

Appendix B

Evidence tables for urological, haematological, skin, head & neck, brain, bone & sarcoma, and childhood chapters

Please note, the evidence tables are in a draft form, and will be checked and edited for the second draft.

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Table 1 UROLOGICAL: signs and symptoms, including risk factors

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Brett, 1998		Men attending a general practice in Perth were offered both digital rectal examination and PSA tests	211 men.	Men aged 50–79 attending a solo general practice in Perth, in 1996		A prostate was regarded as abnormal on examination if there was evidence of nodularity, induration, asymmetry or absence of median sulcus. 199 (91.0%) were found to have a normal prostate, and 19 (9.0%) abnormal. The PSA test was regarded as normal if results were in the 0–4ng/ml range. 191 (90.5%) were in the normal range, and 20 (9.5%) were abnormal. Of the 211 patients, 182 were normal on both tests, 29 having an abnormal finding on one or other test. From the 29, 11 biopsies were performed, with prostate cancer detected in three (27.3%). Twelve patients opted for various reasons not to undergo biopsy (eight had had biopsies in the past), and six were not biopsied because of poor health.		
Bruyningckx et al, 2003		A study of patients attending general practices with macroscopic haematuria. Patients were followed up for 18 months to determine final diagnosis.	83 general practitioners. 409 patients with macroscopic haematuria	all patients attending with macroscopic haematuria 1993–1994 in a network of Belgian general practices		409 patients attended with macroscopic haematuria and 126 patients diagnosed during the same period as having urological cancer. The mean age of patients with macroscopic haematuria was 57 years, but the age of those with cancer was 72 years. 13% of those with haematuria were younger than 40 years and 53% older than 60 years. In 87 patients (70 males, 17 females) bladder cancer was detected, and in 39 other urological cancers were detected. 75 of the 126 patients reported macroscopic haematuria in the weeks before diagnosis, giving a sensitivity for a diagnosis of any urological cancer of 59.5% (95% CI 50.4–68.1%). The PPV of macroscopic haematuria for the diagnosis of urological cancer was 10.3% (95% CI 7.6–13.7%). Occurrence of haematuria with dysuria or increased frequency of micturition did not change the likelihood of cancer		
Buntinx, 1997		This was a systematic review of studies of the diagnostic value of macroscopic haematuria in diagnosing urological	14 studies					

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		cancers in primary care. Studies were sought using Medline and FAML1 databases. From the studies selected, none had been undertaken in primary care, most being based on chart reviews in hospital settings of referred patients					
Burgers, 1992		a comprehensive review of penile cancer				Cancer of the penis is rare, accounting for only 0.4-0.6% of all male malignancies in the US (incidence 0.2/100,000 males/year). Squamous cell carcinoma accounts for at least 95% of cases, sarcomas being the most common non-squamous type. It usually presents in the sixth decade of life, with a mean age at diagnosis of 58. There is an association between absence of circumcision and penile cancer, but the precise aetiology is unclear. The possible role of pre-malignant conditions has not been clarified. Presentation is varied, ranging from innocuous areas of in-duration, erythema or warty growth to obvious extensive carcinoma with sloughing. The earliest symptoms include itching or burning, and ulceration which progresses to a lump, mass or nodule if left untreated. Pain is usually minimal in relation to the other features. It can occur at any anatomical site; 48% develop in the glans, 21% prepuce, both (9%), coronal sulcus 6%, shaft <2%.	
Chamberlain et al, 1997		This was a review of the costs of diagnosis and management.				No data were found on diagnostic procedures in general practice or of delay in diagnosis of symptomatic prostate cancer, although variation in general practitioners' skill in DRE was noted. The authors were unable to make any recommendations relating to diagnosis in primary care.	
Daniels, 2003		Retrospective review of a series of cases presenting 1993-2000 to a UK specialist breast surgeon with breast enlargement or lumps in men	175 men			127 of the men had gynecomastia, eight had breast cancer, and four had testicular cancer, three of whom had a testicular mass at presentation.	
DoH, Referral Guidelines for Suspected Cancer,		Provides information on the incidence of prostate, bladder, kidney, testis and penis cancer.					

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2000								
Fowler et al, 2000		The aim of the study was to determine whether features used to detect prostate cancer are different in black and white American men	179 black and 357 white men	black and white men who had undergone prostate biopsy 1992-1999 at one medical centre		The patients had an abnormal DRE, a PSA of less than 4ng/ml and no history of prostate surgery. Cancer was detected in 38 black (21%) and 65 white (18%) men. There was no difference in the overall or PSA stratified cancer detection rate.		
Gospodarowicz, 1999		A review of testicular cancer.				Testicular cancers are uncommon, occurring most commonly in men aged 15 to 35 years. The majority are primary germ cell tumours (GCT). Although the incidence of germ cell tumours has doubled in the past 30 years, the mortality has declined. There is considerable geographic and ethnic variation in incidence of germ cell tumours, it being less common in non-whites. Men with a history of cryptorchidism have an approximate five-fold risk. Family clusters have been reported, and patients with XY gonadal dysgenesis are at increased risk. Prior testicular cancer is also a risk factor for cancer in the surviving testis. Patients with tumours most commonly present with painless testicular enlargement. Up to 45% have testicular pain. Less common presentations include features of metastasis, for example back pain and dyspnoea.		
Haid et al, 1994	USA	This study involved men who had undergone transrectal ultrasound at a US hospital. The records were reviewed to extract information on findings from digital rectal examination (DRE), prostate biopsy reports, and PSA levels. With biopsy as the gold standard, 32 (32.3%) of the 99 had carcinomas.	99 men			Among those with carcinoma, 24 (77.4%) (of 31 with data) had a palpable nodule on rectal examination, the mean PSA was 32.5, and 15/31 had an abnormality on transrectal ultrasound (48.4%). Among those who did not have carcinomas, 52/64 had a palpable nodule (81.2%), the mean PSA was 8.4, and 26/65 had an abnormality on ultrasound (40.0%).		
Huyghe et al, 2003		a review to identify trends in the incidence of testicular cancer. a Medline search for articles published 1980 to 2002 was carried out.	30 studies.			A trend towards an increased rate over the last 30 years was observed in the majority of industrialized countries, including North America, Europe and Oceania. There were marked differences between nearby countries, for example 2.5/100,000 in Finland and 9.2/100,000 in Denmark, as well as		

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						among regions in the same country. From the limited information available about incidence in ethnic groups, the incidence among white men in the US has increased, but this is not the case among black Americans. Worldwide, only Maori were found to have an incidence as high as that among white males.		
Lobel et al, 1998		These guidelines were developed by an international group, and included reference to 89 original articles, although the methods of guideline development were not described in detail. The guidelines give detailed consideration to initial assessment in primary care, but did state that all patients with gross haematuria should be examined and referred to a urologist for assessment for possible bladder tumour. Patients with asymptomatic microscopic haematuria should be referred if they are aged over 50 years. In those under aged 50, the guidelines were uncertain, but noted that the incidence of cancer in this group was 5% with asymptomatic microscopic haematuria and 10.5% with symptomatic microscopic haematuria.						
Mansson et al, 1999	Sweden	a retrospective case series with being patients identified from a cancer registry and from one district in Sweden (Kungsbacka). The medical records of all patients were reviewed for information about initial symptoms, diagnostic procedures, outcome of diagnostic procedures, level of care, and doctor's delay. The study collected information about new cases of prostate cancer presenting 1980-1984.	86 cases					
Mickisch et al, 2001		These guidelines were prepared by the European Association of Urology following a literature search using Medline, with articles being graded by a panel of experts. The presenting features include haematuria, palpable tumour and flank pain. However, presentation with clinical features is						

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		becoming less common and many cases are being diagnosed at the asymptomatic stage. The majority of tumours are diagnosed by abdominal ultrasound performed for various reasons.						
Morganstern, 1998		A review providing a summary of risk factors for urological cancers				Age is the principal risk factor for prostate cancer. Risk factors for the development of bladder cancer in addition to age include cigarette smoking, and occupational exposure among dye, rubber, textile and leather workers. The risk of bladder cancer with tobacco appears to be dose-dependent and partly reversible with smoking cessation, although the risk associated with occupational exposures appear to be relatively long lasting. Most cases of renal cell carcinoma are sporadic, although a small proportion are familial and related to mutations on chromosome 3p and Von Hippel-Lindau disease. There is a moderate, dose-dependent risk associated with cigarette smoking; Increased risk is also associated with excess body weight, hypertension and/or antihypertensives, increased parity, and a variety of occupational exposures including asbestos, petroleum products, and dry cleaning solvents. Acquired cystic kidney disease with renal insufficiency also poses a risk.		
Muris et al, 1993		In this review, publications were identified from Medline dated 1982 to 1991,	8 studies	those included involved studies of patients with complaints in which rectal examination was indicated		The sensitivity of rectal examination in detecting prostate cancer was 98% and 92% in the two studies, specificity was 53% and 48%, and likelihood ratio 2.09 and 1.77.		
NICE, 2001		This document was classified by NICE as guidance and was commissioned by the Department of Health and the National Assembly for Wales to provide advice to health professionals on the appropriate referral of patients from general to specialist services. A consensus method was used to generate the advice. A multidisciplinary						

DRAFT FOR FIRST CONSULTATION

		<p>panel was established for each topic considered, and selected research evidence was considered. One of the topics considered was urinary tract outflow symptoms. The advice recommended that patients be offered a prostate specific antigen (PSA) test with the reasons for doing the test being explained and the patient counselled with regard to the possible consequences. Patient information on PSA tests can be obtained from the National Electronic Library for Cancer (www.nelc.org.uk). Immediate referral was advised if the patient has acute urinary retention or evidence of acute renal failure; urgent referral was advised if the patient has (a) visible haematuria, (b) there is a suspicion of prostate cancer based on the findings of a nodular or firm prostate, and/or a raised PSA, (c) culture negative dysuria, (d) they develop chronic urinary retention with overflow or night-time incontinence. Referral to be seen soon was advised if the patient has recurrent urinary tract infection or microscopic haematuria. Referral within an appropriate time was advised if the patient has chronic renal failure or renal damage, or symptoms have failed to adequately respond to treatment in primary care. Use of a scoring system such as the WHO International Prostate Symptom Score was encouraged.</p>						
Selley et al, 1997		<p>a systematic review of the diagnosis, management and screening of early localised prostate cancer</p>				<p>From the included studies of digital rectal examination (DRE), it was concluded that 50-95% of localised prostate tumours are palpable and could be detected by DRE. A proportion of the lesions detected on palpation are benign, and include benign prostatic hyperplasia (BPH), retention cysts, prostatic calculi, prostatic atrophy, fibrosis associated with prostatitis, and non-specific granulomatous prostatitis. False positive rates on DRE are as high as 40-50%.</p>		

DRAFT FOR FIRST CONSULTATION

						The sensitivity of DRE ranged from 44% to 97% in the four studies reporting this, and specificity from 22% to 96%. The reasons for these variable findings were probably related to the different sizes of the studies, case selection and variable final diagnostic criteria.		
Summerton et al, 2002		A case series examining people referred to an open access haematuria clinic in the UK. Information was collected prospectively about clinical features and comorbidities at first clinic attendance. Cases were classified into urological and non-urological cancers, and urological and non-cancerous/normal groups. The associations between clinical features and diagnoses were explored using a variety of statistical techniques, including logistic regression.	363	Patients were aged between 18 and 80		172 patients had macroscopic haematuria and 186 microscopic haematuria. Of the 363 referred patients, no abnormality was detected in 260, 42 had benign prostatic disorders, 12 had strictures or stenoses, 13 had calculi, and 36 had urological cancers (28 of which were bladder cancers, two prostate cancers, five renal cancers, and one had both renal and bladder tumours). In multivariate analysis, the variables tending to be associated with urological cancer were older age, male sex, macroscopic haematuria (especially if a single episode), poor stream, history of urinary tract infection and smoking.	final diagnosis was established by cystoscopy and radiological assessment, supplemented by review of the records to check for any changes in diagnoses over time	
Zeegers et al, 2003		This review sought to determine the risk of prostate cancer among relatives of affected patients. Studies published up to 2002	33 studies	Studies published up to 2002		From the pooled findings, the relative risk among first-degree family members was 2.53 (95% CI 2.24-2.85). The risk for second-degree relatives was only slightly elevated (1.68, 95% CI 1.07-2.64). Among first-degree family members, the risk increased with the number of affected relatives and decreased with increasing age of the affected relative.		

