adequate major organ function was	To determine if raising the dose of Methotrexate (MTX) from ≤ 3.5g/m^2 to 8g/m^2 prior to whole brain radiotherapy (WBRT) would improve length of survival in PCNSL patients. WBRT dose varied depending on response to chemo. Patients aged >60yrs were given stereotaxic	Tumour size measured by MRI and patients classified as CR, PR, stable disease (SD), progressive disease (PD) or not evaluated (NE) Actuarial survival curves were estimated by the method of Kaplan & Meier and	18/20 patients had two cycles of MTX. 10 showed CR, 5 PR, 1 SD and 2 NE. 12/20 patients (10 CR plus 2 NE) received WBRT or SRT of which 11 maintained CR. 6/20 patients (5 PR plus 1 SD) received WBRT or SRT at higher dose and all progressed to CR. Patients who achieved CR after MTX showed significantly improved progression-free survival (PFS) (P<0.0228). Median KPS was increased from 75 (range 40-100) to 90 (range 40-100) with improvement in 11/20 patients	Authors indicated that an increased dose of MTX prior to WBRT would probably extend PFS and OS for younger patients. Older patients could tolerate the higher dose of MTX but not WBRT and so SRT was preferable. *Low patient number.*	Prospective case series.	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	demonstrated. 15 patients had solitary tumours and 5 multiple. PCNSL was diagnosed by histology from stereotaxic, open or excision biopsy. JAPAN	radiotherapy (SRT) due to the risk of neurotoxicity with WBRT.	compared using the log rank test. Median follow-up 50/12 (range 11/12-94/12). Terminated in 2001. No patients were lost to follow-up.	12/20 patients had no disease recurrence but 3 died. Of 8/20 patients with recurrence 5 died. Median OS for the whole group = 57/12 (no range). Median PFS for the whole group = 54/12 (no range).	*For the purposes of actuarial analysis, the number of events is probably too low.* *In contrast to other studies, the authors did not find that age was a significant prognostic factor in overall survival.*		
(Harder *et al.* 2004)	19 patients (15 males and 4 females; age 44yrs ± 12yrs) from phase II clinical trial (high dose MTX followed by WBRT for non-AIDS PCNSL) 1997 to 2002. Inclusion for original trial: 16-65yrs, KPS 40-100, NFS = 0-3, histological/cytological proof of CNS NHL and one measurable lesion for response evaluation. Inclusion for	To determine if treatment with high dose Methotrexate (MTX) followed by WBRT adversely affected cognitive status and quality of life (QOL) of PCNSL patients in remission. Neuropsychological evaluation by standard psychometric tests	Quality of life assessment (EORTC QLQ-C30); Neurological function (EORTC BCM20); Fatigue (MDI); Current mood (HADS). In PCNSL patients only: White matter abnormality (WMA) & cortical atrophy evaluated. Non-parametric analyses with Bonferroni alpha	Patients with PCNSL: 63% mild-moderate cognitive impairment, 21% severe - correlated positively with age. Control subjects: 11% mild-moderate cognitive impairment, 0% severe. PCNSL: 14 patients (78%) showed cortical atrophy of which 6 were severe. 67% had cortical atrophy with WMA. Cortical atrophy correlated with age, cognitive function and KPS. PCNSL: QOL 47% reported well to excellent. Group differences in cognitive status and QOL not explained by anxiety, depression or fatigue.	The authors conclude that combined modality treatment for PCNS lymphoma might be associated with cognitive impairment even in patients aged <60 years. *Experimental and control groups in this study differed in both tumour type and treatment modality.* *Cognitive deficit was*	Retrospective cohort study.	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	present study: 6/12 since treatment, full remission. Controls: 19 patients (15 males and 4 females; age 45 ± 12yrs) from a longitudinal cognitive study, treated for either Hodgkin disease or systemic NHL, treated with systemic chemo- or radiotherapy or both. Groups matched for sex, age, education and time since end of treatment. HOLLAND & BELGIUM		adjustment on neuropsychological tests.		*ascribed to treatment but might have resulted from cerebral scarring due to tumour infiltration - this factor could not be addressed since there was no cognitive testing prior to initial treatment.*		
(Mead *et al.* 2000)	38 patients (21 males and 17 females; 17/38 >60yrs) in the experimental group. 15 patients in control group (9 males and 6 females; 3/15 >60yrs)	To determine if CHOP chemo administered after a course of WBRT impacted on the survival of non-immunocompromised patients with proven PCNSL. Following surgery, patients	Primary: length of overall survival measured from time of selection to time of death from any cause. Secondary: length	Patients in RT/CHOP group: 6 patients did not receive chemotherapy and only 22 patients received the 6 full six cycles. At follow-up RT-CHOP group: 6/32 alive (5 recurrence free) and controls: 4/15 alive (2 recurrence free) therefore clinical progression with or without death was 86% for both groups.	Authors state that RT-CHOP gave no clear benefit to overall survival (hazard ratio of 1.45 (95% CI 0.72-2.89)) or failure free survival (hazard ratio of 1.12 (5%CI 0.59-	Randomised Control Trial.	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Patients randomised from 1988 - 1995 at multiple centres. Inclusion: previously untreated PCNSL with proven pathology, suitable level of neurological & mental function for WBRT. Exclusion: immunocompromised, presence of systemic lymphoma. Multi-centre UK	were block randomised into 2 groups by telephone: control group (WBRT only) or experimental group (WBRT followed by 6 cycles of CHOP). Stratified by treatment centre.	of failure free survival, measured from selection time to clinically proven disease recurrence or death from any cause. Actuarial survival curves were estimated by the method of Kaplan & Meier & compared using the log rank test. Potential prognostic variables (age and neurological status) were included in a multivariate analysis (Cox's proportional hazards model).	Survival in RT group was 65% at 1yr and 29% at 3yr compared with the RT-CHOP group - 55% at 1yr and 28% at 3yr. Prognostic factors of age and neurological status both adversely affected outcome and after adjustment for these factors the hazard ratio for overall survival for RT-CHOP treatment was reduced to 1.19 (95% CI 0.51 - 2.76).	2.14). *The study was terminated due to poor accrual hence patient numbers were insufficient to meet the statistical criteria intended by the authors.* *The two patient groups were not balanced with regard to age or neurological performance status. These were shown to be significant prognostic factors.*		
(Robins *et al.* 2003)				Summary: PCNSL has a poor prognosis with median survival time of only 3/12. Age & performance status are adverse prognostic factors. Surgery is used to diagnose and	*Review of primary and metastatic CNS malignancies including a section on PCNSL.*	Review (25 refs).	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				confers no improvement in outcome. Standard treatment is WBRT with DEX - recurrence time is usually ~1yr. Chemotherapy is unsuccessful because the BBB is only temporarily breached by tumour growth - treatment then closes BBB and chemotherapeutic drugs (except MTX) cannot penetrate. MTX with WBRT plus Cytarabine may increase the median time to recurrence and overall survival but high doses may cause delayed neurotoxicity that may be prohibitive, especially in older patients. More recent studies have looked at permeabilisation of the BBB prior to chemotherapy. Rituximab is a new monoclonal antibody that targets CD20 and hence leads to cell destruction by complement and other antibody mediated mechanisms but, since it may not penetrate the BBB, may be most effective when given early. The authors conclude that although most trials are either non-randomised and/or low patient number, the positive results are unlikely to be due entirely to bias and represent the best available evidence to determine a treatment protocol.	*Papers reviewed date 1974-2001*		
(DeAngelis *et al.* 2002)	98 newly diagnosed PCNSL patients (53 males and 45 females,	To determine if combined chemotherapy followed by WBRT and Cytarabine	Primary: Estimation of 2yr overall survival.	Median progression-free survival: 24/12 (38.8/12 in patients <60yrs and 11.1/12 in patients >=60yrs). 50% patients were	The authors claim this to be the first multi-centre trial for PCNSL	Prospective case series.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	median age = 56.5yrs) were evaluated. Inclusion: intracranial mass lesion, histological evidence of PCNSL, adequate renal function. Exclusion: immunocompromised, evidence of systemic lymphoma. Median KFS = 80 and median MMSE score at baseline = 26.5/30. Total excision was performed in 26 patients and biopsy or sub-total resection was performed in 69. Multi-centre USA	treatment extended overall and progression-free survival in newly diagnosed PCNSL patients. Patients were given, over 10 weeks, five cycles of MTX, Vincristine, Procarbazine, with intraventricular MTX every alternative week. Chemotherapy was followed by WBRT then Cytarabine. Evidence (from another source) regarding neurotoxicity caused the RT dose to be reduced.	Secondary: tumour response before the start of RT and frequency & severity of treatment morbidity. Actuarial survival curves were estimated by the method of Kaplan & Meier & compared using the log rank test. Median duration of follow-up: 55.9/12	progression-free after 2yr and 25% after 5yr. Median overall survival: 36.9/12 (50.4/12 in patients <60yrs and 21.8/12 in patients ≥60yrs). 64% patients were alive at 2yr, 52% at 3yrs, and 32% at 5yrs. Achieving CR to chemotherapy did not affect overall survival and for these patients the dose of RT did not affect either overall or progression-free survival. 52 patients developed maximum grade toxicity to chemotherapy. 60/82 patients who received RT developed toxicity, severe in 12 cases, and in 8 causing death.	to demonstrate a marked survival benefit from chemotherapy combined with RT in comparison with studies in which patients received RT alone. *The degree of neurotoxicity may have been underestimated as it was diagnosed by separate investigators.*		
(Bessell *et al.* 1996)	34 patients (18 males & 16 females) were recruited from 1986 - 1994. Inclusion: newly diagnosed with PCNSL. Exclusion: organ	To determine if chemotherapy with drugs that can cross the BBB, combined with WBRT, improves survival in patients with PCNSL.	Improvement of complete response (CR) and toxicity. Actuarial survival curves were	Follow-up consisted of CT scan after surgery: 6 monthly for 2yrs, then annually for sufficient time to provide data at 3 & 5 yrs. 11/17 patients completed CHOD/BVAM without changes to protocol. CR at the	The authors concluded that the BVAM or CHOD/BVAM regimens can be delivered, despite	Prospective case series.	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	transplant, clinical indications of HIV infection. Median age = 60 (range 16-73). 51% patients had KFS >70 (ECOG equiv. of 0, 1), 47% of patients had an ECOG/WHO performance status of 3-4. 14 patients had multifocal disease, 20 patients had unifocal disease Multi-centre: UK (1) & SPAIN (1)	34 Patients were treated in three consecutive regimes: 10 patients received two 42-day cycles of BVAM alone (1986-9), 17 patients were given one cycle of CHOD followed by 1 cycle of BVAM (1990-4), although 2 were given BVAM only, and 5 patients also received CHOD/BVAM but at an increased dose. Subsequently 27/34 patients also received WBRT.	estimated by the method of Kaplan & Meier & compared using the log rank test. Potential prognostic variables (age, performance status, number of tumours present) were included in a multivariate analysis (Cox's proportional hazards model).	completion of chemotherapy was 63% for BVAM and 67% for CHOD/BVAM. Neutropenia occurred more frequently with CHOD/BVAM. Intensified CHOD/BVAM was too toxic to be tolerated and stopped after recruitment of only 5 patients. 3yr survival rate for patients on CHOD/BVAM was 51% (95% CI 17%-85%), compared to 40% (95%CI 10%-70%) for BVAM. 5yr survival for all 34 patients was 33% (95% CI, 14%-52%). 5yr survival for patients on BVAM was 30% (95% CI 2%-58%). Multivariate analysis showed that age (P = 0.0005) and number of tumours at diagnosis (P = 0.0358) were significant prognostic factors.	toxicity, without significant treatment delay or dose reduction in patients < 70yrs. *This report deals with three consecutive treatment regimes, carried out over time in a small number of patients. There were also variations in protocol.* *Only 7 patients were tested for HIV status.* *Initial results of study reported elsewhere.*		
(Bessell *et al.* 2001)	31 patients (19 males & 12 females) were recruited from 1990 - 1996. Inclusion: newly diagnosed with PCNSL. Exclusion: organ transplant, clinical indications of HIV	To determine the efficacy and toxicity of combined modality (CHOD/BVAM chemotherapy prior to WBRT) treatment in the treatment of PCNSL. 31 Patients were treated with 1 cycle of CHOD and 2 cycles	Risk of relapse, overall survival. Actuarial survival curves were estimated by the method of Kaplan & Meier &	Follow-up consisted of CT or MRI scan after surgery: 6 monthly for 2 yrs, then annually for sufficient time to provide data at 3, 4 & 5 yrs. 4/31 patients had 'no lymphoma after surgery', 18/27 patients had CR to chemo. 4/31 patients had PR to chemotherapy and 5/31 patients had no documented response	Authors conclude that treatment/dose regime would enhance survival in patients <70yrs *(although there were no patients >70yrs in this study)* and that dementia was	Prospective case series.	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	infection or previous malignancy. Median age = 59 (range 21-70). Median WHO/ECOG performance status = 2 (39% had poor status of 3-4) Multi-centre: UK(2) & SPAIN (1)	of BVAM, followed by WBRT.	compared using the log rank test. Performance status and evaluation of CT or MRI scans were graded from 0-4. These categorical data were analysed by Fisher's exact test, two-sided.	to chemo. 21/31 patients had 'no PCNSL' at the end of treatment. Survival analysis was performed 44/12 after study completion. Median overall survival was 38/12. 3yr and 5yr survival for all 31 patients was 55% (95% CI 37%-73%) and 31% (95% CI 11%-57%). 4yr survival of patients <60yrs was 58% (95% CI 34%-82%) c.f. patients >60yrs 29% (95% CI 5%-53%). 20/31 patients who survived >1yr after treatment were evaluated for delayed neurotoxicity. 1/12 aged <60yrs suffered cognitive dysfunction but 5/8 >60yrs suffered dementia (p<0.01).	a likelihood in patients >60yrs. *Only 14/31 patients were tested for HIV status.*		
(Corn *et al.* 2000)	98 patients (52 males, 40 females and 6 N/K) recruited between 1983-1987 (RTOG 83-15, 46 patients) and 1988-1992 (RTOG 88-06, 52 patients). 63% patients were >60 yrs. 35% patients had KPS 40-60. Inclusion: Age ≥ 18yrs.	To review the response in PCNSL patients to WBRT treatment in order to recommend a suitable design for future treatment protocols. RTOG 83-15: 40 Gy WBRT then 20 Gy boost to tumour plus 2cm margin. RTOG 88-06: Induction course of CHOD (2 cycles) then if no progression 1 extra cycle of	Overall survival (OS). Actuarial survival curves were estimated by the method of Kaplan & Meier & compared using the log rank test. Potential prognostic	Only 57% patients (29 in RTOG 83-15 and 27 in RTOG 88-06) could be evaluated radiographically. These patients received either MR or CT before treatment and 4/12 after treatment. 83% showed CR to WBRT, 85% showed CR to CHOD/WBRT. 14% showed PR to WBRT and 11% to WBRT/CHOD. 3% showed radiographic progression after WBRT and 4% after WBRT/CHOD. Using aggregated data for all above patients:	The authors conclude that 60 Gy WBRT is associated with increased CR, determined by brain scan. Raising the dose of WBRT may be associated with increased CR but greater risk of toxicity may reduce the benefit in OS.	Prospective case series.	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	PCNSL brain parenchyma involvement, KPS ≥ 40. Exclusion: AIDS (NB only excluded after 1986 in RTOG 83-15). Multi-centre: USA (2)	CHOD prior to 41.4 Gy WBRT with 18Gy boost. If progression then treatment moved direct to WBRT.	variables (age, KPS and response to WBRT) were included in a multivariate analysis (Cox's proportional hazards model). Defined CR as 'absence of enhancement' PR as a decrease in tumour size of at least 50% and tumour progression as a 25% increase in tumour size.	4yr survival was 24% for patients showing CR to WBRT compared with 11% for other patients (P<0.0007). Median survival was 2yrs for patients showing CR to WBRT compared with 0.5yrs for other patients (P<0.0006).	*AIDS positive patients were only excluded from RTOG 83-15 in 1986.* *Some patients were assessed by CT - this may be less efficient at detecting residual tumour.* *Pre-treatment evaluation might have indicated systemic disease but tests were not mandatory.*		
(Batara & Grossman 2003)				The incidence of PCNSL in elderly patients has increased in recent years. The de facto treatment has been WBRT with or without chemotherapy but the prognosis is still poor. WBRT is associated with high neurotoxicity in older patients. A shift from WBRT to high dose MTX has improved the median survival from 1yr to >3yrs but the optimal dose or mode of delivery is yet to be determined and it may be that WBRT should still be given with	*Focuses on advances, investigations and management of PCNSL.* *Papers reviewed 1994-2003.*	Review (41 refs).	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				MTX. Problems should be addressed concerning immunosuppressive effects of MTX and/or DEX: opportunistic infection e.g. *Pneuomocystis carinii*, thromboembolic disease, and renal toxicity. Due to the comparative rarity of PCNSL, clinical evidence is generally only available from small trials with low patient numbers whereas well designed multi-centre trials are needed to address crucial questions regarding etiology and management.			
(Fliessbach *et al.* 2003).	20 consecutive patients were recruited from 1995 - 1998. Of these 10 (6 males & 4 females) were suitable candidates for neuropsychological testing. Median age = 60yrs. Inclusion: HIV -ve, histologically proven PCNSL ? GERMANY	To determine if multi-chemotherapy regimes, including high dose MTX, lead to cognitive impairment and/or changes detectable by MR imaging during long term follow-up. Regime; IV and Intraventricular MTX plus vinca alkaloids (Vincristine, Vindesine) or alkylating agents (Ifosamide, Cyclophosphamide).	Cognitive function in long term follow-up.	MRI scans and neuropsychological tests were given directly before or after treatment, 4/12 and 12/12 afterwards and at the most recent follow-up. Tests were for attention, verbal memory, visual retention, word fluency & visuo-construction. 10/20 of original patients had long term survival without relapse and so could be assessed for cognitive function by neuropsychological testing. Initially, 5 had cognitive impairment (4/5 improved over time), 2 could not be tested & 3 had normal cognitive function (3/3 still normal over time). Median follow-up was for 36/12 (range 21/12 - 69/12). The change scores between successive testing dates were either positive i.e. improvement or negative i.e.	*Treatment response (70%), median time to failure (20.5/12) and median overall survival (54/12) reported elsewhere.* *This study contrasts with others that suggest older patients (>60yrs) do not tolerate combination therapy without adverse long-term cognitive defect.*	Prospective case series.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				deterioration. In patients <60yrs the number of deteriorations did not exceed those expected in a normal population (P=0.33) but improvements were significantly higher (P<0.001). In patients >60yrs, again, deteriorations did not exceed normal (P<0.17) but improvements did (P=0.004). Asymptomatic white matter changes (accredited to treatment) were detected in 4/10 patients but did not prevent these people from achieving improvement in cognitive function over time.			
(Bessell *et al.* 2002)	57 patients (33 males and 24 females) were recruited to one of two trials: CHOD/BVAM (1) from 1990 - 1995 and CHOD/BVAM (2) from 1996 - 1999. Median age in both groups = 59yrs with ranges (1) 21-70yrs and (2) 31-69yrs. Inclusion: Newly diagnosed PCNSL.	To determine if reducing the WBRT dose in patients who have had a CR to prior CHOD/BVAM chemotherapy affects time to relapse and overall survival. (1) CHOD/VBAM + WBRT 45Gy with 10Gy boost (2) CHOD/VBAM (same regime as 1) + WBRT 30.6Gy plus boost or 45Gy if no CR to chemo plus 35Gy if CSF +ve	Achievement of CR, Risk of relapse, Overall survival. Actuarial survival curves were estimated by the method of Kaplan & Meier & compared using the log rank test. Potential prognostic variables (age,	Patients had MR or CT scans after diagnosis, after chemo; after WBRT, every 6/12 for 2yrs then annually. Median follow-up (1) 59/12 (33/12-110/12) and (2) 17/12 (12/12-50/12). CR for group (1) = 20/31 patients (64%) and for group (2) 16/26 patients (62%). 24 patients from (1) & 6 from (2) received WBRT by protocol (1) and 16 patients from (2) received WBRT by protocol (2). 3yr relapse rate for (1) = 29% (95% CI 9%-49%) and for (2) = 70% (95% CI 40%-100%). 3yr median survival for (1) = 55% (95% CI 41%-69%) and for (2) = 36% (95% CI 20%-52%).	The authors conclude that reduction in the WBRT dose from 45Gy (1) to 30.6Gy (2) in patients <60yrs is associated with a higher rate of relapse and a poorer overall prognosis for survival, although there is nsd in patients >60yrs. *Clinical features, response to therapy, toxicity and outcome*	Prospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Exclusion: >70yrs, HIV +ve, organ transplant or previous malignancy Multi-centre UK (2) and SPAIN (1)		ECOG status, uni/multi-focal disease, response to GCs, surgery) were included in a multivariate analysis (Cox's proportional hazards model). Fisher's Exact test two sided or non-parametric test used for categorical data.	3yr relapse rate for patients <60yrs in group (1) = 25% cf 83% in (2) but nsd in patients >60yrs between groups. Age was sig. factor in predicting death within 4/12 of treatment: patients <60yrs cf patients >60yrs (P0.02). Univariate analysis for OS: prognostic factors: age, (P=0.02), poor ECOG (P=0.005), cognitive defect (P=0.02) and lack of response to GCs (P=0.07). Multivariate analysis for OS: Age (<60yrs cf >60yrs) was only predictor with relative risk 2.1 (95% CI 1.4%-2.8%).	*of CHOD/BVAM treatment were reported elsewhere.* *The number of lesions in group (2) patients was significantly higher (before treatment) than in group (1) (62% cf 29% P=0.01) which might have adversely affected prognosis.*		