Table 2 UROLOGICAL: investigations

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Garnick, 1996		This review was one of a series concerned with aspects of prostate cancer. Articles published 1992-1996 were sought in a search of Medline. A largely qualitative analysis of the identified articles was undertaken				Most of the initial screening studies that had assessed an abnormal PSA had used 4.0ng/ml as the upper limit of normal. Several studies have considered methods of refining interpretation of the PSA test. The PSA density refers to a numerical ratio determined by dividing the PSA serum value by the volume of the prostate gland as determined by transrectal ultrasonography. This gives the PSA value per gram of prostate, and densities of 0.15 or more may strongly indicate the presence of cancer. However, estimation of the volume of the prostate gland is subject to error. Prostate-specific antigen velocity refers to the rate of change in the PSA value over time. A value that continues to increase over time may signal cancer. Two studies of the value of PSA velocity were included in the review, and they indicated that a change of more than 0.75ng/ml per year should be regarded with a high degree of suspicion. Recent studies have also suggested that the upper-limit of normal PSA value varies by age, being lower in younger than older men. Some preliminary studies have been undertaken of the potential role of the relative percentage of free PSA and PSA bound to serum proteins.		
Glas et al, 2003		Systematic review of articles that evaluated tumour markers in the diagnosis of primary bladder cancer. The markers included cytology, bladder tumour antigen, BTA stat, BTA TRAK, NMP22, telomerase and fibrin degradation product. Relevant studies that evaluated at least one of these markers were sought in a search of Medline and Embase for articles published 1990 to 2001.	42 studies.					
Selley et al, 1997		This was a systematic review of the diagnosis, management and screening of early localised prostate cancer				PSA is a protease produced almost exclusively by prostatic epithelium. The normal range is between 0-4ng/ml, although some men with cancer have values in the normal range, and high values can be caused by conditions other than cancer. Reports of PSA sensitivity range from 57-99%, and specificity from 59-97%. The gold standard test used in studies of PSA testing is prostate biopsy, but in the primary studies not all men with elevated results would have undergone biopsy. Therefore, the true number of cancers cannot be accurately determined. The review found that evidence to support use of PSA density was equivocal, and that further research was needed into the role of PSA velocity, free and bound PSA and age-specific reference ranges for PSA normal values.		
Thomas et al,		General practices were randomized to receive the intervention for either lower urinary tract symptoms or	66 general practices			General practitioner compliance with the guidelines increased (pre-intervention scores 2.6 and 2.8 in the		

DRAFT FOR FIRST CONSULTATION

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2003		microscopic haematuria, serving as controls for the other condition. The intervention consisted of referral guidelines plus access to the investigation service.				intervention and control practices respectively, and 3.2 and 2.8 post intervention), and the intervention reduced waiting time from referral to initial out-patient appointment (106 and 130 pre-intervention to 36 and 75 days post intervention in the intervention and control groups respectively) and increased the proportion of patients who had a management decision reached at the initial appointment (0.18 and 0.24 pre – and 0.50 and 0.19 post-intervention in the intervention and control groups respectively).		
Vinata et al, 2001		A systematic review. Pubmed was used to identify relevant articles. The tests included were urine cytology, haematuria detected by dipstick, and tests currently undergoing evaluation, including human complement tests, nuclear mitotic apparatus protein testing, cytology plus immunofluorescence, telomerase testing and the hyaluronic acid and hyaluronidase test.				Urine cytology was reported to have a sensitivity of 35-40% (range between studies 16-60%) for detecting bladder cancer. Haematuria can be caused by many conditions other than cancer, and therefore the specificity for cancer is low, but the sensitivity was reported to be 67-90%. There is insufficient evidence available to determine which of the other tests, or which combination of tests, can be recommended as non-invasive methods of detecting bladder cancers.		
Weller et al, 2003	Australia	General practitioners were randomised to receive either an outreach visit or mailed education. There was also a control group. The written materials consisted of printed summaries of evidence on PSA testing, patient education materials and epidemiological information on prostate cancer in Australia.	145 general practitioners.			In the 12 months after the interventions, the educational outreach group undertook significantly fewer PSA tests. This group also had the greatest improvement in knowledge of treatment effectiveness and appreciation of guidance on screening asymptomatic men.		

Table 3 UROLOGICAL: delay and diagnostic difficulties

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Khadra et al, 2002	UK, Primary Care	<p>The aims of this study were to investigate the level of awareness of testicular cancer (TC) and practice of testicular self examination (TSE) in male GP attenders, and to see if TSE was related to age, marital status, education, ethnicity, social class, knowing someone with TC, having attended a Men's Health Clinic and having heard of a TC awareness campaign.</p> <p>The authors recruited men from two English general practices, one inner city and one suburban. Confidential questionnaires were given out to consecutive male patients between the ages of 18 and 50 years attending the GP surgeries over a period of 1 month. The data were analysed using SPSS.</p>	202	Male patients between the ages of 18 and 50 years	Not explicitly mentioned	<p>Although 91% of men claimed to be aware of TC, only 26% knew both the age group most affected (25–34 years) and that TC can be curable if detected early.</p> <p>Forty-nine per cent of responders had carried out TSE in the past year, but only 22% did so according to recommendations, i.e. feeling for lumps on a monthly basis. TSE was associated with age >35 years, white ethnicity, having correct knowledge of TC, knowing someone with TC, having attended a Men's Health Clinic and having heard of a TC awareness campaign.</p> <p>TSE was suggested by the media to 56% of those who examined themselves and by a nurse or GP to only 16%.</p> <p>Forty-eight per cent of those carrying out TSE had received written instructions, and 10% had received a testicular examination by their GP. Only 3% had attended a Men's Health Clinic in the past. Of those 103 responders not carrying out TSE, 71% said they did not know what to do, 27% said they were too busy and 2% were afraid they might discover a lump. Eighty-five per cent (169/199) of the men were keen to find out more about TSE and 67% (136/202) would attend a Men's Health Clinic if one were set up in their GP's surgery.</p>	
Lechner et al, 2002	Netherlands Population based	<p>This study analysed what determinants are important to describe and explain the intention of testicular self-examination (TSE).</p> <p>The authors recruited the subjects by approaching several high schools and asking them if they were prepared to let the researcher administer the written questionnaire among their male high school students aged 15–20. Four schools were needed to get the needed sample for the study, and they were randomly selected from the available six schools.</p> <p>The questionnaire assessed</p>	274	Young men aged 15–19 attending senior high school.	Not explicitly mentioned.	<p>Knowledge of testicular cancer and TSE was very low: 74% had never heard of testicular cancer and only 3% of all students had ever heard of TSE. Of all subjects, only 2% (n = 5) reported that they regularly performed TSE. Since knowledge and behaviour levels were so low, they showed no significant correlation with intention or any of the other determinants related to TSE. After hearing of TSE (through the questionnaire), 41% of students had a positive intention to perform TSE (32% positive, 9% very positive), while 27% had a negative intention to do TSE (20%</p>	<p>Reliability analysis showed that the assessment of some concepts still has room for improvement. Furthermore, there is still limited insight in the validity of the concepts assessed. Therefore, further research is needed in order to get more insight in the validity of the concepts assessed and to find out whether the assessments of the different concepts of the model can still be improved.</p> <p>Since hardly any of the young men in this study performed TSE</p>

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
		determinants, including knowledge, attitude (positive and negative consequences, anticipated regret, and moral obligation), social influence (social norm, social support and modelling) and self-efficacy. Data analysis included basic descriptive statistics of the respondents. Statistical differences between the various intention groups were analysed using one-way ANOVA with Scheffé's multicomparison tests. Linear regression analysis was used to assess the predictive value of the determinants for the intention to perform TSE. All analyses were performed using the SPSS-X statistical program (SPSS Inc., 1988) (differences were significant at $P < 0.05$).				negative, 7% very negative). The rest of the subjects had not yet formed an intention. The highest correlations with intention were found for the moral obligation that subjects experienced to perform TSE, their self-efficacy expectations, the expected positive consequences of TSE, the social norm that subjects experienced and the regret they expected to feel if they did not perform TSE. The various intention groups (positive, neutral and negative) differed significantly on almost all of the determinants. Multiple regression analysis showed that young men who were anxious about TSE and those who were not anxious had different determinants explaining the variance in the intention to perform TSE regularly ($R^2 = 41-57\%$).	regularly, the determinants of behaviour were not assessed. Instead, the determinants of intention were analysed.
Mansson et al, 1993	Sweden, Population based study (Primary and Secondary Care)	The study was undertaken to investigate various factors which may play a role in patient's delay and doctor's delay in the diagnosis of bladder cancer. The authors examined the clinical records of all patients with a diagnosis of bladder cancer as gathered from a regional tumour registry. Variables extracted from the records included onset date and specific pattern of symptoms, date and place of first medical consultation, referral patterns, investigations, and date of diagnosis, amongst others. The extracted variables specially studied in each case were patient's delay and doctor's delay. A questionnaire was sent to patients who were still alive on January 1, 1991. The replies were designed to reflect how seriously the patients viewed their first symptoms of bladder cancer, their experiences of previous serious or protracted illness, and their habitual perception of bodily changes and level of general education. Intergroup differences in patient's and	343	Patients with diagnosis of bladder cancer established in 1988.	Patients with non-malignant disease (n=16), recurrent bladder cancer (8), prostatic cancer (1), pathologist's report dated 1989 (20), or missing records (5).	The clinical records of 343 patients were examined, and 203 patients completed the questionnaire (88.6% of those eligible). Macroscopic haematuria was the commonest symptom bringing the patient to the doctor. Urgency was more common in advanced than in superficial cancer (51% vs.34%, $p<0.002$). No correlation was found between presence of haematuria and tumour category. 161 (67%) patients initially consulted a primary unit of the health services (mostly a general practitioner) and 51 (15%) a private practice (mostly a general practitioner or gynaecologist). The remaining 118 patients presented at a hospital. Three patients (1%) never sought medical advice and were diagnosed at post-mortem examination). The median patient's delay was 15 days (mean 141, range 0-2,857). There was no relationship between this delay and age or gender. The type of symptom was an important factor in patient's delay. Neither urgency of micturition nor pain prompted the patient to seek medical advice as	The power to detect true median differences is low, since the delay variables are very skewly distributed and have large variances. Good retrospective observational study. Some bias may have been introduced as respondents to questionnaire differ from non-respondents, i.e. alive patients, younger, and with earlier tumour stage.

DRAFT FOR FIRST CONSULTATION

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		<p>doctor's delay were analysed with Wilcoxon's rank sum test and Kruskal-Wallis test. The χ^2 test was used to compare categorical variables. All tests were two-sided.</p>				<p>quickly as haematuria (median 45 and 38 vs. 5 days, $p<0.001$). Although the difference was not statistically significant, median patient's delay was longer in patients with advanced cancer than in those with superficial tumour. Amongst the responders to the questionnaire, no correlation was demonstrable between patient's delay and level of education, perceived seriousness of initial symptoms, or civil status.</p> <p>The median doctor's delay was 62 days overall. It was longer for women than for men (76 vs. 59 days, $p<0.05$). The initially consulted health-service level was a major factor in doctor's delay ($p<0.001$), with median range from 78 days for patients initially seen in a primary care unit to 21 days when the patient came directly to a department of urology, but the longer median delay was not due to delayed referral to a specialist, since in the total series doctor's delay phase A was only 6 days, whereas phase B was 47 days (suggesting considerable waiting time in the referral system).</p> <p>The use of urine cytology and intravenous urography in general or private practice was associated with some, but not significant, shortening of doctor's delay. As in patient's delay, the nature of presenting symptoms greatly influenced doctor's delay, which was shorter with haematuria plus pain than with haematuria only, and longest when urgency was the only symptom (median 44, 53 and 114 days, $p<0.001$).</p> <p>Patient's age influenced doctor's delay. The median thus was less in patients younger than 70 years than in older patients, viz. 54 and 69 days ($p<0.01$).</p>	
Mommsen et al, 1983	Denmark, Primary and Secondary Care	<p>The purpose of this study was to elucidate causes of delay.</p> <p>The authors interviewed all consecutive patients with newly diagnosed bladder tumour admitted to a department of Oncology and</p>	212 patients	Patients with newly diagnosed bladder tumour.	Terminal, intractable cases.	<p>The presenting symptom was haematuria, which commonly was painless, in 79% of the patients. The interval from onset of symptoms until treatment averaged 28 weeks (median = 15 weeks). The general practitioner delay comprised half of the total delay.</p>	<p>The authors confirmed the reliability of the time data by comparing the intervals reported by the patients with corresponding information derived from the general practitioner's records in 10% of a random sample of these</p>

DRAFT FOR FIRST CONSULTATION

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		<p>Radiotherapy during a 3-year period beginning in September 1977.</p> <p>The interview concerned symptom, some demographic variables and the time intervals under study (phases A, B, and C).</p> <p>The statistical procedures included χ^2 test.</p>				<p>Half of the patients consulted their general practitioner within a week after onset of the presenting symptom. A higher percentage of men than of women had a delay of ≥ 13 weeks. Fewer women than men (62% and 82%) were referred to hospital within 12 weeks of the index consultation with the general practitioner ($\chi^2 = 8.97$; d.f.=1; $p < 0.005$). Of the patients with haematuria, 13% of the men but 35% of the women were referred to hospital after 13 weeks or more ($\chi^2 = 9.70$; d.f.=1; $p < 0.005$). Cystitis as the presenting symptom was associated with later referral to hospital than haematuria; this was most pronounced for men ($\chi^2 = 12.56$; d.f.=1; $p < 0.005$).</p>	<p>patients. Skewness in distribution of delay. Small study with limited power.</p>
Wallace et al, 1999	UK, Secondary Care	<p>The authors examined the relationship between delay in presentation of patients with bladder cancer and tumour stage and material deprivation. Data on delay periods to treatment, tumour characteristics, occupation and postcodes were collected for patients with urothelial cancer presenting to a Regional Cancer Intelligence Unit. The Townsend material deprivation score was derived from the patient's postcode (the score assesses four variables measuring unemployment, overcrowding, wealth and income).</p>	1537	Patients with urothelial cancer.	Not explicitly mentioned.	<p>A delay of < 2 weeks in the referral to hospital was associated with a 6% improvement in survival ($P = 0.018$); shorter delays to hospital appointment correlated inversely with survival ($P < 0.001$). The overall delay time and delay to hospital admission did not correlate with survival. The deprivation scores showed no correlation with delay times, smoking or T-category of tumour. Material deprivation was correlated with low tumour grade ($P = 0.004$) and better survival ($P = 0.02$).</p>	<p>Poor definition of delay and description of methods (only abstract was available for inspection). Most of the study relates to the association between delay and survival, which as such is not relevant to the guidelines.</p>
Wallace et al, 2002	UK, Secondary care.	<p>The authors attempted to collect data prospectively on all newly diagnosed cases of urothelial cancer in the West Midlands from 1 January 1991 to 30 June 1992. The data collected included the dates of onset of symptoms, first referral by the GP, first hospital appointment and first definitive treatment. Clinical details collected included the presence or absence of haematuria (macroscopic or microscopic), the number, size and type of tumours, and the findings of the bimanual examination. Details of patient characteristics were also collected. In addition, patients were asked to complete a questionnaire on</p>	1537 patients	Not explicitly mentioned	Not explicitly mentioned	<p>The median (IQR) Delay 1 was 14 (0–61) days. Patients with a longer delay were more likely to present with a higher stage tumour ($P=0.04$). Patients with an unknown haematuria status were more likely to have a shorter delay ($P<0.001$). No other patient or tumour characteristics showed a significant difference above or below the median delay. Delay 1 had a significant effect on survival; patients with a delay of <14 days to referral had an improved survival of 5% at 5-years compared with those who had a delay of >14 days ($P=0.02$). Adjusting for tumour stage, there was a trend for patients with a shorter Delay 1 to have a better survival</p>	<p>Clinically based data (presence or absence and degree of haematuria) and more detailed epidemiological data (smoking status, risk of occupational exposure) relied upon clinicians and patients to complete questionnaires and some data are incomplete.</p>

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
		<p>their smoking and occupational history.</p> <p>Associations between the patient characteristics and median delay times were analysed using Pearson's chi-squared test for categorical data and the Mann–Whitney U-test for continuous data.</p>				<p>(P=0.06).</p> <p>The median Delay 2 was 28 (7–61) days. Patients known to have had macroscopic haematuria (n=1032) were more likely to have a shorter delay than those known to have had microscopic haematuria (n=70); patients with an unknown haematuria status were more likely to have a longer delay (P<0.001). There were no other significant differences in patient or tumour characteristics above or below the median delay. Patients who had a shorter Delay 2 had a significantly worse survival (P=0.001). Survival by Delay 2 after adjusting for tumour stage similarly showed that patients with a shorter Delay 2 had significantly worse survival (P=0.001).</p> <p>The median total delay was 110 (62–209) days. Longer delays were significantly associated with women (P=0.05), younger patients (P=0.03), non-smokers (P=0.04) and patients with a low risk of occupational exposure (P=0.04). No other patient or tumour characteristics showed significant differences above or below the median delay. The total delay had no effect on survival (P=0.17); this was also true after adjusting for tumour stage (P=0.43).</p> <p>For prognostic factors, there was no survival difference for sex (P=0.92), haematuria (P=0.39) and number of tumours (P=0.13), both in the log-rank analysis and Cox regression models.</p>	

Table 4 HAEMATOLOGICAL: signs and symptoms, including risk factors

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Allhiser et al 1981	USA Primary Care	A retrospective and descriptive study aimed to determine the annual incidence of lymphadenopathy, analyse the clinical spectrum and management of lymphadenopathy in a representative family practice setting	80	All patients coded as having lymphadenopathy or acute lymphadenitis.	Not included were three patients later identified with the diagnosis of chronic and non-specific lymphadenitis	<p>The annual incidence of the problem of enlarged nodes was 0.5%.</p> <p>56 (70%) of cases were discovered by patients and 15 (19%) were discovered by the physician (previously unknown to patient). It was unclear from the records who discovered the remaining 9 cases. Of those discovered by the patient, the duration of swelling by the time of first visit ranged from one day to six months, with one third reporting swelling of less than one week. Thirty-seven patients (46%) reported pain and 35 (44%) denied it. No mention of pain was found in the charts of eight patients (10%).</p> <p>Seven patients (9%) had nodes measuring less than 0.5 cm, 14 patients (18%) had nodes measuring less than 0.5 cm, 14 patients (18%) had nodes 0.5 to 1 cm, and 36 (45%) had nodes recorded as greater than 1 cm.</p> <p>Several clinical parameters important to the evaluation of lymphadenopathy were incompletely recorded in the medical notes. Excepting node enlargement, few associated physical and laboratory findings were discovered. Isolated cervical nodes accounted for 44% of all cases while 24% had enlarged nodes in more than one anatomic region. The most frequently</p>		

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						performed laboratory test was the full blood count (34%) and the most frequent positive test was the throat culture (30%). Twenty percent of patients received antibiotics.		
Fijten and Blijham 1988	Dutch Primary Care study.	A retrospective investigation into the probability of malignancy in patients presenting with lymphadenopathy as well as the characteristics that may be discriminatory for malignant causes.	82	Patients who had undergone biopsy for unexplained lymphadenopathy between 1982 and 1984	Patients were excluded if they were not referred for unexplained lymphadenopathy or were not living in the Maastricht area.	Of the 82 patients, 29 had a malignant cause. The prior probability was 1.1% (29/2256 patients presenting this problem in family practice) and a posterior probability after referral of 11.0% (29/256) Diagnosis included 14 malignant lymphomas, 15 metastases, 37 reactive lymph nodes without specific diagnosis and 16 benign causes. Age over 40 years (4%) and the presence of an enlarged supracavicular node (50%) were related to an increased likelihood of malignancy (P <0.01). Borderline significance was obtained for an increased sedimentation rate and weight loss. Physician sensitivity of referral for malignant cases was 80 to 90%, 91-98% of benign cases were not referred.	Cytologic or histologic examination was used as the gold standard for malignant and benign lymphadenopathy.	
Servaes et al 2002	Netherlands	A review of the studies examining the relationship between cancer and fatigue The focus was on fatigue observed in patients during and after treatment for cancer using data from empirical studies.	54 articles	Articles from a Medline, current contents and psychlit Search undertaken for the period July 1980-2001.	Review articles, editorials/ comments/ practical guidelines, studies in which the sample size was less than 15, studies investigating a sample of subjects other than adult cancer patients (eg children, caregivers), studies in which evaluation of a fatigue-questionnaire was the only intention, uncontrolled intervention studies, studies published	The results from the studies indicate that fatigue was investigated among patients who were undergoing treatment for cancer rather than at the time of initial diagnosis. There was little information on the relationship between fatigue and haematological cancer. No articles were based on data in a primary care setting		Systematic review. Good review but not related to fatigue in general practice, or not specifically about Haematology.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
					in a language other than English or dutch and studies in which fatigue was measured with one or a few items from a quality of life questionnaires.			
Wang et al 2002	US Cancer Centre. Participants approached in both outpatient clinics and inpatient units. Tertiary care?	A cross-sectional study using a convenience sample aimed to describe fatigue severity, fatigue interference and associated haematological malignancies. Patients being treated for leukaemia and non-Hodgkin's Lymphoma completed the Brief Fatigue inventory so that fatigue severity and functional interference caused by fatigue could be assessed. Data regarding patient demographics, Eastern Cooperative Oncology Group performance status, other physical symptoms, current treatments, and laboratory values were also collected. Descriptive statistics, bivariate correlations, and logistic regression were used for data analysis.	228	Patients were eligible if they were aged 18 years or older, had a pathologic diagnosis of leukaemia or lymphoma, and were able to read and understand self-report questionnaires in English.	--	50% of the sample reported severe fatigue (defined as 'fatigue worst' with a rating of 7 or more). Patients with acute leukaemia were more likely to report severe fatigue (61%) compared with those with chronic leukaemia (47%) and non-Hodgkin's lymphoma (46%) Increased fatigue severity significantly compromised patients' general activity, work, enjoyment of life, mood, walking and relationships. Fatigue severity was strongly associated with performance status, use of opioids, blood transfusions, gastrointestinal symptoms (P<0.001) and sleep disturbance (P<0.001 and pain (P<0.01). In terms of laboratory variables it was also associated with low serum haemoglobin and albumin levels. Regression analysis revealed nausea was the significant clinical predictor of severe fatigue (odds ratio, 13), and low serum albumin was the significant laboratory value predictor (odds ratio, 3.8)		Primary evidence of fatigue relationship to leukaemia
Williamson 1985	US Primary Care	The primary care charts of patients with enlarged lymph nodes were reviewed to provide a primary care database for evaluating lymphadenopathy. Data recoded included age, sex, location of enlarged	249 (238 at follow up)	The study population was selected from patients seen between July 1978 and June 1983. patients studied were all those seen during the 5 year study period whose	--	The mean age of patients was 24 years old and 26% were aged under 15 years. 58% of the patients were female. 51% had been seen once for enlarged lymph nodes, 23% had been seen twice and 26%		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
		nodes, diagnoses made, laboratory evaluation, outcome, referrals, and information to evaluate adequacy of follow-up.		diagnoses were coded 'enlarged lymph nodes, not infected' and 'lymphadenitis, acute'		<p>three times or more. A firm diagnosis was made in 36% of patients despite an average of 1.7 visits and two laboratory tests per patient tested. Lymph nodes were biopsied in 3% of patients. No patient was found to have a prolonged, disabling illness without a prompt diagnosis. 18% had associated upper respiratory tract infection, 8% had infected or inflamed tissue near the node site and 5% had insect bites.</p> <p>No patients with potentially serious diseases presented with lymphadenopathy alone; all had associated signs or symptoms that led to a diagnosis. Older patients were more likely to have a serious disease associated with enlarged nodes</p>		