(Ferreri *et al.* 2000).				In the majority of prospective trials the treatment modality has centred on chemotherapy followed by RT. This strategy has led to a 5yr survival of 22%-40% compared with RT alone (3%-26%). High dose MTX appears to be a most effective chemotherapy drug (it crosses the BBB) with a high response rate and 2yr survival of 60%-65% which has not been improved with the addition of other chemo. drugs. It is suggested that RT dose should be dependent on patient response to chemo. and to the number of lesions [36-40Gy + 10-15Gy boost for one lesion, 30-36Gy + boost after chemo.	*Discusses aspects of trial design and therapeutic guidelines.* *Papers reviewed 1975-1999.*	Review (88 refs)	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				or 30-40Gy in the case of multiple lesions, or up to 50Gy for residual disease]. The authors suggest that the most attractive option would seem to be chemotherapy only with RT reserved for use only in the event of relapse or non-response. They also call for identification of new drugs and more efficient chemotherapy regimes and suggest that the effects of treatment on neuro-psychological function and quality of life be requisite endpoints in all clinical trials.			
(Abrey *et al.* 2000)	52 patients (31 males and 21 females) were treated between 1992 and 1998. Median age = 65yrs (range 27 - 89). Median KPS = 70 (range 30-100). Inclusion: Histologically proven and newly diagnosed (med = 30days) PCNSL. Creatinine clearance of ≥ 50ml per hr. Exclusion: HIV +ve,	To determine an enhanced chemotherapy regime prior to WBRT using MTX with Vincristine and Procarbazine followed by post RT Cytarabine. 52 patients received pre-RT systemic and/or intrathecal MTX with or without additional Vincristine and Procarbazine. 30/52 patients received 45Gy WBRT. The remaining 22 (med age = 70yrs, range 54-89) patients deferred WBRT and were compared with 12 similar patients (med age = 67yrs,	OS and disease-free survival. Delayed neurotoxicity. Actuarial survival curves were estimated by the method of Kaplan & Meier & compared using the log rank test. Potential prognostic variables (age and KPS) were included in a multivariate	Patients were evaluated by MRI following chemo, WBRT and at the conclusion of treatment. Cognitive function was assessed by clinical exam and determination by physician, patient and carer rather than by psychometric testing. Median follow-up for the group = 33/12 (range 10/12-77/12). Median OS for group = 60/12 (range 1/12-77/12). Median OS of older patients deferring WBRT = 33/12 cf older patients treated with WBRT (32/12) but causes of death were, respectively, relapse or delayed toxicity. For patients <60yrs median follow-up = 50/12 with times of median OS or disease free survival not yet reached.	The authors feel that this treatment regime offers improved survival times and disease control. Older patients were able to tolerate high dose chemo well but the majority responded to RT with delayed neurotoxicity. Older patients that did not receive RT had a relapse rate similar to that of younger patients. *There was no formal*	Prospective case series.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	evidence of systemic lymphoma. Single centre USA	range 60-72) in the WBRT treatment group. 35/52 patients received post-RT (or post chemo if no WBRT) Cytarabine.	analysis (Cox's proportional hazards model). X^2 test used to compare single variables.	Response after pre-RT chemo: 56% CR, 33% PR, 4% PD, 4% SD. After all treatment CR and PR combined = 94% with 45/52 achieving complete remission. 18 patients had relapse, of which 16 were given salvage therapy, 10 of which had complete remission with median survival of 27/12 (range 2/12-46/12). Late neurotoxicity occurred in 12 of patients, 10 of which were >60yrs and had received RT. Analysis showed that significant prognostic factors for OS were age (>60yrs P=0.002) and KPS (<80 = 0.006).	*psychometric testing to evaluate cognitive function.* *The patient group enrolled in this study did not have a good prognosis since many of them were >60yrs and/or had poor KPS scores at diagnosis. This may be more representative of a 'typical' PCNSL population.*		
(Gustavsson *et al.* 2003)		Systematic review of 1 low grade RCT, 4 moderate grade prospective case series, 1 low grade case series, 2 low grade retrospective case series, 4 high grade literature reviews, and 2 'others'. 1995-2001.		The authors indicate that RT induces only a short term response in PCNSL patients. In the elderly, when combined with chemotherapy, WBRT is also associated with late neurotoxicity. It is therefore suggested that in these patients RT should be administered only when tumours are refractory to chemotherapy or in case of relapse. High dose MTX is more effective than RT alone and can be included as part of a primary chemotherapy regime given before	A review of radiation therapy in various tumour types including a small section on PCNSL	Systematic review.	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				RT in younger patients. The authors point out, however, that there are no RCTs on MTX treatment in PCNSL An optimal chemotherapy regime is not yet defined and the role of RT in PCNSL treatment also remains to be clarified.			
(Hodson *et al.* 2005)	55 patients (29 males and 26 females, median age = 64yrs (range 32-82 yrs). 54 patients had high grade B-cell tumours and 1 patient had T cell tumour. Cases taken from one clinic database from 1995 - 2003. Patients 'unselected' defined as including those unfit for treatment with HD MTX. Inclusion: HIV -ve, histological confirmation of diagnosis.	To report the treatment outcome on a series of 55 patients with PCNSL, including those unfit to receive HDMTX. Intention to treat all patients with HD MTX with or without WBRT. For those patients that could not tolerate HD MTX, alternative chemotherapeutic drugs were given: (1) Teniposide, Carmustine, Methylprednisone (MBVP), (2) CHOD/BVAM, (3) MTX, Procarbazine, and Cytarabine. From 2002 WBRT was withheld from patients	CR, PD. Actuarial survival curves were estimated by the method of Kaplan & Meier & compared using the log rank test. Stratified by age and treatment regime.	Median survival for group = 8/12 (95% CI 4/12 - 22/12). Age was a prognostic factor for survival since patients <60yrs had median survival = 26/12 (95% CI 22/12 - not yet reached) c.f. patients > 60yrs who had median survival = 2.4/12 (95% CI 1/12 - 4/12) (P = 0.0001). 25 patients (45%) were unfit for treatment with HD MTX and received alternative chemotherapeutic drugs, steroids or palliative RT. Median survival = 46 days (95% CI 24 - 99 days). For the 30 patients that received HD MTX and/or additional chemotherapy and/or WBRT, median survival = 31/12 (95% CI 22/12 - 56/12) and of these 20/30 patients (67%) achieved CR. In 17 patients that survived >1yr, functional ability was assessed and only 4 patients were found to be able to live independently - all	The authors suggest that the low median OS is due to the large no. of patients unfit for treatment with HD MTX but which were included in the analysis. They point out that fitness for treatment, not always reported by other groups, is therefore the most significant prognostic factor. *This study includes patients that might be excluded from studies by other groups but the results may be more realistic.*	Retrospective case series.	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Single centre UK.	achieving CR to chemotherapy.		were < 60yrs of age.	*Disability-free survival is much shorter than overall or disease-free survival but that this is frequently not reported in other studies.* *Treatment regimes varied over time.*		
Patients with medulloblastoma							
(Brandes *et al.* 2003a)	36 patients (aged ≥18 years) with a histologic diagnosis of medulloblastoma. Median age at diagnosis was 26 years (range 18 to 57 years). Median KPS was 78 (range 40 to 90). Participants were staged according to Chang et al.'s classification and two groups were defined as follows:	Aim: To assess the value of prognostic factors and the outcome of medulloblastoma in adults. Treatment: Low risk group: Radiotherapy: 36 Gy to the craniospinal axis, supplemented by a local tumour dose of 18.8 Gy (total dose of 54.8 Gy). High risk group: 2 cycles of chemotherapy	Progression-free survival (PFS) and overall survival (OS), by Kaplan Meier analysis. The following prognostic variables were evaluated using the log rank test: Gender, presence of shunt, residual disease, T stage, M stage, histologic	PFS Median PFS for all patients was 6.7 years. 65.4% (95% CI 49.8 to 86%) of all patients were free of progression at 5 years. PFS at 5 years was higher in low-risk patients compared to the high-risk group: 76% (95% CI 52% to100%) versus 61% (95% CI 42% to 87%) respectively. Patients with M- disease showed a significantly better outcome than M+ patients, with 75% (95% CI 52% to 100%) showing PFS at 5 years versus 45% respectively (p = 0.01). OS Median OS for all patients was 8.15 years. 75.3% (95% CI 59% to 96%) of all patients	Note: 'M-' signifies no detectable metastases to elsewhere on the neuraxis via CSF. 'M+' signifies metastases to sites elsewhere on the neuraxis via CSF. Between 1989 and 1995, chemotherapy was based upon MOPP: nitrogen mustard, vincristine, prednisolone and procarbazine.	Prospective case series study of 36 patients treated over a 12 year period.	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Low risk group: T1, T2, T3a, M0, and no residual disease after surgery High risk group: T3b-T4, any M+ or postoperative presence of residual tumour	were delivered before the same radiotherapy as above, followed by maintenance chemotherapy if M1, M2, or M3 disease was present.	subtype, location of lesions, postoperative KPS, duration of radiotherapy and interval between surgery and start of radiotherapy.	were alive at 5 years. Patients with M- disease showed a significantly better outcome than M+ patients, with 87% (95% CI 72% to 100%) showing OS at 5 years versus 52% (95% CI 25.6% to 100%). Presence or absence of residual disease did not account for a significant amount of difference in survival. Postoperative KPS was not predictive of PFS or OS, and neither were histology or location of lesions. Authors conclude that the overall PFS observed is comparable to that obtained in paediatric patients and suggests that a more effective therapy must be developed for high-risk patients.	After 1995 MOPP chemotherapy was replaced with cisplatin, ectoposide and cyclophosphamide. *Authors do not fully report the results for all explanatory variables included in log rank test.* *Small series.*		
(Abacioglu *et al.* 2002)	30 patients undergoing radiotherapy for medulloblastoma. Patients were identified treated at 2 institutions between 1983 and 2000. Patient age ranged from 16 to 45 years	Clinical presentation, diagnosis, and treatment are discussed.	Presenting signs and symptoms, type of treatment, survival, patterns of relapse and toxicity. Median follow up was 51 months	Presenting signs and symptoms (% of patients) Nausea/vomiting 73% Headache 43% Visual changes 27% Vertigo 23%	Small case series, presence of metastases not reported.	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	(median 27). TURKEY			Type of treatment (% of patients) Complete surgical resection 67% Incomplete surgical resection 23% Radiotherapy (brain and spine) 100% Chemotherapy (Iomustine, vincristine and procarbazine) 33% Overall survival The 5 and 8 year overall survival rates were 65% and 51% respectively. Disease free survival The 5 and 8 year disease free survival rates were 63% and 51% respectively. Patterns of relapse The median time to relapse was 26 months (range 4 to 78 months). The median survival after recurrence was 6 months. Toxicity. One patient became quadriplegic following surgery, because of respiratory arrest. Acute radiotherapy toxicity was limited to alopecia, nausea and haematologic toxicities			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Albright *et al.* 2000).	732 children enrolled in 3 CCG studies, 1986-1992.Histology was 485 medulloblastoma/PNET and 247 malignant glioma. Operations were performed by 269 neurosurgeons: 213 general neurosurgeons, 29 designated paediatric neurosurgeons and 27 ASPN members. USA	Neurosurgery	Extent of residual tumour after surgery (determined from imaging). Transient and permanent operative complications. All outcomes were reported by the treating surgeons and not verified centrally.	Mean number of operations per surgeon was 1.8 for general neurosurgeons, 4.9 for paediatric neurosurgeons and 7.6 for ASPN members Controlling for tumour type (but not reported how this was done), paediatric neurosurgeons were more likely than general neurosurgeons to resect more than 90% of the tumour (58% versus 69% of cases, Chi2=5.04, p=0.025). Paediatric neurosurgeons were more likely than general neurosurgeons to leave <1.5 cc of residual tumour (65% versus 72% of cases, Chi2=4.4, p=0.04). Neurological complication rate was: 22% for general neurosurgeons, 32% for paediatric neurosurgeons and 18% for ASPN members. The difference between paediatric neurosurgeons and ASPN members was significant (p=0.03). There was no significant difference in non-neurological complication rates in the 3 groups.	*Indirect evidence (not an adult population)* *Neurosurgeons may not have enrolled all eligible patients in CCG trials. Overall, case volume is likely to be underestimated.* *Operations were carried out between 8 and 14 years before the study, practice likely to have changed in that time.*	Case series	3+
(Kramer *et al.* 1984)	147 patients with Wilms tumours, 87 with rhabdomyosarcoma	Determination of effect of place of treatment between cancer centres (CC) and non-	Disease free survival (DFS)	Differences in 3yr DFS between CC and NCC were noted for medulloblastoma (52% v 24%) and rhabdomyosarcoma 48% v 10%, but not	*No case mix adjustment. Patterns of care, US orientated.*	Historical case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	and 76 with medulloblastoma.	cancer centres (NCC)		for Wilms tunmours (79%v68%). The principle management contrast found in rhabdomyosarcoma was that multiagent CT was used less often in NCC. Wilms tumour patients were evaluated and treated similarly in the CC and NCC, except for surgical approach and FU.	*Insufficient details of statistical analyses.*		
(Greenberg *et al.* 2001)	17 adult patients with medulloblastoma (11 female, 6 male). Median age 23 years (range 18 to 47 years) All tumors were infratentorial (10 in 4th ventricle and 7 in left or right hemisphere). 10 patients presented with hydrocephalus, and 7 of them were shunted. 8 patients had gross total resection, 7 had subtotal resection (>50% removed), and 2 had partial resection (<50% removed). Postoperatively, 3 patients had positive	Patients received 1 of 2 adjuvant chemotherapy regimens: 10 patients were treated with the "Packer protocol," consisting of CSRT plus weekly vincristine followed by 8 cycles of cisplatin, lomustine, and vincristine. 7 patients were treated with the Pediatric Oncology Group (POG) protocol, consisting of alternating courses of cisplatin/etoposide and cyclophosphamide/vincristine, followed by CSRT.	Progression-free survival, overall survival, and toxicity.	The estimated median relapse-free survival (Kaplan-Meier) for all patients was 48 months. There was no significant difference in median relapse-free survival between groups: for patients on the Packer protocol this was 26 months, and for those on the POG regimen, 48 months (P = 0.410). For the Packer protocol, median survival was 36 months, compared to 57 months for the POG protocol (P = 0.058). Toxicity during the Packer protocol was moderately severe, with only 1 of 10 patients able to complete all therapy. Side effects included severe abdominal pain, peripheral neuropathy, hearing loss, neutropenia, thrombocytopenia, nephrotoxicity and	Prior to chemotherapy, patients were treated with surgery and craniospinal radiotherapy (CSRT) plus local boost. Authors acknowledge that the study is likely to be underpowered to detect any significant difference in relapse-free or overall survival between the POG and Packer protocols. *Appraised on abstract only.*	Retrospective case series of patients treated at 3 centres.	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	cytology and 3 had positive spinal MRI. 5 patients were classified as good risk and 12 were classified as poor risk (Chang staging system). USA			decreased pulmonary function. On the POG protocol, only 1 patient had persistent nausea and vomiting, 2 had peripheral neuropathy, and 3 had hearing deficit or tinnitus. Authors conclude that the POG protocol seemed to have less nonhematologic toxicity. Adults on the Packer protocol appeared to have shorter median survival and greater toxicity than children.			
PINEAL							
(Czirjak *et al.* 1992)	50 patients treated for pineal region tumours in a single institution between 1976 and 1990. Age ranged from 2 to 56 years. HUNGARY	Clinical presentation, diagnosis and surgical procedures are discussed.	Presenting signs and symptoms, type of treatment, operative morbidity and mortality	Presenting signs and symptoms Raised intracranial pressure 74% Eye movement disorder 12% Diabetes insipidus 6% Precocious puberty 4% Epilepsy 1% Subarachnoid haemorrhage 1% Treatment employed Surgery 64% Palliative care only 36%	Pineal region tumours (not just pineal parenchyma) An algorithm for the management of patients with pineal tumours is presented.	Retrospective case series	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				CSF shunt 70% Radiotherapy 64% Operative mortality and morbidity 3 deaths in 32 patients undergoing 40 procedures; operative mortality rate of 7.5%. Morbidity was also 7.5%, 2 cases of visual field defects and one of meningitis. Histology of the operated tumours (n=32) Germ cell 34.4% Pineal parenchyma 9..4% Glial or other supportive tissue 56%			
(Tamaki & Yin 2000)	36 patients with tumours of the pineal region. The mean age was 18.2 years (range 1 to 69 years). The tumours were 24 germinomas (67%), 4 teratomas (11%), 3 pineal cysts and 5 others. All patients were treated at a single institution between	Clinical presentation, diagnosis and surgical procedures are discussed.	Presenting signs and symptoms, type of treatment, response to radiotherapy, tumour recurrence	Presenting signs and symptoms Headache 58% Nausea/vomiting 61% Polyuria 44% Diplopia 39% Diagnosis From 1985 onwards, MRI was the main diagnostic tool. Angiography was done in all patients. Patients with suspected germinoma were given a test dose of radiotherapy (20	Small series, diverse histological types. Ventriculostomy was frequently required. The sample probably included a significant number of children	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	1971 and 1996. JAPAN			Gy) to see whether the tumour shrunk markedly. Treatment employed Craniotomy 22% Biopsy 3% Ventriculoperitoneal shunt 61% Radiotherapy 83% Chemotherapy 14% Response to radiotherapy Response to radiotherapy was seen in all 24 patients with germinoma, and in ¼ (25%) of the patients with teratoma. The patient with pineoblastoma and the one with choriocarcinoma also responded to radiotherapy. Tumour recurrence Recurrence developed in two patients, one with pineblastoma and one with germinoma.			
(Regis *et al.* 1996)	370 stereotactic biopsies of pineal region tumours, from 15 French neurosurgical centres. Biopsies were	Stereotactic biopsy	Diagnostic yield, morbidity and mortality associated with biopsy	Diagnostic yield Diagnostic yield was 94%. The following histological types were noted: Germinoma 27% Pineocytoma/pineoblastom 24%	Includes tumours of the pineal region (not just the pineal body). Series covers a long time with changes in	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	performed between 1975 and 1992. Age range was 2 to 72 years. FRANCE			Astrocytoma 27% Mortality and morbidity The mortality rate was 5/370 (1.4%), post operative CT showed haematoma in each case. 3/370 (0.8%) of patients had severe long term neurological deterioration. In 27/370 (7.2%) patients there was transient postoperative neurological deficit. In one case seeding along the biopsy track was noted. The authors report that the choice of biopsy trajectory was not statistically significantly related to morbidity risk.	technique (e.g. MRI or CT is now used in the centres)		
Optic gliomas							
(Millar *et al.* 1995)	Case report of a 60 year old man with malignant optic glioma. USA	Discussion of the diagnosis and management of malignant optic glioma.		Initial MRI did not reveal tumour, but a non-specific enlargement of optic nerve. Initial diagnosis and treatment was for optic neuritis. 6 months later repeat MRI showed large mass involving both optic nerves, which proved to be anaplastic astrocytoma. The patient received radiotherapy and chemotherapy but died 5 months later. Discussion of the literature suggests that this tumour is extremely rare (30 cases reported		Case report	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				from 1900 – 1989)			
(Bataini *et al.* 1991)	57 patients with chiasmal optic glioma treated with radiotherapy at a single institute, 1970 to 1986. 46% of patients were younger than 10 years of age, and 40% had neurofibromatosis. 21 patients had gliomas involving the anterior optic chiasm (Group B), 36 had gliomas extending beyond the chiasm to adjacent structures (Group C) Gliomas confined to the optic nerve were excluded (Group A). Histological diagnosis was established in 16 patients: high grade glioma (n=2) and low grade glioma (n=14). FRANCE	Radiotherapy, dosages were 40 to 60 Gy given in 5 to 7 weeks. 25 patients underwent surgery.	Presenting signs, overall survival, disease control and visual function.	Presenting opthalmological signs (% of patients) Reduced visual acuity, 91% Reduced visual fields, 91% Optic atrophy, 44% Papilloedema, 32% Proptosis,18% Strabismus, 18% Nystagmus, 11% Presenting neurological signs (% of patients) Headache, 21% Intracranial hypertension, 9% Other signs, 21%% Presenting endocrinological signs (% of patients) Precocious puberty, 9% Growth retardation, 9% Other signs, 25% Overall survival Mean follow-up was 91.5 months (range 30 to 197 months).	The effectiveness of radiotherapy is not evaluable as there no comparison group. Excludes gliomas confined to the optic nerve. Largely paediatric population (more benign form of the disease). Some of the outcomes were incompletely evaluated, e.g. paediatric visual fields, cognitive functioning.	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				The overall survival was 83.5% at 5 and 10 years. Disease control Overall relapse free survival was 89% at 5 years and 82% at 10 years. In group B relapse free survival was 100% at 5 years and 88% at 10 years. In group C relapse free survival was 82% at 5 years and 72% at 10 years. Visual function after therapy Visual fields were not evaluated in 12 young patients. 3 patients experienced progressive visual deterioration. 21/35 patients evaluated showed improved visual acuity. 17/25 patients evaluated showed improved visual fields. Complications of therapy Endocrine dysfunction was seen in 37% of patients, but was usually correctable. There were 2 cases of middle cerebral artery thrombosis.			

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				Some patients experienced mental retardation, but this was poorly evaluated and reported.			

Chapter 11 Supportive care

The questions

a) Do neuropsychological interventions improve outcomes for people with brain & CNS tumours?

b) What is the optimum method for providing information to neuro-oncology patients who are not able to access information (cognitive dysfunction, memory problems, ethnic minorities, learning difficulties, illiterate etc.)?

c) Does physiotherapy or occupational therapy shorten hospital stays, facilitate discharge or reduce re-admission of people with brain tumours?

d) What are the general palliative care needs of patients with brain or other CNS tumours?

The nature of the evidence

a) Do neuropsychological interventions improve outcomes for people with brain & CNS tumours?

The literature searches identified 12 observational studies of neuropsychological testing in patients with brain or other CNS tumours:

- for initial assessment (Choucair *et al.* 1997; Hahn *et al.* 2003) (Herman *et al.* 2003; Meyers *et al.* 2000)
- to monitor treatment effects (Brown *et al.* 2003; Brown *et al.* 2004; Costello *et al.* 2004; Klein *et al.* 2001; Regine *et al.* 2004)
- to detect recurrence (Armstrong *et al.* 2003)
- to determine the prevalence of clinically significant levels of depression or anxiety (Carlson *et al.* 2004; Litofsky *et al.* 2004)

The searches did not identify directly relevant evidence for the neuropsychological rehabilitation of people with brain tumours. There was however, indirect evidence

about the effectiveness of cognitive rehabilitation in patients whose deficits were due to stroke or traumatic brain injury. This included

- systematic reviews (Lincoln *et al.* 2000; Majid *et al.* 2000; Bowen *et al.* 2002)
- health technology appraisals (Blue Cross Blue Shield Association 2002; Chesnut *et al.* 1999)
- an evidence based guideline (Cicerone *et al.* 2005)

b) What is the optimum method for providing information to neuro-oncology patients who are not able to access information (cognitive dysfunction, memory problems, ethnic minorities, learning difficulties, illiterate etc.)?

The literature search identified four studies as follows:

- A systematic literature review (Davies & Higginson 2003), which considered the provision of information for adults with malignant cerebral glioma.
- A UK questionnaire study (Lidstone *et al.* 2003) of symptoms and concerns in outpatients attending a London cancer centre, which included 60 patients with brain tumours.
- A UK study (Sardell *et al.* 2000) evaluated satisfaction with a nurse led telephone clinic during follow up of patients with high grade glioma.
- A UK observational study (Grimes 2000) used interviews with patients with brain tumours to develop a model for the provision of information such patients

c) Does physiotherapy or occupational therapy shorten hospital stays, facilitate discharge or reduce re-admission of people with brain tumours?

Apart from an RCT (Cohen *et al.* 2002) of physiotherapy for vestibular rehabilitation after surgery for vestibular schwannoma, the literature search revealed only non comparative studies:

- observational studies of the rehabilitation of people with brain tumours (Cole *et al.* 2000; Garrard *et al.* 2004; Huang *et al.* 1998; Marciniak *et al.* 2001; Mukand *et al.* 2001; O'Dell *et al.* 1998).

- two reviews of rehabilitation of people with brain tumours (Bell *et al.* 1998; Huang *et al.* 2001)

d) What are the general palliative care needs of patients with brain or other CNS tumours?

Literature searching identified little evidence about general palliative care in this population:

- Two review articles about the palliative care needs of patients with primary brain tumours(Taillibert *et al.* 2004) and brain metastases(Taillibert & Delattre 2005).

Indirect evidence about general palliative care in cancer patients in general is reviewed in NICE guidance on Improving Supportive and Palliative Care in Adults with Cancer

Summary of the supporting evidence for the recommendations

a) Do neuropsychological interventions improve outcomes for people with brain & CNS tumours?

There was no direct evidence relating neuropsychological interventions to patient outcomes.

Disease or treatment related cognitive impairment, however, adversely affects quality of life. There was observational evidence to support neuropsychological testing to measure cognitive impairment during initial assessment (Brown *et al.* 2004; Herman *et al.* 2003; Klein *et al.* 2001) and following treatment (Brown *et al.* 2003; Choucair *et al.* 1997; Costello *et al.* 2004).

Three systematic reviews of the effectiveness of cognitive rehabilitation following stroke (Lincoln *et al.* 2000; Majid *et al.* 2000; Bowen *et al.* 2002) and two evidence based technology appraisals of cognitive rehabilitation following traumatic brain injury (Blue Cross Blue Shield Association 2002; Chesnut *et al.* 1999) were unable were unable to draw firm conclusions about the effectiveness of cognitive rehabilitation. This was due to a combination of scarcity of primary studies and heterogeneity, in both methods and patient populations.

Mood (Carlson *et al.* 2004; Litofsky *et al.* 2004)and personality changes (Salander *et al.* 1999) are often seen in people with brain tumours, suggesting a place for neuropsychological and neuropsychiatric therapies. Although no studies evaluating such interventions for people with brain tumours were identified, systematic reviews support the use of therapeutic psychological interventions for depression and anxiety in people with other cancers (NICE guidance *Improving supportive and palliative care in adults with cancer*).

b) What is the optimum method for providing information to neuro-oncology patients who are not able to access information (cognitive dysfunction, memory problems, ethnic minorities, learning difficulties, illiterate etc.)?

The systematic literature review of Davies and Higginson (Davies & Higginson 2003) found the following:

- In one UK observational study approximately one third of patients and relatives said that the information they received lacked coherence.
- In two observational studies patients reported having to seek out information themselves.
- No studies comparing different methods of providing information were identified. Qualitative data about consultations confirmed that information about diagnosis and prognosis should be tailored to the individual coping of patients and relatives but there was insufficient evidence to suggest a standard approach to disclosure.

The outpatient study of Lidstone and co-workers (Lidstone *et al.* 2003) observed that 38% percent of the 60 patients with brain tumours complained of a lack of information about their illness and treatment. Problems with concentration or memory were reported by 83% of the patients with brain tumours, suggesting that the method of delivery of information is an important consideration for this group of patients.

Two studies reported on interventions to enhance the provision of information for these patients:

- The study of Grimes (Grimes 2000) used patient feedback to improve the provision of information to patients with brain tumours during their stay in hospital.

- Sardell and co-workers (Sardell *et al.* 2000) reported high levels of patient satisfaction with a nurse led telephone based follow up clinic for those with high grade glioma.

The development and distribution of information for patients and carers is considered in the NICE guidance on Improving Supportive and Palliative Care for Adults with Cancer. A systematic review confirms that patients with cancer obtain benefit from accurate and relevant information.

c) Does physiotherapy or occupational therapy shorten hospital stays, facilitate discharge or reduce re-admission of people with brain tumours?

Observational studies report that patients with primary or metastatic CNS tumours show significant functional improvement after a period of rehabilitation (Cole *et al.* 2000; Garrard *et al.* 2004; Huang *et al.* 1998; Marciniak *et al.* 2001; Mukand *et al.* 2001; O'Dell *et al.* 1998) The studies were non-comparative so it is impossible to say how much of the improvement was due to the rehabilitation. Studies measuring cognitive and motor functioning during rehabilitation found greater relative improvement in motor functioning than in cognitive functioning (Garrard *et al.* 2004; Huang *et al.* 1998; Cole *et al.* 2000).

A randomised trial (Cohen *et al.* 2002) did not observe additional benefit from a physical exercise regime for vestibular rehabilitation after treatment for vestibular schwannoma.

d) What are the general palliative care needs of patients with brain or other CNS tumours?

A literature review (Taillibert *et al.* 2004) noted additional difficulties in the assessment of symptoms and concerns in patients with cognitive impairments as a result of a brain tumour.

A second review of palliative care needs in patients with brain metastases (Taillibert & Delattre 2005) emphasised the avoidance of over treatment in patients with poor prognosis.

Indirect evidence in support of the recommendations, originally reviewed in the NICE guidance on *Improving Supportive and Palliative Care in Adults with Cancer,* is summarised below,

Evidence from surveys suggests shortcomings in the assessment of the palliative care needs of patients with advanced cancer in general healthcare settings.