Table 5 HAEMATOLOGICAL: investigations

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Lee et al, 1980	USA, Secondary Care	The authors undertook a retrospective and all-inclusive study of patients who had isolated lymph node biopsies for diagnosis. They then looked at the statistical possibility of various pathological lesions for each of the lymph node biopsies. Data regarding age, sex, and site of node removed were obtained.	925 specimens (collected over a five-year period)	Histological specimens reported that involved only lymph node biopsies	Cases where nodal specimens were taken with resection of any visceral organs, either separately or in continuity (en-bloc) or removed during staging laparotomy for malignant lymphoma	551 (60%) of the nodes removed turned out to be benign lesions, 263 (28%) had carcinomas, and 111 (12%) had malignant lymphoma. Among the peripheral lymph node biopsies, the isolated axillary lymphadenopathy had the highest likelihood (23%) of lymphomatous involvement; second highest, the neck area (18%), and about 8% of the supraclavicular or groin node biopsies. The possibility that any peripheral lymphadenopathy is due to benign process decreases with the patient's age (for patients younger than age 30, 77-85% of the lesions were benign, 2-8% carcinomatous, and 13-23% lymphomatous; for patients 51-80 years old, 35-41% had biopsy for benign lesions, 32-47% for carcinomas, and 11-33% for lymphoma). For patients younger than 30 years old, peripheral lymphadenopathies were more likely to be lymphomatous lesions than carcinomas (mean 15% vs 6%); among patients older than 51 years, carcinomas were more common than lymphomas (mean 44% vs 16%). Sex of the patient did not influence the distribution of benign or malignant diagnosis of the lymph node biopsies. 4% of isolated abdominal lymph node biopsies, 1% of intrathoracic nodes, and 15% of peripheral lymph nodes contained lymphoma.	Histological diagnosis (lymph node biopsy)	Purely descriptive, retrospective study. Evaluation process of specimens insufficiently described. Limited extrapolation of findings to primary care setting.
Montserrat et al 1991	Spain Secondary Care	One hundred and seventeen patients with chronic lymphocytic leukaemia from 14 institutions were included	117	Younger patients with chronic lymphocytic leukaemia (of mean age 44.5 years).	A review of peripheral blood smears, as well as bone marrow aspirate and/or biopsy, was performed to	The number of cases of chronic lymphocytic leukaemia rose with age. There was a significant predominance of males (2.08 v 1.21; P<0.25) and the Hb level		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
		<p>in the study.</p> <p>Three hundred and sixty-two patients with chronic lymphocytic leukaemia from the Postgraduate School of Haematology were used for comparative studies. A sex-and-age matched Spanish population was used to compare survival of patients with chronic lymphocytic leukaemia with normal persons.</p>			exclude lympho-proliferative disorders other than chronic lymphocytic leukaemia.	<p>was slightly increased (13.47 ± 2.70 g/dL v 12.84 ± 2.77 g/dL; $P < 0.05$). No differences were found in the initial lymphocyte and platelet counts. At the time of the report 36 patients had died. Survival of young patients with chronic lymphocytic leukaemia (median 12.3 years) was compared with the control population (median 31.2 years) ($P < 0.001$). The clinical characteristics of 18 patients less than 40 years old included in this series were not different from those of patients 40 to 49 years old.</p> <p>1) Younger patients with chronic lymphocytic leukaemia had no distinctive presenting features compared with older patients, 2) the impact of chronic lymphocytic leukaemia on survival produced the same results regardless of the patient's age.</p>		
Nasuti et al 2000	US Secondary Care	<p>Three hundred and sixty-five FNA specimens from 365 cases performed on palpable and non-palpable masses believed clinically to be lymph nodes, and an additional 22 cases (22 specimens) of extranodal lymphoma specimens diagnosed as representing lymphoreticular tumours at our institution over a five-year period from February 1993 to February 1998 were reviewed.</p> <p>The results of the lymph node fine needle aspirations (FNAs) were divided into categories of benign/reactive, metastatic malignancies, lymphomas, miscellaneous and non diagnostic. The cytologic</p>	387 cases	--	--	<p>The study demonstrated that the use of LFNA alone was effective in staging a variety of non-lymphoid malignancies over a five year span, as evidenced by a 94% correlation with the surgical pathology diagnosis when available. One false-positive fine needle aspiration of the submandibular node, was stated to be due to the paucity of the diagnostic material at the time of aspiration. For the five year duration of this study only 30% of the 191 patients diagnosed with metastases by LFNA cytology underwent subsequent surgical excision of the lymph node to confirm the diagnosis. The diagnostic accuracy of LFNA enabled 135 patients over a five year span to avoid surgical lymph node staging of their cancer.</p>	Excisional biopsy or tissue study was performed to confirm the diagnosis.	<p>The evidence presented was relevant to secondary care.</p> <p>It was concluded that strict adherence to cellular adequacy could provide a rapid, less morbid and more cost effective alternative to surgical lymph node staging of non-lymphoid malignancies.</p> <p>There were non diagnostic cases. Sample size was small which possibly accounted for variations in the higher predictive value of LFNA reported in this study. The authors did not specify when there was inadequate material for FNA to be performed for</p>

DRAFT FOR FIRST CONSULTATION

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		diagnosis in all cases was compared with the results of the concurrent flow cytometric analysis and when available, with subsequent histological and flow cytometric findings of the surgically resected lymph nodes to determine diagnostic accuracy.				Non-diagnostic cases made up 12% (n=43) of the total LNFNAs. The Subsequent findings of malignancy in 23% of cases emphasised the need for follow-up of cases with inadequate material on FNA. There were 13 out of 43 non diagnostic cases. Follow-up results emphasised the importance of further sampling in non-diagnostic cases.		their specific study. The high proportion of non-diagnostic cases comprising 12% (n=43) emphasised the need for follow up of cases with inadequate material on FNA. The relatively high non-diagnostic rate with transbronchial LFNA was explained by the recent introduction of the emerging technology at the institution which required a very bronchoscopist to attempt the procedure.
Pangalis et al 1993	Greece Secondary care	The aim of this study was to determine whether a patient presenting with an enlarged lymph node was within or outside the normal limits. The exact cause of abnormal enlargement was subsequently investigated. This was a Hospital based study combining hospital data with a discussion of the literature review.				The vast majority of pathological lymph node enlargement < 1cm ² in this Greek hospital based study had a non-specific etiology (118 of 186 patients [63.4%]). Among the specific causes, toxoplasmosis, infectious mononucleosis and tuberculosis were the most frequently encountered. A lymph node size of 2.25cm ² (1.5 X 1.5cm) was reported as discriminating between malignant or granulomatous Las from other Las (relative risk = 13.0). Data from the hospital unit suggested that splenomegaly coexists with lymphadenopathy in a small proportion of patients (10 of 220 or 4.5%) The presence of lymphadenopathy and splenomegaly is compatible with infectious mononucleosis (splenomegaly in 50% of the patients) Hodgkin's disease, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, and other leukaemias. Lymph node biopsy was necessary for establishing the diagnosis in 74 out of 220 patients (33.6%).		
Schmidt Et al 1985	Denmark Primary	A retrospective investigation into the	88 cases detected	All cases of previously unknown	Not mentioned.	Approximately 10 000 SPE's were requested and of these 88		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
	care	clinical diagnosis of monoclonal gammopathy (MG)	over a three year period	monoclonal gammopathy detected by GP's via serum protein electrophoresis. (SPE)		cases of MG were found. Results from men and women were similar and therefore grouped together. 15% had malignant monoclonal gammopathy, 5% had non-haematological cancers. In 80% a benign disorder was found MG was most common in patients aged between 60 and 80. 15% had malignancy monoclonal gammopathy (MMG) and 85% had monoclonal gammopathy of undetermined significance (MGUS)(classification adapted from kyle 1980) 28 cases were classified as no recognised disease' but presented with symptoms that made their GP ask for SPE. Only 1 out of 13 individuals below the age of 50 years with MG had a malignant disease. In comparing the age groups; younger than 70 and 70 and above, the results suggest that MMG is more common in the elder group. However even in this group only 19% had MMG.		
Slap et al, 1984	USA, Secondary Care	The authors developed a predictive (discrimination) model to differentiate patients whose biopsy results do not lead to treatment from those whose biopsy results do lead to treatment (granulomatous or malignant nodes – Hodgkin's disease and non-Hodgkin's lymphoma, and metastatic solid tumour). They reviewed the medical records and histopathology slides of patients who underwent biopsies of enlarged peripheral lymph nodes, and then compared the pathological diagnosis with	123 patients	9- to 25-year-old patients who had peripheral lymph node biopsies or excisions	Patients were excluded from the study if: (1) a previous biopsy had revealed histopathology, (2) there was no palpable peripheral lymphadenopathy on physical examination, or (3) the medical record or pathology slides were unavailable for review	The following four clinical findings were associated with granuloma or tumour at $P<0.05$: abnormal chest X-ry, lymph node size on physical examination greater than 2 cm in diameter, history of night sweats, and history of weight loss. A history of recent ENT symptoms (ear ache, coryza, or sore throat) was the only variable associated with the absence of granuloma or tumour at $P<0.05$. A haemoglobin value of 10.0 g/dl or less was associated with granuloma or tumour at $P=0.08$. Three of the variables (haemoglobin, night sweats, and weight loss) did not contribute significantly to discrimination. The model	Histological diagnosis (lymph node biopsy)	Study only relevant to people aged 9 to 25 years, model not valid for other age ranges. Blinded assessors. Small sample size. Several problems associated with the derivation of multivariate models: as the number of variables analysed increases, the risks of finding an association where there actually is none increases; the model performance depends on the fidelity and consistency of its component variables (in this study, for example, lymph node size determined by palpation

DRAFT FOR FIRST CONSULTATION

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		22 clinical findings. The authors retrospectively validated the model with a second sample of patients who had also undergone biopsies.				developed with the other three variables (chest X-ray, lymph node size, and history of recent ENT symptoms) classified correctly 95 to 97% of patients, with a sensitivity and positive predictive value of 95% and a specificity and negative predictive value of 96%. Chest X-ray was found to have the greatest impact on the discriminant score. The diagnostic performance of the model was significantly better than that of chance alone ($P=0.001$)		and external measurement). Model may not perform well in settings different from those in which they were derived (variations in disease prevalence, presentation, natural history, or surveillance).
Vilpo et al 2001	Finland	An informal review related to a set of guidelines issued by the Finnish Medical Society <i>Duodecim</i>				The review indicated that the symptom of bleeding in thrombocytopenia may be caused by leukaemia. Typical manifestations in thrombocytopenia were reported as including skin bruising and petechiae and mucous membrane bleeding. Gum and nasal bleeding was particularly common. Bleeding may take place in the alimentary and urinary tracts. Menorrhagia is common. Acquired causes of thrombocytopenia include aplastic anaemia and bone marrow infiltrates (carcinoma, leukaemia, myelofibrosis and tuberculosis).		The article did not present primary data.
Wang et al 2002	US Tertiary Centre	The hospital based study aimed to describe fatigue severity, fatigue interference and associated factors in haematologic malignancies. The relationship between low albumin and severe fatigue was investigated. Data on fatigue severity was categorised and summarised by diagnosis: acute leukaemia, chronic leukaemia and Non-	228	A convenience sample of cancer patients (n=246) was approached in both outpatient clinics and inpatient units. Patients were eligible if they were 18 years or older, had a pathologic diagnosis of leukaemia or lymphoma.	Ten patients diagnosed with Hodgkin's disease were not included in the report because of their relatively small number.	Fifty-four percent of patients with severe fatigue had haemoglobin levels of less than 10g/dL. Haemoglobin level was significantly different across diagnoses $P=0.000$, with NHL patients having significantly higher haemoglobin levels than patients with AL ($P=0.000$). Fatigue severity was negatively correlated with albumin level ($r=-0.396$; $P<0.001$). Patients with albumin levels lower than the reference range reported significantly higher levels of		The data used in this study was drawn from secondary care. Information on the nonfatigue symptoms experienced was obtained by asking whether these symptoms were present or absent, instead of using ratings. Asking for ratings of the severity of these symptoms (as was used for pain and fatigue) would have helped to clarify the relationship