Surveys of health professionals have identified a need for education and training in the management of patients with advanced stage illness. Evidence from randomised controlled trials supports the use of such training programmes in helping to change clinical practice. There is limited evidence that the use of guidelines can help coordinate referral from general to specialist palliative care services.

A UK survey into trends over a 10-year period showed that, whilst many people wanted to die at home only around 25% of people with cancer did so, the remainder dying in hospital, hospice or care home. Reasons for the change in place of death included lack out-of-hours of nursing care, medication or equipment.

Table 11.1 Does neuropsychological input benefit patients with brain and other CNS tumours?

Abbreviations: ADL, activities of daily living; CI, confidence interval; KPS, Karnofsky performance score; QOL, quality of life; LGG, low grade glioma; MMSE, mini mental status examination; NSCLC, non-small cell lung cancer; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SMD, standardised mean difference.

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Armstrong *et al.* 2003)	34 adult patients with supratentorial low grade brain tumours. USA	Serial neuropsychological examinations to aid early detection of recurrence. Comparison of a general model based on tests sensitive to malignancy compared with a tumour specific model	Tumour recurrence	11/23 patients developed recurrent tumours. The groups (tumour recurrence vs. non recurrence) were comparable (z scores) Only the tumour specific model achieved statistical significance ($p<0.02$). A tumour specific index decline of 1 standard deviation indicated a 5 fold increase in tumour recurrence	Small numbers. Preliminary results that require further testing. Indirect effect on outcomes.	Case series	3-
(Brown *et al.* 2003)	203 adults with supratentorial LGG enrolled in an RCT of radiotherapy dose (50.4 Gy vs. 64.8 Gy) between 1986 and 1994 in a single institution.		Folstein Mini-Mental State Examination (MMSE) - baseline measurement and then every 4 months for 2 years, every 6 months for the next 3 years and then annually post	An abnormal baseline MMSE score was defined as less than 27 points, and a clinically significant change was defined as one of 3 or more points. In patients without tumour progression, significant deterioration from baseline occurred at years 1, 2, and 5 in 8.2%, 4.6%, and 5.3% of patients, respectively. Many patients with an abnormal baseline MMSE score, however, experienced clinically significant increases in	Analysis of prognostic factors for cognitive change was not multivariate. Correlation between MMSE and disease	Case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	USA		therapy.	years 1,2 and 5: 59%, 50% and 67% respectively. Variables such as radiation dose, conformal versus conventional radiotherapy, number of radiation fields, age, sex, tumour size, neurologic function score, seizures, and seizure medications did not predict MMSE cognitive function changes. Authors conclusions: Only a small percentage of patients had cognitive deterioration, as measured by the MMSE, after radiotherapy.	progression is not reported. Baseline MMSE scores were not available for 8% of patients. Median follow up was 7.4 years in surviving patients.		
(Brown *et al.* 2004) Same patients as (Brown *et al.* 2003)	203 adult (≥ 18 years) patients with supratentorial low-grade glioma. Patient had completely or incompletely resected WHO Grade II astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. Patients enrolled between 1986 and 1994. Mean baseline MMSE score was	RCT Lower dose RT (50.4 Gy in 28 fractions) Versus High dose RT (64.8 Gy in 36 fractions). No chemotherapy in protocol though patients could receive chemotherapy post-protocol for progression Aim: to assess the	Value of baseline MMSE in predicting survival and progression-free survival. Comparison of baseline characteristics between patients with abnormal (0 to 26) and normal (27 to 30) MMSE scores	The 36 patients with abnormal baseline MMSE scores had significantly worse 5-year overall survival and worse progression-free 5-year survival than the 151 patients with normal MMSE scores (overall survival: 31% versus 76%, $p < 0.001$; progression-free survival: 27% versus 60%, $p < 0.001$). This applied to both the high and low dose RT treatment groups. Multivariate analyses showed that age, baseline MMSE, tumour size and histological type were significant predictors of survival. There was a trend toward patients with abnormal baseline MMSE scores among patients with tumours ≥ 5cm, astrocytoma and greater extent of surgery.	The authors concluded that the baseline MMSE score should be considered in future prognostic scoring systems. In another study the authors point out that the MMSE has not been validated for patients receiving RT for brain	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	27.9 (median 29, range 2 to 30). USA	prognostic value of baseline MMSE scores in patients with low-grade glioma. .			tumours.		
(Choucair *et al.* 1997)	126 patients aged < 60 years with malignant astrocytoma 310 patients eligible, data from 126 available. Study population characteristics: 92% white; 65% male; 66% < 50 years; 60% KPS 90 to 100; 77% minor or no neurological symptoms. USA	Patients enrolled in RTOG 90-06 (RCT comparing standard radiation therapy with hyperfractionated RT, all received carmustine). Aim: to test the feasibility of performing quality of life and neuropsychological testing on patients enrolled in RTOG 91-14	Quality of life (QOL) and neuropsychological evaluation assessed using the MMSE and Activities of Daily Living Scale (ADLS) Correlations between MMSE, ADLS and 30 pretreatment variables were tested.	The overall ADLS score was associated with gender, KFS, NFS, somnolence, mental status, speech impairment, motor deficit, cranial nerve deficit and corticosteroid use. MMSE scores were associated with memory symptoms, mental status, motor deficit, use of steroids and lateralisation of tumour.	The authors concluded that assessing QOL using MMSE and ADLS was cost-effective. These measures provide more information about day to day functioning than currently used measures. Large number of exclusions though authors state sample was representative of target population. No supporting evidence on costs.	Retrospective case series	3+
(Costello *et*	3 groups were	Radiotherapy:	Cognitive functioning	Cognitive function improved in patients with low grade	Small study, poorly	Case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
al. 2004)	included: low grade frontal brain tumours (n=8), high grade frontal brain tumours (8) and benign meningioma (8). All patients with low grade and benign tumours underwent surgical excision, 4 high grade patients had biopsy only. Only low grade and high grade had radiotherapy. UK	Median dose for low grade tumours was 55 Gy and for high grade was 60 Gy.	assessed using neuropsychological tests. 1st test was 4-30 days post-op, 2nd test was 4.25-10 months post-op (after some had had radiotherapy).	tumours and benign tumours. The group with high grade tumours showed decline (on average). Cognitive decline could be due to radiotherapy or tumour progression, but tumour progression was not measured in all patients. ¾ (75%) of patients high grade tumours that were biopsied only showed significant cognitive decline. ¼ (25%) of patients with high grade tumours that were excised showed such decline.	designed to answer question. Different histological types of the 3 groups, and lack of surgery in some HGG confounds comparisons (needs case mix adjustment). Low grade group was younger than group 2, and group 3 were oldest (although no statistical sig. difference).		
(Cohen *et al.* 2002)	31 patients (after resection of acoustic neuroma) were assigned to either vestibular rehabilitation (n=16) or control (n=15) groups.	Vestibular rehabilitation, consisting of head and body exercises.	Vertigo intensity and frequency, low frequency vestibulo-ocular reflex (VOR), posturography, and path integration. Outcomes measured	Multivariate analyses were carried out to determine the effect of age, tumour size and rehabilitation on each outcome. Vertigo Age, tumour size and rehabilitation did not predict vertigo intensity or frequency.	Small study with no power calculation. No details of randomisation. Loss of 29% of	RCT	1-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Mean tumour size (»2cm) and age (»50 years) were similar in both groups. Surgical approach was predominantly translabyrinthine in both groups. USA		on discharge from hospital (around 1 week post-op) in all patients and post-discharge in 22/31 (71%) patients.	VOR VOR anomalies were related to tumour size, but not age or rehabilitation group. Posturography and path integration Functional motor skills were related to tumour size, but not to age or rehabilitation group. Authors' conclusions Compensation is influenced by tumour size but not by age or early postoperative vestibular rehabilitation.	patients to long term follow-up.		
(Hahn *et al.* 2003)	68 patients with brain tumours prior to radiotherapy. Surgical status not reported. Tumour type was: GBM (n=30), anaplastic astrocytoma (16), anaplastic oligodendroglioma (4), oligodendroglioma (5) and other (13). Mean age varied between tumour groups and	None, aim was to determine the prognostic factors for cognitive deficits in order to target future interventions in patients with malignant brain tumours.	Cognitive functioning assessed using neuropsychological tests. Patients and carers perceived QOL, rated on a number of scales.	Patients with glioblastoma had poorer psychomotor speed and visual tracking than the other patients. Differences in patients with left or right hemisphere lesions were noted on some of the tests. No significant differences were observed between the functioning of patients with small lesions (<5cm) and those with larger lesions. Patients and carer's assessment of QOL were correlated.	Multiple measures (>15) and statistical tests but a priori hypotheses are unclear.	Case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	was included as a covariate in the analysis. USA						
(Herman *et al.* 2003).	30 patients with brain metastases (17 women, 13 men). Primary cancers were: 14 lung, 7 breast, 4 melanomas, 2 unknown primary and 3 others. 15 patients had 3 or more brain metastases. Median age 56 years (range 18 - 85). USA	Neuropsychological test battery.	Cognitive functioning, time taken to complete tests, and compliance with testing	100% compliance with testing was reported. Mean time taken to complete test battery was 23 min (SD 6 min). Authors interpret this as a demonstration of the feasibility of neuropsychological testing in this group.	No comparison group and no real research question. Criteria for feasibility not defined beforehand.	Case series	3-
(Klein *et al.* 2001)	68 newly diagnosed and histologically confirmed high-grade glioma patients and 50 newly diagnosed patients with histologically confirmed locally advanced or metastatic non-small	All patients were tested before radiotherapy/ chemotherapy Glioma patients had had surgery (biopsy, gross total or subtotal resection). Aim: to determine the HRQOL and	KPS Activities of daily living (ADL) Neurological function using the Neurological Functional Status Scale developed by Order et al.	HRQL was similar for glioma and NSCLC patients. HRQL was lower for both patient groups than healthy controls. Patients with glioma had significantly more neurological symptoms and poorer objective and subjective functioning than the NSCLC group. Compared with the healthy controls, all glioma patients had cognitive impairment as had 52% of NSCLC patients. Visual and motor deficits in the glioma group	The authors concluded that systematic assessment of cognitive function and QOL should be included in clinical trials. Authors report one	Observational with matched comparison group	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	cell lung cancer (NSCLC) . Patients had to have no clinical evidence of brain metastases and a life expectancy > 3 months and be eligible for radiotherapy. NSCLC patients were matched for age and sex with glioma patients. Healthy controls were individually matched with glioma patients and NSCLC patients for age, sex and educational level. The Netherlands	neuropsychological functioning of newly diagnosed, high-grade glioma patients who had undergone a biopsy or resection and to compare results with those of patients with NSCLC and with healthy controls	Self-reported cognitive functioning using a six-item scale developed for the Medical Outcomes study. Health related quality of life (HRQL) assessed using the MOS SF-36 Brain tumour specific HRQL assessed using the Brain Cancer Module Neuropsychological status assessed using a battery of standard tests.	seemed to be responsible for poorer cognitive functioning in glioma patients. The extent of tumour resection was not associated with neurological functioning.	limitation as being the lack of testing before surgery in glioma patients. A high proportion of eligible patients with NSCLC declined to participate (40/90[44%] versus 18/90[20%] with glioma). Included patients with NSCLC may not have been representative.		
(Klein *et al.* 2002)	195 patients with low-grade glioma (astrocytoma, oligodendroglioma, or oligoastrocytoma) were compared with	Glioma patients had been treated with radiotherapy (53%) and without radiotherapy. Patients receiving RT	KPS Barthel Index of Daily Living Neurological functional status scale developed by	Significantly more glioma patients had cognitive impairment than haematological cancer patients (34% versus 22%, p = 0.035 after adjusting for age, sex, education and disease duration). More irradiated patients had impaired cognitive function compared with non-irradiated patients but the difference	The authors concluded that findings suggest that it is the tumour itself that has the most deleterious	Observational with comparison group	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	100 patients with low grade haematological cancers (non-Hodgkins lymphoma or chronic lymphatic leukaemia) without signs of CNS involvement. Patients had to have no clinical signs of tumour recurrence for > 1 year after diagnosis and primary treatment and no radiological signs of recurrence in the 3 months before testing. Both groups were also compared with healthy controls matched individually with patients by age, sex and educational level. The Netherlands	had to have received RT as the primary treatment within 2 month of diagnosis Aim: to compare the cognitive function of glioma patients with haematological malignancy patients and healthy controls and to identify the factors associated with cognitive impairment. .	Order at al. Battery of tests of cognitive function. Cognitive disability defined as a score 2 SD below mean for healthy control. Overall disability score calculated using the number of impaired tests Self-reported cognitive function assessed using the 6-item scale developed for Medical Outcomes study	was not statistically significant (39% versus 26/29%, p = 0.145) Cognitive disability in the memory domain was only found in radiotherapy patients treated with fraction doses > 2Gy but this was a post-hoc analysis. Antiepileptic drug use was associated with impaired attention and executive functioning (RR for perception and psychomotor speed was 6.48).	effect on cognitive function and that radiotherapy mainly results in additional long-term cognitive disability when high fraction doses are used. The influence of multiple outcome measures on the level of significance was not considered.		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Lincoln *et al.* 2000)}	Inclusion criteria: RCT studies of patients with attentional deficits following stroke, as confirmed by neurological examination or CT scan. Exclusion criteria: Trials in which more than 25% patients had attentional deficits with non-stroke aetiology. Drug treatments were not included.	Included studies of interventions involving practice on attentional tasks.	Alertness, concentration and activities of daily living.	Only 2 RCTs were included and neither study measured outcomes blind to the intervention group. Meta-analysis suggested improved alertness (SMD 0.77; 95% CI [0.21, 1.33]) and concentration (SMD, 1.03; 95% CI [0.45, 1.61]) with the intervention. Significant heterogeneity was seen in both analyses. One of the studies considered activities of daily living, but did not find any effect due to the intervention.	Of indirect relevance.	Systematic review.	1+
(Majid *et al.* 2000)	Inclusion criteria: Randomised or quasi-randomised trials comparing memory treatment to control in patients with stroke. Exclusion criteria: Trials in which more	Included studies of interventions that attempted to modify memory function by means of practice, internal mnemonics or other coping strategies.	Memory impairment, subjective assessment of memory function and functional disability.	A single RCT was included which showed that memory training had no significant effect on memory impairment or subjective memory complaints.	Single RCT with only 6 people in each study arm. Indirectly relevant.	Systematic review.	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	than 25% patients had non-stroke aetiology. Drug treatment studies.						
(Bowen *et al.* 2002)	Inclusion criteria: Randomised or quasi-randomised trials comparing cognitive rehabilitation to control in patients with spatial neglect following stroke. Exclusion criteria: Trials in which more than 25% patients had non-stroke aetiology. Drug treatment studies.	Included studies of therapy designed to reduce cognitive deficit or disability.	Visual scanning and attention skills; activities of daily living.	Scanning and attention skills 13 studies were included. Evidence from studies which measured attention using cancellation and line bisection tasks suggested benefit (in the short term) from cognitive rehabilitation. 4 studies did not observe long term benefits of such therapy. Activities of daily living 6 studies reported a measure of disability. The overall effect of cognitive therapy on this outcome was not significant.	Of indirect relevance. Sample sizes of the primary studies were small (often less than 10 people in each study arm). 3/15 of the studies were classed as adequate for randomisation and allocation concealment.	Systematic review.	1+
(Blue Cross Blue Shield Association 2002)	Study inclusion criteria Studies of >8 adults, results reported for patients with traumatic brain injury, controlled trial	Studies reporting cognitive rehabilitation treatment programs.	Functional ability, activities of daily living and return to work.	Four studies met the inclusion criteria. Evidence of the effectiveness of cognitive rehabilitation in people with traumatic brain injury was inconclusive. Two studies reported benefits from such treatment and two studies reported no difference between treatment and control groups. The reviewers noted heterogeneity in the study populations and in the interventions.	Indirectly relevant to people with brain tumours.	Systematic review conducted for health technology assessment.	1+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	reporting health outcomes, adequate description of methods and published 1996–2002						
(Cicerone *et al.* 2005)	Aim was to develop an evidence based guideline for the cognitive rehabilitation of people with traumatic brain injury or stroke Study inclusion criteria Studies about the rehabilitation of people with attention, visuospatial, communication, memory or problem solving deficits, following stroke or TBI. Exclusion criteria Non-intervention studies (or those with	Studies reporting cognitive rehabilitation for deficits of attention, visuospatial, communication, memory or problem solving.	Reviewers synthesised data on clinical effectiveness and treatment efficacy.	Recommendations were based on evidence from at least one RCT (practice standards): Attention deficits Guideline recommends the use of strategy training for people with TBI in the post-acute period (but not in the acute period). Visuospatial deficits Visuospatial rehabilitation is recommended for those with visuospatial deficits following right hemisphere stroke. Apraxia Gestural or strategy training is recommended for apraxia during acute rehabilitation. Communication deficits Cognitive linguistic therapy is recommended during acut and post acute rehabilitation for people with language deficits following a left hemisphere stroke. Specific interventions for functional communication deficits are recommended for those with TBI. Memory deficits	Guideline developed by the American Congress of Rehabilitation Medicine. Indirectly relevant to people with brain tumours.	Clinical guideline.	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	inadequate description of intervention), non stroke or TBI aetiology and non-treatment studies.			Memory strategies may be effective for those with mild impairment due to TBI. Such memory aids include internal strategies (like visual imagery) and external memory aids (such as notebooks). Practice guidelines and options were also proposed, but were not as strongly evidence-based.			
(Chesnut *et al.* 1999)	Inclusion criteria: Studies of the cognitive rehabilitation of people who sustained traumatic brain injury between the ages of 18 and 65 years whose functional status level allowed for employment and/or community integration, but who required an intervention to facilitate success.	Cognitive rehabilitation.	Various neuropsychological and psychometric test items.	Overall, evidence for cognitive rehabilitation was inconclusive. Five RCTs reported outcomes which the reviewers considered of clinical importance (usually neuropsychological tests). One of these trials reported a treatment effect in favour of cognitive rehabilitation, the remaining four did not. Six RCTs reported intermediate outcomes (outcomes which the reviewers considered of debatable clinical importance). Beneficial effects of cognitive rehabilitation were seen in three of these trials, the remaining three did not observe treatment effects. Three out of the four non-randomised comparative studies observed positive treatment effects.	Indirectly relevant to people with brain tumours.	Systematic review conducted for health technology assessment.	1+
(Meyers *et al.* 2000)	80 patients with either recurrent glioblastoma multiforme (68%) or	Patients had already received treatment with radiation and chemotherapy.	Neurocognitive function assessed using standardised tests (Digit Span,	Overall median survival was 35 weeks (95% CI: 30, 53 weeks). 26 week survival was 66%	The authors concluded that assessment of cognition, QOL and	Retrospective case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	anaplastic astrocytoma (32%). Characteristics: median age 48 years (range 25 to 67); 65% male; KPS range 60 to 100; median time from diagnosis to study entry was 7 months (range 3 to 216 months) USA	Aim: to assess the contribution of cognitive function in predicting the survival of patients with recurrent brain tumours	Digit for graphomotor speed, Hopkins Verbal Learning Test, Controlled Oral Word Association, Trail Making test part A and B, Grooved Pegboard) Activities of daily living (ADL) using Functional Independence Measure. Quality of life (QOL) using Functional Assessment of Cancer Therapy with brain tumour specific module Outcomes were assessed monthly	52 week survival was 39% After adjusting for age, KPS, histology and time from diagnosis to test using multivariate Cox regression analysis, the cognitive variables significantly associated with survival were: performance on the memory test ($p < 0.0001$); Digit span ($p = 0.0002$); and Digit symbol ($p = 0.015$). These 3 test and clinical variables accounted for 49% of the variance in survival. ADL and QOL were not related to survival after adjusting for clinical variables.	function is practical for patients with brain tumours and can provide additional information about new treatments.		
(Carlson *et al.* 2004)	3095 people (>18 years of age) with cancer attending a single cancer centre	Aim was to measure levels of distress in a large group of people with cancer, and	Levels of distress measured using questionnaires and brief symptom	Levels of distress by primary cancer site: People with lung cancer reported the highest levels of distress, followed by a cluster containing pancreatic, Hodgkin's lymphoma, brain, head and neck, leukaemia	Unclear how criteria for a distressed case were defined.	Cross sectional	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	were invited to complete the questionnaires. 2776 people agreed to participate of whom 81 had a brain tumour. Data were collected over a 1 month period in 2003. CANADA	assess their awareness and use of psychosocial services.	inventory. Awareness and use of psychosocial resources.	and lymphoma. A second cluster of primary tumour sites, gynaecological, breast, melanoma, colon and prostate, reported lower levels of distress. 45% of people with brain cancer met the criteria for a distressed case. Awareness and use of psychosocial services 68% of patients were aware of such resources. 18% had used the services in the past, 7% were currently using them and 20% planned to use them in the future. Past, current and future users combined made up 36% of the sample. Approximately half of the patients identified as distressed cases had not used psychosocial services offered by the hospital, and did not intend to in the future.	Most patients (51.9%) were attending the hospital for follow-up.		
(Litofsky *et al.* 2004)	Patients enrolled in the Glioma Outcomes Project (1997–2000), a longitudinal multicentre observational study. 598 of the 788 patients in the project were included in this analysis. The remaining patients were excluded due to	Aim was to report the incidence of depression	Patient and doctor reported depression. Treatment for depression. Patient satisfaction and survival.	Denominators varied because of missing data. Patient reports of depression Patients scoring 61 or less on the SF-36 Mental Health Scale were classed as reporting depression (MHS-61 depression). 315/340 (93%) defined themselves as MHS-61 depressed in the immediate post operative period. 126/359 (35%) reported experiencing at least 2 weeks depression in the year preceeding surgery. 94% of patients were MHS-61 depressed at 3 months post surgery (denominator not reported), and 91% at 6	Significant amounts of missing data, especially for patient reported depression. Discordance between patient and doctor reported depression.	Case series	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	missing clinical data. Patients had a diagnosis of grade III or IV glioma. Missing data also meant varying totals in subgroup analyses. USA			months post-surgery. Doctor reports of depression Doctors reported depression less frequently than the patients. In the immediate post operative 87/573 (15%) of patients were reported as depressed by their doctor. This figure increased to 22% at 3 post operative months and 22% at 6 months. At all time points patients' and doctors' reports of clinically significant depression were discordant (Cohen's kappa: k=0.02 initially, k=0.01 at 3 months and k=0.05 at 6 months). Treatment for depression The pharmacological treatment for depression lagged behind its diagnosis, with 6% of patients recieving antidepressants, 7% in the immediate post operative period, 15% at 3 month follow up and 16% at 6 month follow up. Depression and survival Depression (MHS-61) was not a significant prognostic factor for survival in the group as a whole. In the subgroup of patients with glioblastoma multiforme doctor reported depression was related to reduced survival, median survival was 34 weeks for depressed patients compared to 41 weeks for those not reported as depressed ($p<0.01$). Similarly patient reported depression was a significant adverse prognostic factor	Approximately half those reported as depressed by their doctor received antidepressants. The study relied upon voluntary enrolment of patients by their doctors. Audits estimated that centres enrolled between 15 and 41% of eligible patients. Possible selection bias, depressed patients may have been less likely to enrol.		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				in this group. Patient satisfaction Most patients reported satisfaction with their care, whether depressed or not.			
(Regine *et al.* 2004)	55 patients enrolled in an RCT (RTOG-BR-0018). Inclusion criteria: CT or MRI measurable brain metastasis (82% had more than one brain metastasis), with proof of primary tumour. Zubrod performance status of 0–1. Neurologic performance status of 0–2. Life expectancy >3 months. Exclusion criteria: Hematopoietic primary or evidence of leptomeningeal	A test battery of 5 cognitive measures and a quality of life instrument. The aim of the study was to establish the feasibility of performing a neuropsychological and QOL test battery in people with brain metastases	Compliance with neuropsychological test battery. Proportion of assessments generating usable data.	Compliance with test procedure The pre-treatment compliance rate was more than 95% for all of the tests. Immediate post treatment compliance was at least 84% for all tests, and fell to 78% at one month after treatment. Non-compliance with the tests was usually due to patient factors (refusal, incomprehension or being too ill to participate). Data quality There were errors in the administration or scoring of 10% of the tests overall.	Compliance was reduced at 1 month post treatment. Use of neurocognitive status as an outcome measure could be subject to bias if patients with especially poor performance cannot be evaluated. Multi-centre trial at 36 sites, but inter-site variability was not analysed. Investigators at each site received training and certification in the use of the tests.	3-	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	tumour spread.						