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
		Hodgkin's lymphoma				fatigue than patients with albumin levels within the reference range (fatigue worst, 7.1 v 5.3; P<0.001).		between the severity of the symptoms and fatigue. The study was limited by its cross sectional design. Fatigue was expected to vary over the course of treatments. Patients could experience fatigue caused by disease and treatment.
Wright et al 1992	UK Secondary and Tertiary Referral Centre	<p>A review of case notes to investigate sources and types of referrals to a haematology department over one year. The following information was recorded: age and sex. Source of referral, reason for referral and time interval between referral and appointment.</p> <p>The following outcome measures were also analysed: diagnosis, number of subsequent clinic visits and length of follow-up.</p>	226 new patients	All new patients attending the haematology outpatient department during 1989.	--	<p>56% of referrals were initiated by GP's, 30% were from consultants in other hospital departments and 25% were cross boundary referrals from hospitals outside the district. 1.8% of referrals were initiated by haematology medical staff (contacting GP's and suggesting patients be referred following an abnormal full blood count) 56% of GP referrals were prompted by abnormal full blood counts or blood film findings- with haematologists often enclosing a written report suggesting referral. The remaining 1.3% of patients were transferred from private practice.</p> <p>Lymphadenopathy was the most common abnormality leading to referral (11%), followed by an iron deficient picture on a full blood count report (9%), Easy bruising (8%), Neutropenia (6%) and a full blood count report suggesting a myeloproliferative disorder (6%).</p> <p>GP's referred all patients with suspected iron-deficiency and 79% of referrals with lymphadenopathy. Hospital consultants referred most cases of thrombocytopenia for investigation, all cases of paraprotein and all cases of lymphoma proven by histology before referral.</p> <p>GP's referred 95% of case which subsequently iron</p>		Good GP based data though small study.

DRAFT FOR FIRST CONSULTATION

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						<p>deficient (17% of all GP referrals). No haematological abnormality was found in 13% of GP referrals requiring follow-up, in comparison with 5% from hospital referrals.</p> <p>96% GP referrals also requested a diagnosis compared with 59% of hospital initiated referrals</p> <p>45% of GP referrals were discharged from follow-up during the study period compared with 32% from hospital referrals.</p>		

Table 6 HAEMATOLOGICAL: delay and diagnostic difficulties

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Norum 1995	Norway Secondary care	A retrospective hospital study was undertaken of the records of 50 patients treated for primary Hodgkin's disease in Northern Norway between 1985 and 1993. The diagnostic delay related to clinical stage, age, sex, relapse or death. Diagnostic delay was defined as the time period between the patient's first symptoms of lymphoma and the histological or cytological diagnosis of Hodgkin's disease.	50 patient records	Records of all patients treated a 1 hospital for primary HD		the lymphocyte predominance Hodgkin's disease sub group had a significant delay (P+0.038). The median delay was four months (range 0-48 months) in the subgroup lymphocyte predominance Hodgkin's disease compared to four months (range 0-27months) in the other subgroups. The median age at diagnosis was 41 years (range 15-70 years). There was no statistical correlation between delay in diagnosis and age, sex, symptoms, stage of disease, recurrent disease or death of disease. The diagnostic delay in patients with Hodgkin's disease did not seem to have any significant influence on stage distribution, relapse rate or short-term survival. Those dying of disease had had a short delay. The aggressiveness of the tumour could be the important parameter. All six patients dying of Hodgkin's disease had a diagnostic delay of six months or less (median 3.2 months). The same tendency was revealed for relapse and diagnostic delay. Nine of ten relapsing patients had a delay of six months or less. There was no statistical correlation between delay in diagnosis and age, sex, or symptoms. There was no improvement in diagnostic delay during the study period (1985-93).	Purely descriptive, retrospective study. Evaluation process of specimens insufficiently described. Limited extrapolation of findings to primary care setting.
Summerfield et al 2000	UK Secondary Care	Delays in the diagnosis and treatment of lymphoma in district hospitals in the northern region of the UK were audited in order to assess the appropriateness of the requirement of the National Priorities Guidance (NPG) Cancer Targets that all new patients with suspected cancer be seen by a specialist within two weeks of a referral by their GP. Sources of delay were analysed in all 89 consecutive cases presenting to hospitals in 1997-9.	89 cases			The results of the audit showed that among four hospitals during the period of study, delay from GP referral to hospital appointment averaged 3.9± 1.2 (mean ± SE weeks). Further delay in the diagnostic process was observed from hospital appointment to biopsy 4.7 ± 1.0 (mean ± SE) weeks (n=87), followed by delay from biopsy to local histology report 1.2 ± 0.1 (mean ± SE weeks (n=83), and then from local histology to review panel report 3.1 ± 0.6 (mean ± SE) weeks (n=48). In addition a delay from diagnostic biopsy to bone marrow examination was recorded of 2.8 ± 0.3 (mean ± SE) weeks (n=70), furthered by delay from diagnostic biopsy to CT scan 2.8 ± 0.41 weeks (n=85). This results in a delay from completion of investigations to treatment of 2.5 ± 0.6 weeks (n=84). Therefore, the total delay recorded was 7.5 ± 1.0 (mean ± SE months (n=76), and of that patient delay accounted for 3.9 ± 0.8 (mean ± SE) months (n=76). Diagnostic delay amounted to 2.8 ± 0.4 (mean ± SE) months (n=88), with treatment delay	

DRAFT FOR FIRST CONSULTATION

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						being 1.2 ± 0.2 (mean \pm SE) months (n=87). Overall patient diagnostic and treatment delay for high-grade non-Hodgkin's lymphoma was recorded as n=41, for low-grade non-Hodgkin's lymphoma it was n=35, and for Hodgkin's disease it was n=9.	

Table 7 SKIN: signs and symptoms, including risk factors

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Australian Cancer Network, 1999		<p>These guidelines for melanoma were based on a systematic review of evidence that was considered by a multidisciplinary panel. The recommendations relating to clinical diagnosis were:</p> <p>Good lighting and magnification is recommended when lesions are examined. All clinicians should be trained in the recognition of early melanoma. A good clinical history of the change in the lesion (if any), a past history of skin lesions, and a family history of melanoma should be obtained. A family history is defined as melanoma in a direct-line family member – grandparent, parent, sibling or child of the patient.</p> <p>Lesions which are suspicious or cannot be diagnosed after a period of observation should be biopsied, or the patient referred for a specialist opinion. High risk individuals should be advised of the specific changes which suggest melanoma and encouraged to perform self-examination.</p>						
Brady et al, 2000	USA	A case series with newly diagnosed patients with cutaneous melanoma presenting to a US specialist cancer centre between July 1995 and May 1998. All patients were asked to complete a questionnaire at their first visit to the cancer centre.	454	Patients for which the information regarding Breslow thickness of the melanoma was available.	Patients with an unknown primary site, noncutaneous melanoma, distant metastases or recurrent disease	<p>Most patients presented with melanoma > 0.75mm in Breslow thickness (62%; N=283 patients). The remaining patients (38%) had thin melanomas (≥ 0.75mm; N=122 patients) or in situ disease (N=49 patients). The majority of patients detected their own melanomas (N=270; 57%). Patterns of detection were influenced by patient gender. Females were more likely to self-detect than males (69% vs. 47%; P<0.0001). Physicians detected the melanoma in 16% of patients (N=74), followed by spouse in 11% (N=51). Physicians were three times more likely to detect thin lesions (≤ 0.75 mm) compared with nonphysician detectors (95% confidence interval [95% CI] 2.1, 6.5; P=0.0001). Physician detection occurred in only four of 84 males under age 50 years compared with 43 of 166 males age ≥ 50 years (P<0.0001). Patients who reported a family history of</p>		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						melanoma had a 2.7 fold increased likelihood of presenting with a thin lesion (95% CI, 1.6, 4.7; P=0.003). Family history information was available for 451 patients. Of these, 84 patients (19%) reported a family history of melanoma, and 366 patients (81%) reported no first or second degree relative with the disease. Despite a trend towards thinner melanomas in females, the difference in the median Breslow thickness between females and males was not significantly different (1.10 mm vs. 1.13 mm; P=0.07). There was no significant association between tumour thickness and age, gender or lesion visibility.		
Cassileth,1987	USA	In this case series, a retrospective analysis of the charts of patients treated between 1972 and 1981 for superficial spreading melanomas was undertaken. Information was recorded routinely for all patients by clinic nurses using a structured interview guide during the patient's first clinic visit. Patients were asked about the presence of each of seven symptoms (size, elevation, colour, bleeding, ulceration, itching and tenderness) plus other features. Information was recorded about the type, number and duration of individual symptoms noticed by the patient; catalyst symptoms or the particular event that preceded the patient's request for medical attention; and location, thickness and level of the melanoma	568 patients	Patients who had attended a single specialist US centre, only data for patients over 17 years of age and with no prior primary melanomas	--	Forty-eight percent of patients who met the eligibility criteria were men. Forty-six percent of patients reported the simultaneous occurrence of more than one catalyst symptom; 35% reported experiencing one catalyst symptom only; and 19% claimed that they had noticed no changes in existing lesions. The most common catalyst symptom pattern, a combination of size, elevation and colour was reported by 60 patients, who were diagnosed an average of 11.2 months after observing this combination. The mean tumour thickness at diagnosis for this group of patients was 1.26 mm (\pm 1.8 mm). The second most common catalyst symptom, bleeding, was reported by 49 patients, who were diagnosed after an average of 2.3 months. A total of 75 different catalyst symptoms or symptom combinations were described. Patients who sought medical attention in response to bleeding alone (N=49) had thicker lesions (mean 1.77 mm) than did the 45 patients who sought medical attention in response to changes in both size and colour (mean 0.54 mm). A total of 109 patients, 19% of the sample, could not identify any change in an existing lesion. The average lesion thickness for these 109 patients was 0.93 mm (\pm 1.4 mm) compared with the average lesion thickness of 1.37 (\pm 1.8 mm) for all other patients (P<0.01).		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
DoH, Referral Guidelines for Suspected Cancer, 2000		<p>Cancers tend to be larger (>1cm) than actinic keratoses and have a palpable component deep to the skin surface.</p> <p>Basal Cell Carcinoma Very common, but metastasize very rarely, so there is no need to refer urgently. Location: majority are on the face, particularly around the inner canthus and nose. Appearance: Slowly growing red pearly nodule on skin surface. Later may break down with crusting to give classic 'rodent ulcer'. The slow growth and low metastatic potential of these lesions mean that they do not need to be seen within two weeks. Nevertheless patients with suspected basal cell carcinoma should be seen by a specialist within three months.</p> <p><u>Urgent referral</u></p> <p>Melanoma Pigmented lesions on any part of the body which have one or more of the following features: Growing in size, Changing shape, Irregular outline, Changing colour, Mixed colour, Ulceration, Inflammation. NB. Melanomas are usually 5mm or greater at the time of diagnosis, but a small number of patients with very early melanoma may have lesions of a smaller diameter than this.</p>						
Elwood et al 1998	Canada	<p>A report from a larger case control study of risk factors. Information on all confirmed cases of newly diagnosed cutaneous malignant melanoma was obtained from treatment centres and cancer registries in four provinces of Canada. Identified patients were interviewed about initial presentation and symptoms.</p>	651	patients aged 20 to 79 years	Patients with acral lentiginous melanoma	<p>415 patients (64%) had superficial spreading melanoma, 128 (20%) had nodular melanoma, 52 (8%) had unclassified or borderline melanoma and 56 (9%) had lentigo maligna melanoma. Most patients reported 1 or more of a set of 4 symptoms related to an existing mole or pigmented spot: Each of the 651 presenting with melanoma were asked to describe first indications of their disease. The results were as follows: Major symptom group- Enlargement, colour change, pain or bleeding (65%), Suspicious lesion, no other detail (24%), New mole (8%), Miscellaneous (3%). Frequency of classic symptoms- Enlargement (43%), Colour change</p>	Histology	

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Hawrot et al, 2003	USA	A summary of the literature regarding the incidence, causation, clinical and histologic presentation, prognosis, treatment, follow-up, and prevention of cutaneous squamous cell carcinoma.	--	--	--	(32%), Pain (22%), Bleeding (16%). Long term follow-up studies of patients who undergo treatment with high doses of PUVA show a relative risk of four to six compared with individuals not exposed to such treatments. PUVA effects appear to be dose related and although lesions may occur as early as five years after therapy, the strongest correlation is seen in the second decade after therapy completion. The incidence rate of cutaneous squamous cell carcinomas is increased in organ transplant recipients. Patients with transplants are at a three to four fold increased risk of systemic and cutaneous. An increased incidence rate of squamous cell carcinomas after transplantation is associated with time after transplantation, decreasing latitude and older age as well as childhood, duration of immunosuppression, intensity of immunosuppression, and history of skin cancer before transplantation. In some studies the relative risk of squamous cell carcinomas has been found to be approximately three times higher in people born in geographic areas receiving high amounts of ultraviolet radiation than in residents who moved to such areas only in adulthood; two to five times higher in those with very light skin colour, hazel or blue eyes and blonde or red hair; five times higher in individuals with exclusively outdoor occupations and three to eight times higher in people with severe versus no solar elastosis, freckling and facial telangiectasias. Although fair skinned whites, especially men in their 60s and 70s are at highest risk for cutaneous squamous cell carcinomas, other racial and ethnic types with intermediate skin types may be susceptible given predisposing environmental conditions		
Motley et al, 2002	UK	These British Association of Dermatologists/British Association of Plastic Surgeons guidelines addressed squamous cell carcinoma. Squamous cell carcinoma was defined as a malignant skin tumour of keratinizing						

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
		cells of the epidermis or its appendages, which is locally invasive and has the potential to metastasize. The guidelines state it usually presents as an indurated nodular keratinizing or crusted tumour that may ulcerate, or may present as an ulcer without evidence of keratinization. Other forms of squamous cell carcinoma include (a) actinic and radiation keratoses, which are scaly erythematous papules or plaques on sun damaged or irradiated skin that may develop into invasive squamous cell carcinoma; (b) pre-invasive carcinoma (carcinoma in situ): (i) Bowen's disease, which is crusted, keratotic or a velvety erythrematous plaque; (ii) erythroplasia of Queyrat, which appears on the glans penis as a red, velvety patch; (iii) erythroplakia and malignant leukoplakia, on mucous membranes other than the glans penis; (c) verrucous carcinoma, a warty tumour that occurs most often on the hands, feet, anogenital area and oral cavity; (d) keratoacanthoma.						
Osborne, 1999		A retrospective case series. The aim was to investigate possible predictor variables for false negative gradings using the seven point checklist in a population of patients with confirmed malignant melanomas presenting in Leicestershire between 1982 and 1996. The case notes of the included patients were examined retrospectively. False negatives were defined as those patients in whom another diagnosis was made or in whom there was evidence in the case notes that the diagnosis was thought not to be malignant melanoma. Demographic data were recorded together with clinical diagnosis, clinical features of each lesion according to the revised seven point checklist, and site of the lesion.	778 cutaneous malignant melomas.	The case notes of all patients presenting with cutaneous malignant meloma in a UK city between 1982 and 1996	--	No clinical diagnosis had been given in the records for 43 of the 778 lesions, 599 were suspected of being melanoma, and 136 had not been suspected on clinical grounds. The clinical false negative diagnosis rate was 18.5% and the diagnostic sensitivity 81.5%. There were 476 females and 257 males, giving a ratio of 65% females. Sex had no effect on false negative rate; the proportion of females in the diagnosed group being 66% and the non-diagnosed group 60% (=0.20). The false negative rate varied markedly with site and was lowest for the trunk and leg (12 and 13%), but was 21% for the arm. More rarely occurring sites gave higher false negative rates from 31% to 42%. Comparing the false negative rate on the trunk (the lowest rate) with the other sites, the odds ratio for the face was 3.4 (P=0.0007), head and neck 5.1 (P<0.0001), arm 2.0 (P=0.02), leg 1.0 (P=0.6), sole 3.4 (P=0.06) and subungual	histology	

DRAFT FOR FIRST CONSULTATION

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						<p>5.5 (P=0.007). The false negative clinical diagnosis rate varied markedly with the presence of features of the seven point checklist (P<0.00001). It was lower if major features were present (8-18%), and greater if the minor features were present (13-35%). Major features associated with a particularly low rate were irregular shape and irregular pigmentation, 8 and 10%, respectively. Clinical features of lesions associated with a higher false negative rate were lack of irregular pigmentation and shape, altered sensation, the presence of inflammation and size < 7mm. The multivariate logistic regression of all parameters showed that the relationships of false negative rate and melanoma site, irregular pigmentation, irregular shape, sensation, inflammation and diameter >6 mm were significant and independent. For the individual sites, results of univariate and multivariate analysis were similar, although the adjusted odds ratio and its significance, for the face compared with the trunk increased markedly on multivariate analysis. The results suggested that the face is a particularly difficult site. All of the clinical features except surface oozing/crusting/bleeding retained significance on multiple regression.</p>		
Roberts et al, 2002	UK	<p>Guidelines for melanoma were produced jointly by the British Association of Dermatologists and the Melanoma Study Group. The seven-point checklist was recommended for both patient and general practitioner education. Lesions with any of the three major features (change in shape, irregular shape, irregular colour) or three of the minor features (largest diameter 7mm or more, inflammation, oozing, change in sensation) are suspicious of melanoma, and should ideally be seen by specialists (that is, clinicians routinely treating large numbers of patients with pigmented lesions). Specific recommendations were:</p>						

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
		<p>Patients with lesions suspicious of melanoma should be referred urgently to a dermatologist or surgeon/plastic surgeon with an interest in pigmented lesions.</p> <p>These specialists should ensure that a system is in place to enable patients with suspicious lesions to be seen within two weeks of receipt of the referral letter.</p> <p>All patients who have had lesions removed by their general practitioner that are subsequently reported as melanoma should be referred immediately to specialists. (Grade C, level III)</p>						
Schwartz et al, 2002	USA	A case series, in which patients presenting between January 1998 and December 1999 with in situ or invasive cutaneous melanomas were questioned about their signs and symptoms	1515	All patients with with in situ or invasive cutaneous melanomas presenting between January 1998 and December 1999	--	<p>The mean age at diagnosis of the first primary melanoma was 52.6 years. The majority of patients (72%) were between the ages of 21 and 65, 26% being older than 65 years, and only 2% younger than 21 years. Females (48.9 years) were younger than males (56.1 years) at diagnosis of their first primaries (P<0.001). Physician detected lesions were thinner (0.40mm) than either self-detected (1.17 mm; P<0.001) or spouse-detected (1.00 mm; P<0.001) lesions. In males the Breslow depth of self-detected lesions (1.42 mm) was greater than that of the lesions detected by either the spouse (1.04 mm; P<0.005) or physician (0.42 mm; P<0.001). In females, the mean Breslow depth of self-detected lesions (0.98 mm) was greater than physician detected lesions (0.35 mm; P<0.001) but was not significantly different from spouse-detected lesions (0.72 mm; P=0.2).</p> <p>The most common changes noted by patients were the colour, size, and/or shape/elevation of a lesion. Less common changes included ulceration, bleeding, tenderness, and itching. Mean Breslow depths associated with a change in colour (1.15 mm), size (1.33 mm), shape/elevation (1.47 mm) and itching (1.70 mm) were less than mean Breslow depths associated with ulceration (2.69 mm), bleeding (2.63 mm) and tenderness</p>	All histology slides were reviewed by a skin pathologist to confirm the diagnosis of primary cutaneous melanoma.	

DRAFT FOR FIRST CONSULTATION

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SIGN, 2003 (risk factors)		<p>The SIGN guidelines involved a systematic literature search that included assessment of risk factors. The findings were presented in a table, reproduced here. In the table, odds ratios are given, based on the findings of one or more primary studies, odds ratios being the odds in favour of exposure to a risk factor in people with melanoma to the odds in favour of exposure to the same risk factor among people who have not developed melanoma. The SIGN guideline observed that the odds ratios for someone who has skin that does not tan easily (1.98) is modest in comparison with the ten fold or greater risk of developing lung cancer in someone who smokes cigarettes compared to a person who has never smoked.</p> <p>SIGN recommended that: Genetic testing in familial or sporadic melanoma is not appropriate in a routine clinical setting and should only be undertaken in the context of appropriate research studies (D).</p> <p>The SIGN guidelines cite a consensus document, which estimated that one to two percent of melanomas were attributable to the inheritance of melanoma susceptibility genes. 'Members of such families are at significantly increased risk of developing melanomas. Many more melanoma patients have only one relative who also has melanoma. An intensive search for putative melanoma susceptibility genes has identified mutations in the CDKN2A gene in 20-30% of melanoma prone families in Scotland, reflecting rates reported in other parts of the world. Current expert consensus recommends that genetic testing in familial or sporadic melanoma is not appropriate in a routine clinical setting and should only be undertaken in the context of appropriate research studies and when appropriate</p>				(2.44 mm; all P<0.005).		