Table 11.2 What is the optimum method for providing information to neuro-oncology patients with special needs?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Lidstone *et al.* 2003)	480 outpatients with a cancer diagnosis. Sixty patients from each of eight primary tumour groups (lung, breast, gastrointestinal, gynaecological, urological, head and neck, brain and lymphoma) were recruited	Measurement of symptoms and concerns of people with cancer This study aimed to define and prioritize the need for specialist palliative care (SPC) in cancer outpatient clinics	The checklist that was used, contained 29 items concerning symptoms and concerns of cancer patients that were highly relevant to palliative care of cancer outpatients	Out of the 8 cancer types investigated in this study, patients with brain tumours reported the second highest level of symptoms and concerns. With a mean of 11.4 +/- 5.2SD items recorded. Fatigue was common problem experienced by 79% of all the patients involved and 90% of brain tumour patients reported this as a common symptom and concern. 83% of this group also reported problems with concentrating and memory loss. Around 70% of brain tumour patients reported having concerns about the future and not being able to do things as they usually do. 38% reported a lack of information about the illness or treatment.	This descriptive study provided important information about the needs of cancer outpatients which is relevant to specialist palliative care. It highlighted important communication problems about lack of information about illness and treatment.	Cross sectional	2-
(Davies & Higginson 2003)	Patients 18 years and older, diagnosed anywhere in the world with malignant glioma. Studies of patients with other cancers were excluded.	The authors aimed to review the evidence on communication, information and support for adults with malignant cerebral glioma.	Outcomes were measured using questionnaire, interview or observation and included patient or relative: awareness of the diagnosis and prognosis, satisfaction with	Twelve observational studies were found, although many were limited by sample selection, description and setting. Patient awareness of their prognosis varied, and relatives appeared more aware. There was no direct evidence about what patients and relatives wanted to know, but qualitative studies suggested that an individual approach to disclosure and maintaining hope were important. Most patients and relatives valued specialist nurse support highly. No specific studies of interventions to break bad news,	Qualitative and quantitative studies were assessed, graded for methodological quality and combined.	Systematic review	2++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
			information or care, psychological distress, uptake of new services or information and professional communication skills.	giving information or training staff were found for these patients. Evidence from observational studies suggests that these patients need individually tailored communication and information, and specialist support. Existing intervention studies of patients with other cancers may suggest effective strategies			
(Sardell *et al.* 2000)	43 patients were completing primary therapy for high grade glioma and who were suitable for CCF and offered NTF as an alternative	Nurse-led telephone follow-up (NTF) for patients with high-grade glioma as an alternative to conventional clinical follow-up CCF. The nurse conducted telephone follow up with patients, monthly for 3 months. The patient was seen in an outpatient clinic in the 4th month. In the absence of recurrent /progressive disease NTF continued.	Patient satisfaction, assessed using surveys.	254 telephone calls were made, of which 234 were routine and 20 non-routine, being initiated by the patients or their carers. NTF was considered as a sufficient replacement for CCF during the stable phase of the disease. There were 41 unscheduled clinic visits, of which 31 were at the time of progression and usually initiated at NTF. The majority of unplanned visits were due to a change in symptoms and would not have been avoided with CCF carried out at the same time intervals. Patient satisfaction Patient satisfaction was high, with a median satisfaction score of 9, (range 3.6-10) on a scale of 0-10. NTF provides an alternative approach to conventional hospital attendance and moves the emphasis away from cancer surveillance to a more patient centred supportive model. It can be carried out without apparent detriment to the patient and is associated with high satisfaction rating	Quasi-intervention study (pilot study), no control measurement was reported (control was conventional clinic follow-up)		3
(Grimes 2000)	A random set of 50 people with brain	Two multi-disciplinary teams were set up,	Key problems, identified though	The communications group developed a new package of documentation which guides staff through the issues	This study provided a	Cross sectional	3

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	tumours (who attended the service as in patient or out patient) were interviewed in their own homes.	one working on the out-patients service, and the other determining how bad news was given to patients. Skilled change facilitators helped the teams to analyse why problems occur, and to develop and implement solutions.	analysis of the patients' comments.	that should be discussed with a patient at appropriate points during the stay in hospital. The turnaround time for biopsy results has been reduced, and these are now given to patients at a structured meeting coordinated by a nurse. Training programmes have been introduced, and new written information is now available for patients. New processes have been introduced into the out-patient department in order to improve the availability of clinical scans, increase capacity reduce waiting times, and improve the quality of clinical consultations. A range of key performance indicators, devised to measure the impact of the improvements, shows that the new systems have been very effective.	valuable tool for a change process at this hospital, to improve health care services for patients with brain tumours. It involved relevant practitioners in the process.	study	

Table 11.3 Does physiotherapy, occupational therapy or allied health professional input shorten hospital stays/facilitate discharge/prevent re-admission of patients with brain tumours?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Bell *et al.* 1998)	Patients with CNS tumours Review undertaken in the US	None: discusses findings of primary studies	Reports published outcomes of primary studies of aetiology, treatment and rehabilitation.	Authors report that: Early ambulation may help prevent deep vein thrombosis (DVT) Multidimensional scales to measure functioning that encompass cognitive, emotional and social dimensions may be the most useful scales. Rehabilitative interventions should consider the pathology of the tumour and expected course of progression, and may be preventive, restorative, supportive or palliative. Motor, self care and bladder / bowel rehabilitation should be approached as in other neurological conditions, whilst accounting for tumour progression. Family involvement and teaching is paramount, and spousal relationships can be seriously affected by CNS tumours A small amount of evidence suggests that some patients with glioma return to work. On going aggressive therapy need not preclude rehabilitative strategies and strategies for patients with head injury may be efficacious.	*Describes pathology and classification of CNS tumours, treatment strategies and rehabilitative interventions*	Review (127 references)	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Cohen *et al.* 2002)	31 patients (after resection of acoustic neuroma) were assigned to either vestibular rehabilitation (n=16) or control (n=15) groups. Mean tumour size (»2cm) and age (»50 years) were similar in both groups. Surgical approach was predominantly translabyrinthine in both groups. USA	Vestibular rehabilitation, consisting of head and body exercises.	Vertigo intensity and frequency, low frequency vestibulo-ocular reflex (VOR), posturography, and path integration. Outcomes measured on discharge from hospital (around 1 week post-op) in all patients and post-discharge in 22/31 (71%) patients.	Multivariate analyses were carried out to determine the effect of age, tumour size and rehabilitation on each outcome. Vertigo Age, tumour size and rehabilitation did not predict vertigo intensity or frequency. VOR VOR anomalies were related to tumour size, but not age or rehabilitation group. Posturography and path integration Functional motor skills were related to tumour size, but not to age or rehabilitation group. Authors' conclusions Compensation is influenced by tumour size but not by age or early postoperative vestibular rehabilitation.	Small study with no power calculation. No details of randomisation. Loss of 29% of patients to long term follow-up.	RCT	1-
(Cole *et al.* 2000)	Patients referred to an inpatient rehabilitation facility from 1995	Inpatient rehabilitation from a multidisciplinary team.	Cognitive and motor functioning measured using components of	Four subgroup analyses were performed according to: the site of primary tumour, specific impairment (asthenia, CNS dysfunction, orthopaedic, or postoperative),	*Although many patients showed improved functioning, this cannot be*	Retrospective case series	3-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	to 1998. Of 302 patients referred with a history of cancer, 102 were excluded from the analysis for the following reasons: their current need for rehabilitation was not due to cancer (n=84), they were discharged to another facility (n=15) or their records were incomplete (n=3). In the 200 included patients, cancer site was: 33 had haematological, 33 lung, 32 breast, 32 genitourinary, 21 GI, 13 intracranial, 12 head or neck, 12 gynaecological and 12 other.		the Functional Independence Measure (FIM).	cancer stage and active treatment (or not) during rehab. FIM scores on admission and discharge were compared. Motor function All subgroups showed an improvement in the motor function component of the FIM. For people with intracranial neoplasm (n=13) admission (mean 43, SD 10.2) and discharge scores (mean 48.8, SD 6.2) were significantly different ($F=5.99$, $p<0.05$). For people with CNS dysfunction (n=34) admission (mean 42.7, SD 7.6) and discharge scores (mean 48.8, SD 8.0) were significantly different ($F=23.3$, $p<0.0001$). Cognitive function In the subgroup analyses 3 groups did not show an improvement in the cognitive function component of the FIM between admission and discharge. For people with intracranial neoplasm (n=13) admission (mean 48.7 SD 11.3) and discharge scores (mean 49.1, SD 9.1) were not significantly different ($F=0.13$, $p>0.05$). Similarly for people with CNS dysfunction (n=34) admission (mean 48.9, SD 13.0) and discharge (mean 50.6, SD 12.2), ($F=2.08$, $p>0.05$) and for people with stage IV	*directly attributed to rehabilitation due to the design of the study, there was no control group.* *Very small sample of people with brain tumours (n=13). 34 people were referred for CNS dysfunction – possibly brain metastases.* *Ordinal FIM scores were transformed using 'Rasch analysis' and parametric stats were done.*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	USA			disease (Deitz classification) (n=11) admission (mean 52.0, SD 6.8) and discharge scores (mean 53.4, SD 6.9), (F=2.6, p>0.05).			
(Garrard *et al.* 2004).	21 patients with primary or secondary neurological malignancy Patients were in-patients at the Neurological Rehabilitation Unit of the National Hospital for Neurology and Neurosurgery. 8 patients had primary CNS tumours. 14 patients had tumours metastatic to the CNS. Mean age at referral was 54	Aim: to describe the benefits and problems associated with rehabilitation of patients with neurological malignancy.	Disability on admission and at discharge measured by the Functional Independence Measure (FIM) and the Barthel index. Comparison was made between patients with primary versus secondary malignancy. Rate of achievement of patient goals.	Vascular events accounted for the neurological disability in 47% of cases (commonly as a complication of surgery or radiotherapy), and compression / invasion of neural structures in 42% of cases. Mean length of stay at the unit was 39 days and The majority of patients had poor prognosis (< 3 months). 19/21 patients were discharged home and 2/21 patients were discharged to acute hospitals. 4/19 required readmission from home to acute hospital. Mean FIM score improved significantly from admission to discharge in terms of motor function (improvement by 17.6 points, p<0.001), total function (improvement by 17.5 points, p<0.001) but no significant improvement was seen in FIM score for cognitive function (no improvement, p = 0.922). Mean Barthel score increased by 5.8 points (p<0.001).	*Patients with benign tumours excluded, as were patients treated ant the centre with remote history of cancer, but with unrelated neurological deterioration.* *Small sample size. No confidence intervals provided and minor numerical / statistical errors apparent.* *Limited generalisability since study population was young and had received specific referral route.*	Retrospective case series study.	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	years. **UK**			Mean rate of goal achievement was 88%. Authors conclude that patients with malignancy can benefit from in-patient rehabilitation, although rapid deterioration may occur in a significant proportion.	*Authors discuss findings in the context of interface between palliative and rehabilitative care.*		
(Huang *et al.* 1998).	78 patients with primary or metastatic brain tumours matched one-to-one by age and side of lesion with 78 patients with traumatic brain injury (TBI). Patients had mean age 58 years (SD 14.5), range 23-84 years. **US**	Aims: To test whether patients with brain tumours make similar functional gains through rehabilitation to patients with TBI. To assess whether length of stay in rehabilitation is different between the two groups. To assess whether discharge rate to the community setting is similar between the two	Length of stay in rehabilitation. Functional independence measure (FIM) score, with sub scores reported for activity of daily living (ADL), mobility and cognition. FIM efficiency as a function of length of stay.	The two groups were demographically similar but for gender ($p<0.01$) with more female patients in the tumour group. On admission FIM scores were similar between groups except that TBI patients had lower cognitive FIM score ($p=0.01$). On discharge there was no significant difference between groups for total FIM score or for any FIM sub score. Both groups improved significantly for FIM score. Change in FIM score was significantly greater in the tumour group for total FIM score ($p<0.01$), ADL FIM score ($p<0.01$) and mobility FIM score ($p<0.01$). No differences were noted for change in cognitive FIM between groups ($p=0.06$).	*78 patients with brain tumours were selected on the grounds that they were medically stable and willing and fit candidates for rehabilitation with support arrangements for discharge to the community.* *Only patients who completed their rehabilitation scheme were analysed.* *The TBI patients included patients with pre-existing*	Prospective case series with analysis by matched pairs	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
		groups.		FIM efficiency was similar between groups (p=0.3). Length of stay: TBI patients stayed an average of 6 days longer in acute care (p<0.05) and 10 days longer in rehabilitative care (p<0.01) than tumour patients. Discharge environment: TBI patients were more likely to be discharged to institutional care than tumour patients (p<0.05). Author concludes that patients with brain tumours can achieve comparable discharge functional status to patients with TBI.	*neurological conditions or with substance abuse* *Length of stay in the acute setting may be a retrospective analysis* *Possible confounding since clinicians may have been eager to discharge patients with tumours sooner due to poor prognoses.* *Patients were not matched for admission FIM.*		
(Huang *et al.* 2001).	Aim: To review literature on quality of life and functional outcome in patients with brain tumour, from a rehabilitation perspective.	Considers rehabilitation interventions of primary studies.	Study notes findings of primary studies, with outcomes organised by studies of functional outcome, quality	Authors conclude that: Few studies measure functional outcome for patients with brain tumour in the rehabilitation setting Rehabilitation in both in patient / outpatient settings can improve functioning. Outcomes for clinicians to monitor should		Expert review	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
			of life and areas for future research.	include quality of life as well as survival It is uncertain for how long patients retain their functional status after discharge from rehabilitation, particularly for patients with longer prognosis such as those with LGG.			
(Marciniak *et al.* 2001).	120 patients who underwent an acute rehabilitation programme. CNS tumour type by admission was: Metastases (21) Astrocytoma (33) Meningioma (44) Other (33) **US**	Acute rehabilitation provided at a specialist centre. Aim of study = To assess the extent of functional gains measured before and after inpatient rehabilitation in patients who have primary or metastatic brain tumours, and to identify whether the tumour type, recurrent tumour, or ongoing radiation influences outcomes.	Motor and cognitive function were assessed on admission and after intervention by FIM score. Motor and cognitive efficiency were calculated as change in FIM divided by length of stay.	Mean FIM efficiencies +/- standard deviation for motor (.82 +/-.69) and cognitive (.15 +/-.24) functions were equivalent across primary and metastatic tumour types (F =.42, df = 3,103, p = NS; F =.45, df = 2,104, p = NS, respectively); Patients with metastatic disease had a significantly shorter length of stay at 18 +/- 12.3 days (t30,6 = 2.3, p =.03). Patients who received radiation during rehabilitation had a significantly greater (F = 4.1, df = 1,105, p <.05) motor efficiency score (1 +/-.79) than those who did not (.78 +/- 0.7). Patients with recurrent tumours made FIM cognitive changes equivalent to those of persons undergoing rehabilitation after their initial diagnosis, but their motor efficiency scores were significantly smaller (.55 +/-.39 vs.98 +/-.68, respectively) (F = 5.77, df =	*120 patients analysed as 132 admissions to the unit* *Distribution of tumour types in this series represented population based averages.* *Referred sample from a tertiary centre may not be representative of practice elsewhere*	Retrospective case series	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				1,85, p =.018), which reflected a significantly smaller FIM motor change. 85 (65%) of the 132 admissions were discharged home. Authors conclude: Metastatic or primary brain tumour type does not affect the efficiency of functional improvement during inpatient rehabilitation. Patients receiving concurrent radiation therapy make greater functional improvement per day than those not receiving radiation. Patients with recurrent tumours make significantly smaller functional motor gains than those completing inpatient rehabilitation after the tumour's initial diagnosis.			
(Mukand *et al.* 2001)	51 admissions, representing 49 patients with brain tumours: Glioblastoma 31.3% Meningioma 25.5% Metastatic 25.5%	Aim: To report on the neurological outcomes for a series of patients with brain tumours admitted for rehabilitation at a single centre.	Neurological deficits observed during rehabilitation. Change in FIM score from admission to discharge.	Mean length of stay was 19.7 days (range 3-57 days). The most common deficit was impaired cognition (80%), followed by weakness (78%), visual-perceptual deficit (53%), sensory loss (38%), and bowel and bladder dysfunction (37%). Less common problems, in decreasing	*Some patients had received limited rehabilitation in acute care.* *All patients had received surgery (82%), radiotherapy (41%) or chemotherapy (21%) in acute care*	Retrospective case series	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Mean age 59.7 years (range 27-85 years). **US**			incidence, were cranial nerve palsy, dysarthria, dysphagia, aphasia, ataxia, and diplopia. Thirty-eight (74.5%) patients had three or more concurrent neurologic deficits, and 20 (39.2%) patients had five or more deficits. Concurrent deficits among patients with hemi- and tetraparesis involved cognition (n = 29 patients), visual-perceptual function, sensation, cranial nerve palsy, and neurogenic bowel/bladder. The average admission FIM score of 67.2 (range 34-100) increased to 87.1 (range 37-121) at the time of discharge, with similar gains between patients with primary brain tumour and metastatic disease. Thirty-five patients were discharged home, seven to a nursing home, and one to hospice care; there were eight acute transfers. The authors conclude that comprehensive, interdisciplinary rehabilitation for patients with primary and metastatic brain tumours is beneficial.	*Statistical significance was not assessed for change in FIM scores*		

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(O'Dell *et al.* 1998)	40 consecutive patients with a variety of tumour types (40% were either glioblastoma multiforme or meningioma) and a mean age of 53.1 (SD 15.4) years. Sixty percent were men, 25% had recurrent tumours, and 15% had metastatic disease. Patients had the following tumours: Glioblastma multiforme (20%) Meningioma (20%) Astrocytoma (12.5%) Metastasis (12.5%) Oligodendroglioma (5%) Pituitary adenoma (5%)	Specialist rehabilitation received at a brain injury rehabilitation unit Aim: to document functional outcome in persons with brain tumours undergoing inpatient rehabilitation and to compare outcomes with a group of traumatically brain injured (TBI) patients.	FIM status on admission and on discharge Change in FIM scores, length of rehabilitation stay (LOS), and discharge disposition.	The mean LOS for the tumour group was 17.8 (SD 9.9) days, mean FIM gain was 25.4 (SD 20.1) points, and 82.5% were discharged home. No demographic or tumour characteristic was statistically significant in predicting functional outcome at discharge, but greater gains were seen for persons with the diagnosis of meningioma, those with left-sided cerebral lesions, and those not receiving radiation therapy. TBI patients made statistically significant greater gains in total FIM change (34.6 vs 25.4), self-care (12.3 vs 8.5), and social cognition (5.2 vs 3.6). However, FIM efficiency and LOS were not statistically different between the TBI and tumour groups (1.9 vs 1.5 FIM points/day and 22.1 vs 17.8 days, respectively). 33 (82.5%) of patients were discharged home. Authors conclude: Daily functional gains made by persons with brain tumour undergoing rehabilitation were similar to those made by a group of persons with TBI matched by age, gender, and admission	*Patients who had received radiotherapy may have had poorer prognoses at outset* *LOS between patients with brain tumour and patients with TBI may be affected by tendancy for early discharge for patients with brain tumour due to poor prognosis*	Retrospective case series	

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Other (25%) Also, 40 patients with traumatic brain injury (TBI) matched for age, gender, and admission functional status. **US**			functional status. Further research should use larger samples and address the impact of psychosocial and team factors on LOS and discharge disposition.			

Table 11.4 What are the general palliative care needs of patients with brain or other CNS tumours?

Abbreviations: QOL, quality of life

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Taillibert & Delattre 2005).	People with brain metastases	Palliative care	The authors selected and reviewed papers published in 2004-2005, which they thought were relevant to the palliative care of people with brain metastases.	The authors review treatments for symptoms caused by brain metastases (excluding tumour specific chemotherapy). They make the following points: • The avoidance of side effects is crucial to optimize QOL – many have poor prognosis and over treatment should be avoided. • The importance of correct steroid dose, balancing effectiveness with side effects. • These patients may experience seizures; indications for antiepileptic drugs are discussed. • Many patients will experience pain, cognitive disorder and fatigue. • Chemotherapy and radiotherapy side effects	Much of the cited literature is generic (not about people with brain metastases).	Review	4
(Taillibert *et al.* 2004)	People with primary brain tumours	Palliative care	The authors selected papers published in 2003, which they thought were relevant to the palliative care of people with brain tumours.	Authors stress that people with brain tumours present with more severe and specific symptoms in comparison with many other cancer patients. These include: • Epilepsy • Physical disability • Cognitive disorders • Pain • Side effects from steroid use • Fatigue	The recommendation for MDT management is based on an unpublished and highly biased study (Flowers, 2003). Most of the literature cited is generic: not	Review	4

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
				• Appetite/weight problems • Psychological problems The authors suggest that care should be by a multidisciplinary team. The assessment of patients needs should take account of any communication problems or cognitive impairments. They also make suggestions about ways to involve the patient's caregivers and family.	specifically about people with brain tumours.		

Chapter 12 Specialist palliative care

The question

What are the specialist palliative care needs of patients with brain or other CNS tumours?

The nature of the evidence

- A UK questionnaire study (Lidstone *et al.* 2003) of symptoms and concerns in outpatients attending a London cancer centre, including 60 patients with brain tumours.

- A UK cross sectional survey (Addington-Hall & Altmann 2000) attempted to identify factors associated with receipt of community specialist palliative care. 10% of the sample had a tumour of the thyroid, brain or other CNS.

- A Canadian cross sectional study (Carlson *et al.* 2004) measured levels of distress and fatigue in patients with cancer. A proportion of the sample had brain or other CNS tumours, and their results were presented separately.

Summary of the supporting evidence for the recommendations

There is consistent evidence, reviewed in the NICE guidance on *Improving Supportive and Palliative Care for Adults with Cancer,* to show that specialist palliative care teams in hospital, hospice and community settings are effective for the control of pain and symptoms of people with cancer. Patients cared for by such teams were also more satisfied than those cared for elsewhere. It follows that involvement of specialist palliative care, as soon as is appropriate, should benefit CNS tumour patients.

The importance of early involvement of specialist palliative care teams for the specific, and often severe, symptoms experienced by people presenting with CNS cancer is supported by the questionnaire study of Lidstone and co-workers (Lidstone *et al.* 2003). This study identified a high level of unmet need for specialist palliative care, especially amongst those with lung cancer or brain tumours. Similarly the study of Carlson and co-workers (Carlson *et al.* 2004) reported that 45% of patients with brain or other CNS tumours were distressed.

Addington-Hall and Altmann (Addington-Hall & Altmann 2000) noted that patients with brain tumours were less likely to receive specialist palliative care in the community. This may have been related to the severity of their symptoms.

Table 12.1 Specialist palliative care needs of patients with brain or other CNS tumours.

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Lidstone *et al.* 2003)	480 patients with a diagnosis of cancer; 60 patients from each of 8 primary tumour groups (lung, breast, gastrointestinal, gynaecological, urological, head and neck, brain and lymphoma). Patients attending outpatients clinics in a single cancer centre (in Feb-May 1999) were invited to participate. 95% of the patients with brain tumour had advanced disease, 5% were in remission. UK	The aim of the study was to define the need for specialist palliative care in cancer outpatient clinics using questionnaires.	Symptoms and concerns assessed using a questionnaire (the 29 item symptoms and concerns checklist).	Prevalence of symptoms and concerns The highest number of symptoms and concerns were reported by people with lung cancer, followed by those with brain tumours. Patients with a brain tumour reported the highest prevalence for 8 of the 29 items: fatigue (90%), memory or concentration problems (83%), not being able to do things (67%), treatment or care (44%) and lack of information (38%). In people with brain tumours the prevalence of problems likely to benefit from specialist palliative care was: pain (53%), mouth or taste problems (52%), sleep (50%), change in weight or appetite (47%), constipation (32%) and feeling or being sick (17%). 15% of the patients with a brain tumour reported receiving specialist palliative care input, 57% did not receive such input and for 35% input was unknown.	High response rate, 98% of those asked agreed to participate. Referral to specialist palliative care was not well documented in the medical notes, the authors had to ask patients themselves about this.	Cross sectional study.	3+
(Addington-Hall & Altmann 2000).	District health authorities were asked to participate and 20 agreed. In each of these districts 270 deaths were	The aim was to investigate the differences between people who receive care from community specialist palliative	Receipt of community specialist palliative care (CSPC).	The investigators used logistic regression to identify independent factors predicting whether patients received CSPC. From 23 original factors the following factors were significant at $p<0.05$ level: • Cancer site not lymphatic or haematopoietic tissue, • dependent with dressing or undressing,	Retrospective collection of data which relied upon accounts from relatives or carers. These people may	Cross sectional	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	sampled at random (cancer was the cause of death in 54% of cases, n=2915). The investigators then attempted to find out about each deceased person's last year (through relatives or carers). Response rate was 2074/2915 (71%) for cancer deaths. Sudden deaths (n=12) were excluded from the analysis. In 268 cases death was due to primary cancer of the brain, eye, thyroid or other part of the nervous system. UK	care nurses and those who do not by retrospectively tracing the details of people who had died of cancer.		• patient was less than 75 years, • dependent managing at night, • cancer site not brain or unspecified, • cancer site breast, • experienced nausea or vomiting, • experienced mental confusion Patients with brain tumours were less likely to receive CSPC ($p<0.01$).	not have been able to distinguish general from specialist palliative care.		
(Carlson *et al.* 2004)	3095 people (>18 years of age) with cancer attending a single cancer centre were invited to complete	The aims were to measure levels of distress in a large group of people with cancer, and assess their awareness and	Levels of distress measured using questionnaires and brief symptom inventory. Awareness and use of	Levels of distress by primary cancer site: People with lung cancer reported the highest levels of distress, followed by a cluster containing pancreatic, Hodgkin's lymphoma, brain, head and neck, leukaemia and lymphoma. A second cluster of primary tumour sites, gynaecological, breast, melanoma, colon and	Unclear how criteria for a 'distressed case' were defined. Most patients	Cross sectional	3+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	questionnaires. 2776 people agreed to participate of whom 81 had a brain tumour. Data were collected over a 1 month period in 2003. CANADA	use of psychosocial services.	psychosocial resources.	prostate, reported lower levels of distress. 45% of people with brain cancer met the criteria for a distressed case. Awareness and use of psychosocial services 68% of patients were aware of such resources. 18% had used the services in the past, 7% were currently using them and 20% planned to use them in the future. Past, current and future users combined made up 36% of the sample. Approximately half of the patients identified as distressed cases had not used psychosocial services offered by the hospital, and did not intend to in the future.	(51.9%) were attending the hospital for follow-up –possible selection bias.		