DRAFT FOR FIRST CONSULTATION

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SIGN, Cutaneous melanoma: A National Clinical Guideline, 2003 (signs and symptoms)		<p>counselling services are available.</p> <p>The SIGN guidelines were developed following a detailed literature review. recommendations: Clinicians should be familiar with the seven point or the ABCDE checklist for assessing lesions (D). Clinicians using hand held dermatoscopy should be appropriately trained (D). Health professionals should be encouraged to examine patients' skin during other clinical examinations (D) Patients with suspicious pigmented lesions should be seen at a specialist clinic in a time commensurate with the level of concern indicated by the general practitioner referral letter (recommended best practice). Emphasis should be given to the recognition of early melanoma by both patients and health professionals (recommended best practice). Targeted education can enhance professionals' ability to diagnose melanoma (recommended best practice). Healthcare professionals and members of the public should be aware of the risk factors for melanoma (B). Individuals identified as being at higher risk should be (C) Advised about appropriate methods of sun protection, Educated about the diagnostic features of cutaneous melanoma, Encouraged to perform self-examination of the skin. Brochures and leaflets should be used to deliver preventive information on melanoma to the general public (D) Leaflets and brochures used in melanoma prevention work should be non-alarmist (recommended best practice). If computer-based learning programmes are used they should be interactive in nature (recommended best practice).</p>						
Sober et al,1983	USA	A questionnaire was administered to patients by a trained interviewer to evaluate the frequency with which signs	598 patients	Patients were seen either with the primary	--	For thin lesions (<0.85 mm) increase in size was noted in more than half and was the most frequent sign or symptom		

DRAFT FOR FIRST CONSULTATION

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		and symptoms were associated with melanoma.		tumour intact or within 30 days of its removal.		present for 'thin' tumours. This was closely followed by colour change, which was present in half. Bleeding, ulceration and tenderness were infrequently seen (present in five to 13%). Conversely, increase in height was the most frequent feature noted with the thickest tumours (≥ 3.65 mm), observed by more than 80% of patients. Bleeding and ulceration were reported in more than half. There was a direct relationship between increase in height and increasing tumour thickness. Itching of the lesion occurred in 20-46% of patients.		
Telfer et al, 1999	UK	These guidelines were produced on behalf of the British Association of Dermatologists, and dealt with basal cell carcinoma. Basal cell carcinoma was defined as a slow-growing, locally invasive malignant epidermal skin tumour, which occurs most commonly in caucasians. Metastasis is extremely rare, and morbidity is related to local tissue destruction, particularly on the head and neck. The clinical appearances are diverse, and include nodular, cystic, ulcerated ('rodent ulcer'), superficial, morphoeic (sclerosing), keratotic and pigmented variants.						
Whited, 1998	USA	a systematic review of the accuracy of skin examination for melanoma using the ABCD(E) and revised seven point checklists. A literature search was performed using MEDLINE for the years 1966 through 1996 to identify relevant retrospective and prospective studies	12 studies	Articles were evaluated and included if they had been given a quality rating of C or above	--	Two studies reported information about the sensitivity for the ABCD checklist, in one it was 92%; (CI 95%, 82%-96%), and in the other 100% (95% CI 54%-100%); one study reported specificity to be 98% (95% CI, 95%-99%). The revised seven point checklist has been reported to have a sensitivity of 79% (95% CI, 70%-85%) to 100% (95% CI 94%-100%) and specificity of 30% (95% CI, 21%-39%) to 37% (95% CI, 21%-39%). Physicians' global assessments for detecting the presence or absence of melanoma were estimated to have a specificity of 96% to 99%, while sensitivity ranges widely from 50% to 97%. Non-dermatologists' examinations were less sensitive than those performed by dermatologists.		
Wick et al, 1980	USA	This case series investigated the clinical	786	--	--	The most useful features for early	Histology	

DRAFT FOR FIRST CONSULTATION

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		characteristics of the primary tumour in patients with confirmed superficial spreading melanoma.				diagnosis were change in size and change in colour, present in 71% and 55% respectively of patients with level II lesions. Increase in height of lesion correlated with more advanced disease. Ulceration and bleeding were predominantly found in advanced primary lesions and were judged of limited use in early recognition. The data revealed that primary lesions were of substantial size and generally much larger than acquired naevi (<7mm) from which they must be differentiated. The results suggested that site was not a major determinant for the presentation of early lesions. There was however a higher proportion of level II lesions (42%) on the head and neck. Conversely, a higher percentage of deeper lesions were encountered on the foot. Characteristic features of early (II, III) lesions associated with tumour growth were colouration and size. The features characteristic of advanced lesions were tenderness, ulceration and bleeding. Elevation became common at level III and above.		
Wong et al, 1989	UK	An authoritative review. The aim was to provide a comprehensive overview of basal carcinoma, concentrating in particular on incidence, risk factors, molecular genetics, clinical features, and treatment.	Not stated	Information obtained from a Medline search with basal cell carcinoma, rodent ulcer, and non-melanoma skin cancer as key words.	--	Exposure to ultraviolet radiation is the main causative factor in the pathogenesis of basal cell carcinoma. However, the precise relationship between risk of basal cell carcinoma and the amount, timing and pattern of exposure to ultraviolet radiation remains unclear. The magnitude of the risk associated with increased exposure seems to be insufficient to explain why particular people get these tumours whereas others do not. Several studies have shown an association between cumulative ultraviolet exposure and risk of basal cell carcinoma, although the magnitude of risk conferred has been small, with odds ratios in the region of 1.0 to 1.5. Other studies have failed to find a significant association between estimated cumulative sun exposure in adulthood and the presence of basal cell carcinoma. Skin type 1 (always burns, never tans), red or blonde hair and blue or green eyes have been shown to be risk factors for the development of basal cell carcinoma with		

DRAFT FOR FIRST CONSULTATION

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						<p>an estimated odds ratio of 1.6. Development of basal cell carcinoma is reported to be more frequent after freckling in childhood and also after frequent or severe sunburn in childhood. This is in contrast to a story of sunburn as an adult, which does not seem to be associated with the development of basal cell carcinoma. Recreational sun exposure in childhood was identified as an important risk factor.</p> <p>A positive family history of skin cancer seems to be a predictor of development of basal cell carcinoma with an odds ratio estimated at 2.2. Several genetic conditions associated with the risk of developing basal cell carcinoma are albinism, xeroderma pigmentosa, and Bazex's syndrome. Patients on immunosuppressive treatment also have an increased risk of basal cell carcinoma. The risk of developing a squamous cell carcinoma is increased slightly after a basal cell carcinoma, with a 6% risk at three years.</p>		

Table 8 SKIN: investigations

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Bricknell, 1993	UK	This study reviewed histopathology reports at one UK hospital with an aim to examine the difference between skin biopsies of pigmented skin lesions taken by general practitioners and those taken by hospital specialists	1205 biopsies involving 1000 patients	The histopathology reports for all skin biopsy specimens from pigmented skin lesions from the period 1 June 1986 to 31 May 1991. Only records with a comment in the clinical summary or in the description of the macroscopic appearance mentioning colour or pigment were included.	--	15 patients had melanomas. General practitioners had undertaken 55% of the biopsies on the 1000 identified patients. Features recorded on pathology forms included size increase (general practitioner 15.0%, specialists 25.1%), bleeding 13.6% vs. 6.6%, colour change 4.8% vs. 11.7% (all P<0.001). Hospital specialists excised significantly more lesions that had increased in size (P < 0.001) or changed in colour (P < 0.001). General practitioners excised more lesions that had bled (P < 0.001). Hospital specialists excised more of the 15 melanomas diagnosed (80%) (P < 0.05), and general practitioners excised more squamous papillomas (P < 0.01). Of the melanomas excised, 40% were not suspected by the clinician.		
Cox 1992	UK	In this study, the findings of skin biopsies by general practitioners examined at one UK hospital were reported.	1017 skin biopsy specimens.	All skin biopsy specimens received by the pathology laboratory from general practitioners from 1 January 1989 to 31 March 1991	--	Of the total of 1017 biopsies, 56 (5.5%) were for malignant lesions. Of 21 basal cell carcinomas, nine had been considered by the general practitioner to be malignant. Six of the 21 had been inadequately excised. None of the four melanomas had been suspected, although they had been adequately excised. Additionally 21 squamous cell carcinomas were excised. Excision was adequate in eight, and the diagnosis had been suspected in only one.		
Department of Health, 2000		The Department of Health guidelines stated: 'It is not recommended that patients with suspected melanoma are biopsied						

DRAFT FOR FIRST CONSULTATION

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		in a general practice setting. Patients should be referred with the lesion intact to the local specialist.'						
Herd, 1992, UK	UK	A retrospective case-control study. The aim was to examine the management of patients who had a malignant meloma excised initially by general practitioners in Scotland in the previous 10 years and to assess the impact of the April 1990 contract on this.	42 malignant melomas were excised. 39 General practitioners.	All patients registered who had malignant melomas excised initially by general practitioners over the last 10 years. Random controls were also selected from among patients who had excisions carried out in the same period. All general practitioners who had excised a malignant meloma during the study period	Those that had primary wide excisions in hospital and those who were judged not to require a subsequent wider re-excision. General practitioners whose patients had subsequently developed metastases	42 biopsies performed by general practitioners were found to be melanoma, compared to 84 randomly selected biopsies carried out in hospitals. The Breslow thickness of lesions was not significantly different. Ten of the general practitioner excisions were incomplete compared with only three incomplete in the hospital sample (P<0.001). Only six (15%) of the 40 general practitioner request forms mentioned the possibility of melanoma. Six had been excised for cosmetic reasons alone. The other reasons were change in size (N=25), and patient worry about malignancy (N=16).		
Hillan, 1991		This study reviewed 149 specimens referred by UK general practitioners to one hospital laboratory	149 specimens			The specimens included one melanoma, and two basal cell carcinomas. No squamous cell carcinomas were identified. 10% of the general practitioner specimens and 11% of a comparison group of specimens referred from the hospital were inadequately excised		
Khorshid, 1998	UK	A survey of pathology reports and interviews of UK general practitioners who had submitted samples for analysis	819 pathology reports 55 UK general practitioners	All GP's who had excised melanomas	GP's that had retired or left the surgeries.	819 melanoma biopsies were identified, of which 59 were excised by the general practitioner. Various specialists excised the remaining melanomas. 15% of general practitioner excisions compared to 36% of non-general practitioner excisions were complete and adequate (P<0.001). General practitioners made an accurate clinical diagnosis in only 17% of cases.	pathology	

DRAFT FOR FIRST CONSULTATION

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Lowy, 1997	UK	This study reviewed pathology specimens before and after the introduction of a policy of referring all removed tissue in the UK in order to examine whether histological examination of all tissue removed by general practitioners in minor surgery increases the rate of detection of clinically important skin lesions. A random sample of specimens sent by 257 general practices referring to 19 pathology laboratories was undertaken.	5723 specimens during the intervention period. 4430 during the control period.	Practices were selected at random from a register.	Practices that did not perform minor surgery and practices that did not keep records of hospital referrals by name.	This study reviewed pathology specimens before and after the introduction of a policy of referring all removed tissue in the UK in order to examine whether histological examination of all tissue removed by general practitioners in minor surgery increases the rate of detection of clinically important skin lesions. A random sample of specimens sent by 257 general practices referring to 19 pathology laboratories was undertaken.		
McWilliam, 1991	UK	A retrospective analysis of histology records at one UK hospital, it included skin biopsy specimens by general practitioners and general and plastic surgeons. The purpose was to evaluate and appraise skin biopsies performed by general practitioners and compare their performance with that of hospital doctors.	292 skin biopsy specimens by general practitioners and 324 by general and plastic surgeons	All records of skin biopsy specimens submitted by GP's for histological examination during 1984-1989.	--	General practitioner cases included six (2%) basal cell carcinomas, five (1%) squamous cell carcinomas, and one (0.3%) melanoma. 36% of all general practitioner's samples compared with 16% of surgeons' samples were incompletely excised. Agreement between clinical and pathological diagnosis in malignant cases was 29% for general practitioners and 90% for surgeons.		
O'Cathain, 1992	UK	This study reported a prospective comparison of patients undergoing minor surgery in general practice and at one hospital	A total of 161 patients were compared, 67 of those in general practice and 94 in hospital	Patients undergoing minor surgical procedures in the participating practices.	--	9.8% of general practitioner cases and 1.2% of hospital cases were malignancies diagnosed as benign. 4.9% of general practitioner cases compared to 0% of hospital cases had not been adequately excised.	histology	
SIGN, 2003		The SIGN guideline included the following recommendations: GPs should refer urgently all patients in whom melanoma is a strong possibility rather than carry out a biopsy in primary care (recommended best practice). The local availability of fast-track services for patients in whom melanoma is suspected should be advertised widely to general practitioners (recommended best						

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
		practice). A suspected melanoma should be excised with a 2mm margin and a cuff of fat (D) If complete excision cannot be performed as a primary procedure a full thickness incisional or punch biopsy of the most suspicious area is advised (D). A superficial shave biopsy is inappropriate for suspicious pigmented lesions. (C).						
Williams, 1991		This retrospective review of pathology records in one UK hospital evaluated skin biopsy specimens from general practitioners	571 skin biopsy specimens			26 (4.6%) biopsies were malignant (14 basal cell carcinomas, eight squamous cell carcinomas, four melanomas).		The study did not assess completeness of excision