Chapter 13 Information management

The question

How complete is the registration of primary brain tumours in the UK?

The nature of the evidence

- A comprehensive review of international primary and secondary brain tumour incidence studies (Counsell & Grant 1998), published between 1966 and 1995, provided indirect evidence of the incompleteness of existing data sources.

- A 2001 cohort study (Pobereskin 2001) of primary brain tumour registration between 1992 and 1996 compared a clinical database with official figures from the Devon and Cornwall regional cancer intelligence unit.

- A cohort study of the incidence of primary and secondary brain tumours from 1989 to 1990 in the Lothian region of Scotland (Counsell *et al.* 1996), compared incidence using multiple methods of case ascertainment with that recorded in the regional cancer registry.

Summary of the supporting evidence for the recommendations

Limited evidence suggests that the registration is of primary brain tumours in the UK is likely to be incomplete. There is also some evidence that patients recorded in official cancer registries may not be a representative sample of the population with CNS tumours.

In the review of Counsell and Grant (Counsell & Grant 1998) studies using a single source (such as a cancer registry or hospital database) to identify patients reported incidence rates that were 30% lower than studies using two to four sources, and 50% lower than studies that used more than four sources.

In the cohort study of Pobereskin (Pobereskin 2001), only 52% of potential cases identified from the clinical database were entered in the official registry, suggesting that figures from registries could significantly underestimate the incidence of primary brain tumours. The study also reported that patients in the registry were not a

representative sample of the clinical population with brain tumours. Factors increasing the likelihood of registration were: having had an operation, being older than 60 and requirement for radiotherapy. Survival analysis using registry data could underestimate survival, since patients with poorer prognosis were more likely to be registered

The incidence study of Counsel and co-workers (Counsell *et al.* 1996), using multiple methods of case ascertainment, identified 442 patients only 34% of whom were entered in the Scottish Cancer Registry

Table 13.1 How complete is the registration of primary brain tumours in the UK?

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Pobereskin 2001)	The investigators identified 1480 people with primary brain tumours. They reviewed CT with contrast or MRI scans of the head carried out in Devon and Cornwall (1992-1995) to find cases with brain tumours. Secondary sources included pathology and operative databases in the two relevant neurosurgical centres. They also requested registrations coded as primary brain tumour (between 1992 and 1996) from the South West Cancer Intelligence Unit. Inclusion criteria	Ascertainment of patients with primary brain tumours in Devon and Cornwall	The incidence of primary brain tumours in the Devon and Cornwall. The registration rate of people with primary brain tumours in the region. Factors influencing a patient's chance of being recorded in the cancer registry.	The authors identified from the clinical databases 1480 patients fulfilling the criteria for registration. The official registry contained only 52% of these potential cases, suggesting that figures from registries could significantly underestimate the incidence of primary brain tumours. Patients in the registry were not a representative sample of the clinical population with brain tumours. For example, malignant (high grade) tumours were more likely to be registered than benign (72% and 42% registered respectively; OR 3.67; 95% CI 2.91 to 4.60) on univariate analysis. The significant predictors of registration on univariate analysis were included in a multivariate logistic model. On multivariate analysis, 3 factors increasing the likelihood of a patient being registered: • having had an operation (OR 5.47; 95%CI 4.19 to 7.17) • being older than 60 (OR 1.62; 95% CI 1.26 to 2.07) • having a malignant tumour (OR 2.52; 95% CI 1.74 to 3.66).	Survival calculated using registry data could be underestimated, since patients with poorer prognosis were more likely to be registered.	Cohort	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Patients with primary brain tumours diagnosed in Devon or Cornwall (1992-1995). Exclusion criteria Patients with the rarer tumours not routinely recorded by the cancer registry were excluded from the analysis. UK						
(Counsell & Grant 1998)	The investigators reviewed incidence studies published between 1966 and 1995 to identify differences in the incidence of brain tumours, by time, place, age and sex. 20 studies from 11 countries were included.	Ascertainment of the incidence of intracranial tumour, from a range of sources.	Incidence of intracranial tumours.	The reported incidence of primary brain tumours ranged from 4.3 to 18.6 cases per 100,000 per year (world age-standardised incidence rate). Studies based solely on existing cancer registries gave consistently lower incidences. The studies using a single source to identify patients reported incidence rates that were 30% lower than studies using two to four sources, and 50% lower than studies that used more than four sources.	None of the four UK studies relied solely on cancer registry data – so the reported figures do not necessarily reflect UK cancer registration rates.	Systematic review	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	Inclusion criteria Studies recording the incidence of primary intracranial tumours, published in English and recorded in MEDLINE 1966-1995. Exclusion criteria Studies reporting a single histological tumour type, studies reporting only childhood tumours or those published in abstract form.						
(Counsell *et al.* 1997)	228 people with incident primary intracranial tumours (1989-1990) identified from a population based incidence study. Inclusion criteria Patients with primary intracranial tumour	Case ascertainment using the Scottish Cancer Registry or using multiple sources (surgical and clinical databases and radiology records). .	The incidence of primary intracranial tumours and the completeness of their registration in the Scottish Cancer Registry.	The population based incidence study (using multiple methods of ascertainment) identified 228 new cases. The Scottish Cancer Registry contained 124 of these cases (54%). There were large differences in the sensitivity of the registry (the proportion of cases recorded) for different tumour types. The sensitivity of the registry was: • 84% for high grade neuroepithelial tumours (95% CI, 77 to 90%) • 87% for low grade neuroepithelial tumours (95% CI,	Patients requiring more therapy would have been in more clinical databases – more likely to be identified. Patients with poor prognosis more likely to be registered.	Cohort	2+

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	resident in the Lothian region of Scotland. Patients registered in 1989-1990. Patients with benign tumours were not consistently recorded in the cancer registry, although they were still included in the analysis. UK			79 to 93%) • 22% for meningeal tumours (95% CI, 11 to 37%) • 29% for sellar tumours (95% CI, 15 to 46%) • 0% for cranial nerve tumours (95% CI, 0 to 31%) • 0% for primary CNS lymphoma (95% CI, 0 to 31%) • 100% for germ cell tumours (1 tumour only) • 0% for cystic lesions (2 tumours only) • 54% for all primary tumours (95% CI, 48 to 61%)	Although benign brain tumours can be just as serious as malignant ones in some cases. The registry used ICD-9 coding system. The ICD-10 system now in use has some improvements with respect to the differentiation of intraspinal and intracranial tumours of uncertain behaviour.		

Chapter 14 Research

Summary of the supporting evidence for the recommendations

The research team did not do a separate literature search for this section. The limited volume of evidence identified during the searches for the preceding review demonstrates the incompleteness of the evidence base for the management of patients with many types of CNS tumour.

A recent study (Burnet *et al.* 2005) estimated years of life lost using data from the East Anglian Cancer Registry to represent the population burden from 17 cancers. While patients with tumours of the brain or other CNS had the highest average years of life lost per patient, this tumour group attracted only 1.5% of NCRI research spending (using 2002 figures).

There is some evidence to suggest low enrolment rates of patients with CNS tumours in clinical trials. Investigators from the Glioma Outcomes Project (Chang *et al.* 2005) reported in 2005 that only 15.1% of their group of 788 American patients with high grade glioma were in clinical trials.

The incompleteness of the evidence base for the management of CNS tumours is reflected in the number of systematic reviews unable to draw useful conclusions due to lack of high quality research. A recent review of randomised clinical trials in low grade glioma (Papagikos *et al.* 2005), for example, identified only three completed randomised controlled trials of radiotherapy and one of chemotherapy which was terminated prematurely. In the absence of high quality randomised controlled trials reviewers must rely on evidence from studies with diverse protocols which are often low powered. It is reasonable to assume that collaboration between research centres should improve the quality of evidence base both by increasing trial accrual and through the use of agreed protocols.

Table 14.1 Research

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
(Chang *et al.* 2005)	788 patients were enrolled into the Glioma Outcomes Project between 1997 and 2000. 134 doctors from 52 institutions enrolled the patients. Inclusion criteria Age at least 18 years. People with high grade glioma (III or IV) undergoing a first or second operation for diagnosis or treatment. Exclusion criteria Patients admitted for their third or subsequent operation. Patients who could not read or understand English, or who could not give written consent to	Any active treatment was recorded.	Morbidity and overall survival. Proportion of patients enrolled in clinical trials.	Place of care On univariate analysis (Chi square), patients treated at a university hospital was associated had better survival than those treated at community hospitals (54.6 weeks vs. 40.1 weeks; p=0.002). Patients treated at university hospitals were less likely to be discharged to supportive or hospice care than those treated at community hospitals (1% vs. 6.4%; p<0.001). In multivariate analysis (Cox proportional hazards model), however treatment at at university was not an independent prognostic factor for survival - the authors speculate that this is due to the younger age of the patients treated at academic medical centres. Clinical trials In multivariate analysis there was no difference between the overall survival of patients enrolled in clinical trials when compared to those not enrolled in trials. Only 15.1% of patients were enrolled in such trials.	*Multiple statistical tests reported. The study was unlikely to be adequately powered for all the reported comparisons and putative prognostic factors.*	Prospective case series	3++

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
	inclusion. CANADA and USA						
(Papagikos *et al.* 2005)	Patients with low grade glioma (WHO grades I or II).	Randomized trials of radiotherapy timing or dose, and trials of chemotherapy.	Overall and progression free survival. Some trials recorded QOL and cognitive status.	Timing of radiation One completed RCT (EORTC 22845). Dose of radiation Two RCTs identified (EORTC 22844 and an American intergroup trial) Chemotherapy One trial identified (SWOG) that terminated prematurely	Appraisals of the individual RCTs are in the treatment of low grade glioma evidence table.	Review	4
(Burnet *et al.* 2005).	Data from the East Anglian cancer registry for 1990 to 1994 were used to calculate "years of life lost" (YLL). Data for 17 tumour types was available. UK	Extraction of survival data for 17 tumour types from the East Anglian cancer registry.	Years of life lost (YLL) (the proportion of life years lost in the population for each tumour type). YLL was intended to represent the impact of each tumour type on society. Average life years lost (AYLL) was calculated as the YLL for each tumour type divided by the	Years of life lost Brain and CNS cancer was responsible for 4.1% of the life years lost in the cohort, and for 2.3% of the mortality. Average years of life lost On average patients with brain on CNS cancer in the cohort lost 20.1 years of their life to the disease. This was the highest figure for any of the 17 cancer sites considered. The authors considered four cancers sites as "Cinderella" cancer sites – because they had high AYLL	Total number of people with brain or CNS tumours is not reported. Unclear whether people with benign brain and CNS tumours were included. Study based on a single registry source - likely to underestimate the	Cohort	2-

Study	Population	Intervention	Outcomes	Results	Comments	Design	Level
			number of patients in each group, a measure of the burden of cancer for the individual patient.	but attracted a relatively low percentage of NCRI spending: • Brain and CNS cancer (AYLL 20.1 years, 1.5% NCRI spend) • Cervical cancer (AYLL 17.3 years, 3.5% NCRI spend) • Melanoma (AYLL 15.1 years, 3.0% NCRI spend) • Kidney cancer (AYLL 12.8 years, 1.5% NCRI spend)	incidence and life expectancy of those with brain/CNS tumours.		

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Appendix A Sample search strategy

The Information Specialist constructed systematic search strategies to identify published evidence for the research questions set by the GDG. The generic search strategy shown below was used to identify the population of patients with brain tumours as set out in the document titled *Scope - Improving outcomes for people with tumours of the brain and central nervous system* (NICE, 2003). In each search strategy, search terms were added for interventions, comparisons and outcomes, accordingly. The search strategy was written using search terms for the MEDLINE database.

1. exp brain neoplasms/
2. exp cranial nerve neoplasms/
3. central nervous system neoplasms/
4. exp spinal cord neoplasms/
5. ((brain or midbrain or brainstem or intracranial or cranial or cerebell$ or cerebr$ or CNS or central nervous system or (meninges or meningeal or leptomeningeal or pontine)) adj2 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$ or sarcoma$ or metastas$ or secondar$)).tw.
6. exp neuroma, acoustic/
7. ((spinal or spine) adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$ or metastas$ or secondar$)).tw.
8. ((brain or intracranial or cranial or cerebell$ or cerebr$ or CNS or central nervous system) adj1 myeloma$).tw.
9. neurosarcoma$.tw.
10. neurocytoma$.tw.
11. chordoma/
12. (chordoma$ or chordocarcinoma$ or chordoepithelioma$ or notochordoma$).tw.
13. (choroid plexus adj (carcinoma$ or tumo?r$ or neoplas$ or malignan$)).tw.
14. (acoustic adj1 neuroma$).tw.
15. neurinoma$.tw.
16. neurofibroma$1.tw.
17. neurilemmoma$.tw.
18. schwannoma$.tw.

19. exp glioma/
20. glioma$.tw.
21. (glial adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$)).tw.
22. (glioneuronal adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$)).tw.
23. ependymoma$.tw.
24. (ependymal adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$)).tw.
25. ependymoblastoma$.tw.
26. glioblastoma$.tw.
27. glioneurocytoma$.tw.
28. (subependymoma$ or sub-ependymoma$).tw.
29. (oligoastrocytoma$ or oligo-astrocytoma$).tw.
30. (oligodendrogli$ or oligodendrocytoma$).tw.
31. ganglioglioma$.tw.
32. ganglioblastoma$.tw.
33. gangliocytoma$.tw.
34. ganglioneuroblastoma$.tw.
35. gliosarcoma$.tw.
36. (ependymoastrocytoma$ or ependymo-astrocytoma$).tw.
37. exp astrocytoma/
38. astrocytoma$.tw.
39. astroblastoma$.tw.
40. astroglioma$.tw.
41. ((brain or intracranial or cranial or cerebell$ or cerebr$ or CNS or central nervous system) adj2 ((germ cell adj2 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$)) or (germinoma$ or dysgerminoma$))).tw.
42. ((brain or intracranial or cranial or cerebell$ or cerebr$ or CNS or central nervous system) adj1 teratoma$).tw.
43. (haemangioblastoma$ or hemangioblastoma$).tw.
44. ((brain or intracranial or cranial or cerebell$ or cerebr$ or CNS or central nervous system) adj1 angioma$).tw.
45. meningioma$.tw.
46. meningiosarcoma$.tw.
47. exp Neuroectodermal tumors/

48. PNET.tw.
49. (Neuroectodermal$ adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$)).tw.
50. medulloblastoma$.tw.
51. medullocytoma$.tw.
52. medullomyoblastoma$.tw.
53. Pinealoma/
54. pinealoma$.tw.
55. (pinealocytoma$ or pineocytoma$).tw.
56. (pineal?blastoma$ or pineoblastoma$).tw.
57. (pineal adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$)).tw.
58. (craniopharyngioma$ or cranio-pharyngioma$).tw.
59. pituitary neoplasms/
60. (pituitary adj1 (cancer$ or neoplas$ or tumo?r$ or adenoma$ or carcinoma$ or lymphoma$)).tw.
61. (rathkes$1 adj1 (pouch or cleft) adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$)).tw.
62. spongioblastoma$.tw.
63. (posterior adj1 fossa adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$)).tw.
64. (infratentorial adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$)).tw.
65. (supratentorial adj1 (cancer$ or neoplas$ or tumo?r$ or carcinoma$ or lymphoma$)).tw.
66. or/1-65

Appendix B High level search sources

The following sources of information were searched for evidence relevant to this review:

Agency for Healthcare Research and Quality (AHRQ)

Appraisal of Guidelines for Research & Evaluation (AGREE) Collaboration

AltaVista

Audit Commission

Agency for Quality in Medicine (AZQ)

Cancer and Public Health Unit

Cancer and Public Health Unit, London School Hygeine & Tropical Medicine

Cancer Care Ontario Practice Guidelines Initiative

Cancer links - Cancer guidelines and standards

Cancer Management Guidelines British Columbia Cancer Agency

Cancer Research UK - Science and Research

Cancer Research UK Home

Cancer Services Collaborative Group

Cancer.gov - Cancer Information

Cancer.gov - Cancer Literature in PubMed

CancerBACUP

Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

Centre for Evidence Based Medicine

Centre for Health Services Research - Population and Health Sciences -

University of Newcastle

Centre for Reviews Dissemination

College of Health

Commission for Health Improvement

Department of Health

Department of Health - Cancer

Department of Health National Specialist Commissioning Advisory Group (NSCAG)

Eastern Cooperative Oncology Group (ECOG)

Effective Professional Practice Initiative

Evidence Network - The UK Centre for Evidence Based Policy

Evidence-Based Medicine

Finnish Medical Society Evidence-Based Medicine Guidelines for primary care

French Cancer Resources Directory - CancerIndex

Guidelines International Network

Google

Guide to Internet Resources for Cancer - CancerIndex

Health Care Policy Research Development Unit

Health Development Agency

Health Evidence Bulletins

Health Management Information Consortium

Health of Wales Information Service

Health Technology Assessment.Programme

http—www.anaes.fr-ANAES-anaesparametrage.nsf

International Agency for Research on Cancer

International Network of Agencies for Health Technology Assessment

Kings Fund

Leitlinien.de

Macmillan Cancer Relief Fund

National Assembly for Wales

National Cancer Research Network

National Comprehensive Cancer Network

National Electronic Library for Health (NeLH) - Cancers

National Guideline Clearinghouse

National Electronic Library for Public Health

National Horizon Scanning Centre

National Institute for Health and Clinical Excellence

National Public Health Service for Wales

NeLH Guidelines Finder

New Zealand Guidelines Group

NHS Centre for Reviews and Dissemination

NHS Modernisation Agency

The National Research Register

OncoLink

Oncology Tools

Organising Medical Networked Information

Public Health Information

Public Health Institute of Scotland

Public Health Knowledge

Scottish Intercollegiate Guidelines Network (SIGN)

Société Française du Cancer (SFC)

SUMSearch

Swiss Network on Health Technology Assessment

Trent Research Information Access Gateway

Turning Research Into Practice (TRIP) Database

UK Cancer Links

UpToDate

World Health Organisation

Appendix C Evidence Levels and Quality Grading

(modified from NICE Methodology Manual)

Level of evidence	Type of evidence
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2^{++}	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2^{+}	Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2^{-}	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example case reports, case series)
4	Expert opinion, formal consensus

Quality grading: ++ = good quality; + = fair; - = poor

Appendix D Expert position paper

Cancer Service Guidelines – improving outcomes in Brain and CNS tumours.

The role of Neuropsychiatry in the treatment of neuro-oncology patients – a position paper.

Dr Howard Ring MRCPsych MD, Chair of the Neuropsychiatry Special Interest Group of the Royal College of Psychiatrists.

November 17 2004

1. Background

i. Epidemiology of psychopathology in neuro-oncology patients.

In a Canadian study of 60 patients with on-going treatment for a primary brain tumour, 38% scored within the "clinically depressed" range on a self-completion mood questionnaire. In this study the presence of depressive symptoms was the single most important independent predictor of quality of life (Pelletier, Verhoef et al. 2002). Wellisch et al (Wellisch, Kaleita et al. 2002), in an American study of 89 ambulant patients being treated for a primary brain tumour, found that 28% had a depressive condition meeting DSM IV criteria for a major depressive disorder. In this study risks of depression were greatest in those with a tumour within the frontal lobes and in those with a family psychiatric history. In the UK, Pringle et al (Pringle, Taylor et al. 1999) found that of 109 patients with a single intracranial tumour, prior to surgery 19% had symptoms suggesting a diagnosis of depression whilst 30% had symptoms suggesting the likely presence of anxiety. In 71 Finnish patients with a primary brain tumour awaiting surgery, Mainio et al (Mainio, Hakko et al. 2003) reported that questionnaire-based assessment of mood revealed raised anxiety levels, more so in those with a right-hemisphere tumour. In this latter group anxiety levels reduced after surgery. An Australian study of 72 patients with a meningioma found that 17% presented initially with affective symptoms (Gupta and Kumar 2004). In summary, there is evidence that psychiatric states of depression and anxiety are relatively common in those with a range of brain tumours, being observed in between 17 and 30%. These symptoms may present both before and after diagnosis of the tumour.

ii. Neuro-oncology patients in neuropsychiatry practice

Information requested from 20 consultant Neuropsychiatrists and Liaison psychiatrists around the country provides the following picture. Referrals fall into two main groups. First, there are urgent requests to see inpatients who are either pre-surgery or in the early post-surgery phase. The clinical problems leading to these urgent referrals are generally acute organic confusional states or acute psychiatric states (depression, anxiety, acute adjustment reactions). Organic confusional and affective states may arise as direct tumour effects or as a consequence of corticosteroids administered to control cerebral oedema. The occurrence of relatively high rates of organic psychiatric states in those with CNS tumours referred to psychiatric services is supported by the results of a study from the Memorial Sloan-Kettering Cancer Center in which 41% of inpatient psychiatric referrals were diagnosed with organic mental disorders, 11% with depression and 26% with an adjustment disorder (Passik and Ricketts 1998).

The second category of referrals is for outpatient management. These patients tend to be referred after initial treatment for their tumour is completed and most commonly have affective states. These states sometimes develop secondarily to complications of the tumour or its management (for instance in association with the development of seizures). Pituitary tumours may be directly associated with neuropsychiatric symptoms as may associated endocrine disturbances and hormone replacements. A minority of the outpatient referrals (10 - 20%) are for management of psychiatric states that are interfering with oncology treatments (for instance acute anxiety episodes interfering with radiotherapy).

A small but clinically important number of referrals from both inpatient and outpatient settings relate to issues of mental capacity and consent and ask for a psychiatrist's assessment of these. There are also small numbers of referrals for assessment and management of severe acquired brain injury.

In terms of intensity of referrals, rates currently vary around the country. Neuropsychiatrists surveyed reported that between 1 and 10% of their referrals were for patients with brain tumours. In terms of numbers of patients seen these rates equated to between 3 and 40 per year. The number and proportion of patients seen around the country thus reflect considerably lower referral rates than surveys of the

prevalence of psychopathology in neuro-oncology patients suggests would be appropriate. This agrees with anecdotal reports from patients, who in several centres have reported that they found it difficult to be referred to psychiatry, only succeeding after making several such requests to their oncology teams. It also agrees with impressions gained by the psychiatrists that some oncology clinicians tend to refer more than others. Several psychiatrists have commented that failure to refer seems to be related to a therapeutic nihilism on the part of the oncology clinicians with respect to the value of referral for psychiatric treatment. The psychiatrists surveyed on the other hand believed that they could improve the mental states of the majority of those referred to them. Optimal referral of neuro-oncology patients to neuropsychiatry would be supported by the development of clear management guidelines that indicated the role and value of referral to neuropsychiatry.

2. Delivery of neuropsychiatry care

Neuropsychiatry is currently a relatively rare resource. A recent survey by the Neuropsychiatry Group of the Royal College of Psychiatrists identified 75 psychiatrists who delivered at least one session per week of what they considered to be a neuropsychiatry service. There has never been a national plan for the development of neuropsychiatry and services have grown up sporadically in areas where recognition of clinical need and the local efforts of individuals with the skills to develop or deliver neuropsychiatry have co-existed. Hence the services are not uniformly distributed around the Country and where they do exist they have not necessarily developed in the same locations as neuro-oncology services. In some centers a psychiatric service to neuro-oncology patients is provided from liaison psychiatry which at a national level is more widely available than neuropsychiatry. Of those delivering a neuropsychiatry service only 30% are employed in a full-time neuropsychiatry post, with the remainder working from other psychiatric subspecialties including adult psychiatry (23%), old age psychiatry (11%), liaison psychiatry (10%) and learning disability psychiatry (9%). A total of 60% of neuropsychiatry services currently have access to specialist beds. The remainder provide an out-patient or community-based service or a liaison service to patients in non-psychiatric in-patient settings. Just over half the neuropsychiatry services identified are based in undergraduate teaching hospitals. The majority (75%) of those working in neuropsychiatry are NHS funded with a further 15% being academically

funded and 10% being funded from the private sector. Considering all the posts, 75% are funded from Mental Health budgets, with just 5% being funded out of Regional Neuroscience Centres.

The expansion of neuropsychiatry services is not limited by a lack of trained staff. There are psychiatric trainees with appropriate training in neuropsychiatry well in excess of the number of posts currently available. In addition, there is general recognition by clinical neuroscience specialties of the clinical value of neuropsychiatry. The limiting factor in the expansion of services has been funding as most neuropsychiatry posts are supported from Mental Health Budgets where they must compete with the pressing demands from acute child and adult general mental health services.

Overall there are limits in the current provision of specialist psychiatric services to neuro-oncology patients. This arises as a consequence of the restricted availability of neuropsychiatry and the fact that liaison psychiatry services, which could also provide some support, are also relatively limited and often do not see patients considered to have brain injuries, who would be considered to be more suitable for neuropsychiatry services, should these exist.

3. Current evidence for accepted best practice.

In the absence of controlled trials of different treatment approaches in the neuropsychiatric management of patients with brain or CNS tumours, recommendations for best practice come from a consensus gained from those providing such management.

The neuropsychiatric treatments indicated can mostly be considered under the following headings;

i. In-patients with an acute organic confusional state:

These patients are often in the early post-surgical phase although occasionally they are pre-surgical and may be being treated with steroids. The management of these patients generally follows the principles of management of an acute delirium in a medically sick patient and some accounts with particular relevance to cancer have been published in the literature (eg. (Olofsson, Weitzner et al. 1996).

ii. Patients undergoing active oncology treatments for ongoing disease:

The neuropsychiatric problems faced by this group include epilepsy and psychiatric states, most commonly depression or anxiety states. The relationship between psychiatric states and the cancer and its treatment may involve both emotional reactions to the stress of these processes and their biological consequences. Patients in this group are often outpatients. The need for psychiatric input may be more or less urgent depending on the severity of the psychopathology and its consequences for other treatments, (for instance management of an acute anxiety state with panic attacks that interferes with radiotherapy or chemotherapy regimens). The recognized treatments for severe acute panic attacks include cognitive behaviour therapy and, particularly in the USA, alprazolam treatment (Passik and Ricketts 1998), (Wein 1999).

iii. Patients in whom active malignant disease is not present but who have persisting epilepsy or psychiatric, generally affective, disorders:

These patients are outpatients and may be in only occasional contact with Cancer Services. The psychiatric treatments employed are very largely psychological and pharmacological. Whilst a variety of psychological approaches have been employed, it is the use of cognitive behaviour therapy that has been most researched and developed for use in people with cancer (Moorey and Greer 2002). A literature search does not reveal any formal trials of outcome in the pharmacological management of affective disorders in neuro-oncology patients. However, considering the population of those who develop depression across a wide range of physical illnesses, treatment with antidepressants has been shown to be more effective than either placebo or no treatment (Gill and Hatcher 1999) and management guidelines for the treatment of depression in those who are also physically ill have been published (Voellinger, Berney et al. 2003). When pharmacological treatments are considered it is recognized that in the context of potentially extensive physical brain disruption patients may be particularly sensitive to central side-effects of psychotropic medications such as sedation, confusion and lowering of the seizure threshold (Passik and Ricketts 1998). Drugs should therefore be initiated at low doses. For similar reasons short-acting drugs without active metabolites are preferable to long-acting agents.

An important point which is made repeatedly by clinicians who work to treat psychopathology in people with cancer (of all types) is that it is “incorrect” to think that significant depression is understandable in a person with cancer and that therefore there is no need for or no possibility of treatment. Depression should be and can be successfully treated (Wein 1999). The importance of this is supported by the observation that the presence of depression impacts negatively on both psychological and physical quality of life outcomes in patients with brain tumours (Huang et al 2001). Given the relatively common development of cognitive and psychiatric disturbances in neuro-oncology patients it is appropriate to draw an analogy with other progressive brain diseases that have significant associated psychopathology. In both Huntington’s disease and Parkinson’s disease, conceptualization of these conditions as neuropsychiatric disorders encourages consideration of the psychiatric and cognitive deficits alongside the physical disease process (Marsh and Berk 2003), (Rosenblatt and Leroi 2000).

4. The relationship between neuropsychiatry and neuropsychology services and what they have to offer to neuro-oncology patients

Neuropsychiatrists and Neuropsychologists may be considered to have complimentary skills, as outlined by Dr Katherine Carpenter in her paper ‘Psychological Support Services’.

As outlined by Dr Carpenter, neuropsychologists have particular expertise in assessment of cognitive and personality changes and emotional adjustment and in interventions to support emotional and cognitive rehabilitation, family work and carer support.

Neuropsychiatrists (and liaison psychiatrists) are skilled in the diagnosis and management of organic brain syndromes (delirium) and severe mental health problems including severe affective and personality disturbances, psychotic disorders and substance abuse. They also have expertise in clarifying the relationship between the physical consequences of disease and disturbances of mental state. If the management of psychopathology is likely to require the use of pharmacological interventions then psychiatrists should be involved. Psychiatrists are also skilled in assessments of mental capacity and consent and if the severity of psychiatric disturbance is such that its assessment or treatment may require the provisions

available under the Mental Health Act then a psychiatrist approved under section 12 of the Act will need to be involved. In general it is more likely that emergency out-of hours intervention will be available from psychiatric than from psychological services as there is in any case a round-the clock psychiatry service available across the country. However, the on-call mental health team is unlikely to have specialist skills in the neuropsychiatry of neuro-oncology.

Both psychiatrists and psychologists (and in some centres also behavioural nurse specialists) are able to offer psychological treatments such as cognitive behavioural therapy for mild to moderate depressive and anxiety disorders. Both professional groups will also be able to provide support and supervision to cancer clinicians (for instance palliative care teams) who are working with patients with psychological needs or psychiatric conditions.

In summary, the two specialties have both unique and shared skills. Neuropsychologists have specialist skills in cognitive assessment and rehabilitation. Neuropsychiatrists have specialist skills in the diagnosis and management, including the pharmacological management, of delirium and more severe psychiatric and behavioural disturbances. There is also a middle ground in the area of psychological management of mild to moderate affective disturbances in which both specialties are likely to be able to provide the necessary input, so long as they are adequately resourced to do this. (For instance, in a hard-pressed service in may be difficult for a clinician with the requisite skills to make available 12 sessions of cognitive therapy over an optimally short time scale). In a comprehensive service neuro-oncology patients should have access to both specialties and these should be adequately resourced to be able to deliver the interventions that are clinically indicated and within the practitioner's capabilities.

5. Key commissioning recommendations to improve the current delivery of care.

Currently there is insufficient data available to address this issue fully. In the first instance it would be useful to perform an audit of all recognized neuro-oncology centres in order to establish what level of neuropsychiatric and neuropsychological support they currently have available.

The patients seen by Neuropsychiatry services tend to receive their other specialist care (eg. oncology, neurology, neurosurgery) in specialist regional centres and it is at this level that the development of neuropsychiatry would be most justified. At this level commissioning would be most appropriately performed by consortia. The specialist and cross-disciplinary nature of the service in question means that within the commissioning group there might not at the outset be the appropriate expertise and this may need to be obtained.

The commissioning process may include a needs assessment which should incorporate views from neuro-oncology services and from neuro-oncology service users. Within cancer services consideration should be given to the role of neuropsychiatry through the whole process from symptoms at the time of initial presentation and diagnosis to support during terminal illness. The commissioning process will also need to consider the range of clinical work provided by a neuropsychiatry service beyond cancer services since in order to establish a cost-effective service of sufficient critical mass it is likely that its work-load will extend beyond neuro-oncology. Beyond cancer services the commissioning of neuropsychiatry should therefore consider needs across the whole range of clinical neurosciences (including general neurology and neurosurgery services as well as specialist services such as those for neurotrauma, movement disorders and epilepsy.

In order to minimize additional funding pressures and make best use of existing resources the commissioning process should consider existing neuropsychiatry and liaison psychiatry services as well as current neuropsychology and nurse-specialist resources which, as noted above, should be included in a comprehensive service for neuro-oncology (and other clinical neuroscience) patients.

6. Future developments in neuropsychiatry

Within the past two years the Royal College of Psychiatrists, as part of its revision of higher specialist training across psychiatry, has published core competencies for the training of neuropsychiatry. The definition of the relevant skills and knowledge to be possessed by a neuropsychiatrist has already led to the recognition of the specific contributions to medical care made by this sub-specialty. In addition, the Neuropsychiatry Special Interest Group within the Royal College of Psychiatrists is currently producing a service development protocol for use by both

neuropsychiatrists and commissioning agencies. These initiatives will support the establishment of new neuropsychiatry posts across the country. Hence, independent of the needs of neuro-oncology services, additional neuropsychiatry posts are slowly being created. Both services would be supported, with optimal benefits to patients and a more cost-effective use of neuropsychiatry resources, by communication between neuro-oncology services and those developing neuropsychiatry services during the stages of identifying clinical need and planning such a service.

7. Audit criteria

The auditing of outcomes is well developed in the field of general psychiatry (Joy, Adams et al. 2004), (Furukawa, Streiner et al. 2001).Audit criteria should include the following;

- The referral process:
- Referral rates by the neuro-oncology service as a whole.
- A record that mental state has been considered by the neuro-oncology team.
- A record of whether referral was initiated by the neuro-oncology team or requested by the patient.
- A record of the clinical speciality to which the psychiatric referral has been made.
- The interval between referral and initial assessment.
- That all patients with indications for referral to neuropsychiatry were referred.
- Management:
- A record of whether initial assessment led to a psychiatric diagnosis.
- A record of whether initial assessment led to further neuropsychiatric management.
- A record of what, if any, psychological treatments are initiated.

- A record of what, if any, pharmacological treatments are initiated.
- A record of the assessments used to measure the efficacy of the interventions used.
- A record of the feedback from the neuropsychiatric service to the referrer.

The criteria against which the audit results should be judged will include; reported rates of psychopathology in neuro-oncology patients (section 1i - above) and outcomes associated with specific interventions in the treatment of other patient groups with affective disorders (section 3iii - above).

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