Table 9 SKIN: diagnostic difficulties

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Brochez, 2001	Belgium	This study aimed to compare the diagnostic abilities of general practitioners and dermatologists in Belgium concerning pigmented skin lesions in general and melanoma in particular. The study design was a 'before and after' evaluation of a health education programme for general practitioners. A test set of 13 pigmented skin lesions on 35 mm colour slides as presented to participating general practitioners and dermatologists during a monthly educational course.	160 GP's 60 dermatologists	All GPs educational groups in the province of East-Flanders, Belgium were invited to participate	--	The frequency of melanomas encountered was one in seven years for the general practitioners and one in eight months for dermatologists. Consultations for advice about pigmented lesions were encountered once in 30 days by general practitioners and once per day by dermatologists. Sensitivity of general practitioners before the course in diagnosing melanoma from the slides was 72%, and 84% afterwards (dermatologists 91%). Specificity among general practitioners was 71% before and 70% after, and 95% among dermatologists. The positive predictive value (PPV) of general practitioners before was 61%, and 63% after (dermatologists 92%). The negative predictive value was 80% before and 87% after among general practitioners (dermatologists 95%).	
Chen 2001	USA	This systematic review was undertaken in order to compare the diagnostic accuracy and biopsy or referral accuracy of dermatologists and primary care physicians. Studies that presented sufficient data to determine the sensitivity and specificity of dermatologists' or primary care physicians ability to correctly diagnose lesions suggestive of melanoma and to perform biopsies on or refer patients with such lesions. Studies published between January 1966 and October 1999 in MEDLINE, EMBASE and CancerLit databases were retrieved.	32 studies	Strict criteria for inclusion were applied to ensure results were comparable across studies. Studies were selected if they presented sufficient data to determine the sensitivity and specificity of dermatologists' or PCPs' ability to correctly diagnose lesions suggestive of melanoma and to perform biopsies on or refer patients with such lesions.	--	None of the studies reported specificity for dermatologists. One study reported specificity for primary care physicians (0.98). For biopsy or referral accuracy, sensitivity ranged from 0.82 to 1.00 (from five studies) for dermatologists and 0.70 to 0.88 (from six studies) for primary care physicians. The range of specificity was 0.70 to 0.89 (from three studies) for dermatologists and 0.70 to 0.87 (from four studies) for primary care physicians. Most of the studies included in the review evaluated only diagnostic accuracy and not biopsy or referral and did not report either sensitivity or	

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
						specificity, and did not have an adequate sample size or describe the lesions shown to subjects.	
Del Mar et al,1995	Australia	Randomised controlled trial of an intervention to improve diagnostic abilities of GP's. Australian practitioners were offered an algorithm and the use of an instant developing camera in a trial to test whether this intervention would reduce the number of benign melanocytic lesions excised from the skin. Doctors in the city randomised to receive the intervention were offered a protocol to assist in the management of any melanocytic lesion for which a diagnosis of malignancy was entertained.	Control group: 45 general practitioners, seven surgeons and one dermatologist. Intervention group: 48 general practitioners and four surgeons. During the study, nine new doctors entered and two left the control community, and seven new doctors entered and five left the intervention community. All new incoming doctors agreed to take part except for one general practitioner in the intervention city.	The two cities were selected on the basis of their similarity.	Doctors refusing to take part.	. Reports from the previous six months were collected as a baseline to check that the excision rates of benign and malignant melanocytic lesions were comparable between the two cities. In the six months before the introduction of the intervention a total of 1358 melanocytic lesions were reported by the pathology laboratories: 752 (55%) from the control community and 606 (45%) from the intervention community. More than a hundred practitioners in total participated in the study but no power calculation was given. During the 24 months after the intervention was introduced a total of 4465 lesions were excised in the two study cities, of which 1995 (45%) were excised in the intervention city, the same proportion as at baseline. Nosignificant difference in the percentages of benign lesions reported in the intervention and control cities before the algorithm and camera were used (93.6% and 94.0% respectively) but there was a significant difference afterwards (88.8% and 93.8%, P < 0.001). There was no difference in the percentage of invasive melanomas excised per month in the intervention city (3.4%) compared with control city (3.4%). Offering doctors a diagnostic algorithm and providing them with a camera reduced the relative proportion of benign naevi they removed	

DRAFT FOR FIRST CONSULTATION

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English, 2003	Australia	<p>This Australian randomised control trial was undertaken to determine whether the use of a camera and algorithm aided the diagnosis of pigmented skin lesions by reducing the ratio of benign lesions to melanomas in general practice. The trial built upon the earlier randomised control trial conducted by Del Mar et al (1995) in which participants were randomised by town rather than practice.</p> <p>Intervention practices were given an algorithm and instant camera to assist with the diagnosis of pigmented skin lesions. All practices were given national guidelines on managing melanoma</p>	<p>223 practices participated.</p> <p>468 general practioner participated in the trial.</p>	<p>General practioners on the mailing lists of the divisions of general practice in Perth were eligible. General practioners who joined a practice after randomisation or with whom no contact had been made before randomisation were also eligible.</p>	--	<p>During the two periods, the participants excised 8563 pigmented skin lesions: 295 (3%) melanomas (180 invasive and 115 in situ), 529 (6%) dysplastic naevi, 5065 (59%) other naevi and 2674 (31%) seborrhoeic keratoses. At baseline the ratios of benign to malignant lesions were lower in the intervention than the control group. During the trial period the ratios were higher in the intervention group (19:1 vs. 17:1 without seborrhoeic keratoses and 29:1 vs. 26:1 with seborrhoeic keratoses). After adjustment for patients' age, sex and socioeconomic status, the ratio was 1.02 times higher (95% CI 0.68 to 1.51, P=0.94) in the intervention group when seborrhoeic keratoses were not included and 1.03 times higher (0.71 to 1.50, P=0.88) when seborrhoeic keratoses were included.</p> <p>General practitioners in the intervention group were less likely than those in the control group to excise the most recent pigmented skin lesion they had managed (22% vs. 48%, P<0.001) and to refer the patient to a specialist. Neither group showed substantial changes in excision rates within practices between the baseline and trial periods. The overall rates showed little change in the control group, but decreased in the intervention group between periods largely because of substantial reductions in a few practices with large numbers of baseline excisions. The imbalance between practices was due to specialist general practitioners</p>	

DRAFT FOR FIRST CONSULTATION

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						(to whom others refer patients with pigmented lesions and those who perform a substantial proportion of all excisions). Four of the total (five) were in the intervention group. When these general practitioners were excluded the number of benign lesions excised was similar.	
Gerbert et al 1998	USA	This study sought to determine whether a brief, multicomponent educational intervention could improve the skin cancer diagnosis of primary care residents to a level equivalent to that of dermatologists. The intervention comprised an interactive seminar, which included a slide show lecture, videotape and demonstrations on how to conduct a total body skin examination. This randomised control trial was suited to assessing the effects of an educational intervention with pre-test and post test measurements of residents' ability to diagnose and make evaluation plans for lesions indicative of skin cancer. The pre-tests and post-tests consisted of lesions shown on slides, computer images, and patients.	26 primary care residents were assigned to a control group and 26 to an intervention group, and 13 dermatologists completed a pre-test and post-test.	Residents in primary care and family medicine.	--	No significant differences between control and intervention primary care residents on the demographic and dermatology experience variables or pre-test overall diagnosis and overall evaluation planning scores. The control group, the intervention group and the dermatologists all demonstrated improved performance over time, with the intervention group experiencing the largest gains. The intervention group showed significantly greater improvement than control in overall diagnosis and diagnosis of malignant melanoma and seborrheic keratosis. Intervention group primary care residents performed as well as the dermatologists on five of the six skin cancer diagnosis and evaluation planning scores with the exception of the diagnosis of basal cell carcinoma. The control group performed as well as the dermatologists on three of the six skin cancer diagnosis and evaluation planning scores. The dermatologists had significantly higher scores than the control group in 11 of the 14 diagnoses and evaluation planning categories. The intervention group showed greater improvement than the	Some caution is required in applying the findings of this study to clinical practice. The sample of primary care residents was relatively small and lacked variation. The pre-test may have been more difficult than the post-test, as suggested by the higher scores of all three groups of subjects at the post test. Routine clinical practice is likely to differ from the test situation used in the study.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
						control group across all six diagnostic categories (a gain of 13 percentage points vs. five, P<0.05) and in evaluation planning for malignant melanoma (a gain of 46 percentage points vs. 36, P<0.05) and squamous cell carcinoma (a gain of 42 percentage points vs. 21, P<0.01). The intervention group performed as well as the dermatologists on five of the six skin cancer diagnosis and evaluation planning scores with the exception of the diagnosis of basal cell carcinoma.	
Girgis et al 1996		Questionnaires were sent to randomly selected family physicians in one region in Australia to investigate their beliefs and practices in relation to skin cancer prevention, early detection and management.	97 family physicians	Family physicians were randomly selected from the regional telephone book.	Ineligible participants were those who were unable to be contacted, were specialists or were retired.	91% of family physicians (N=86) indicated that they thought skin examinations were very/extremely worthwhile in the early detection of melanoma and other skin cancers. The three issues in which they felt most confident were performing a surgical excision (72%), diagnosing a basal cell carcinoma (71%), and advising patients on signs of skin cancer (69%). A total of 65% (53) of family physicians considered that they currently detected 90 to 100% of their patients with melanoma. Family physicians indicated that the factors most likely to encourage them to offer screening were patients being more informed about its benefits, patients initiating the procedure having instructions about the signs to look for, having long consultation times and a reduced patient workload (59%; N=57), and having consistent information about who needs screening and how often (57%; N=55). The factors that were most likely to discourage family physicians from screening their	Compared with family physicians throughout Australia, the survey had significantly fewer family physicians aged less than 30 years, and a significantly higher proportion aged 40 to 49 years

DRAFT FOR FIRST CONSULTATION

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						patients included lack of time (32%; N=31), forgetting (26%; N=25), lack of financial incentive (20%; N=19), not being familiar with the patients' screening history (14%; N=14) and inability to convince patients who refuse (13%; N=13).	
Raasch et al, 2000	Australia	A randomised control trial to assess the value of an educational intervention based on audit and feedback to family physicians. Clinical performance of family physicians was judged by the ability to make a correct clinical diagnosis based on histology of the excised lesion and to provide adequate surgical treatment. The doctors' individual skin cancer practices were compared within and between groups before and after the intervention. Data were recorded on 1) the proportion of all lesions correctly diagnosed 2) unrecorded clinical diagnosis 3) inadequate excisions and 4) certainty of diagnosis.	41 Family physicians (21 in intervention group and 20 in the control group)	Family physicians working three or more sessions per week in a primary-care situation, who were available for the whole of the proposed 9 months of the study	--	The intervention group doctors showed improved performance in providing clinical information on pathology requests and in adequate surgical excision of skin lesions. Diagnostic performance did not improve significantly but physicians' certainty of diagnosis did. When a skin cancer was present (based on the histology of the lesion) the intervention group doctors, before receiving the intervention, had made a correct diagnosis in 72.2% (95% ci 65.8–78.6) of cases. After the intervention 77.1% (95% ci 68.7-85.5) of malignant lesions had been correctly diagnosed (P=.38). There also was no significant difference in sensitivity of diagnosis for malignant lesions between intervention and control group before or after the intervention. When a lesion was benign, the study group had made a correct diagnosis in 44.7% (95% ci 39.5-49.9) of cases before the intervention, compared with 28.5% (95% ci 23.8-33.2) in the control group. After the intervention 37.3% (95% ci 29.1-45.4) diagnoses were correct, compared with 22.4% (95% ci 11.7-33.1) in the control. The change in correct diagnoses before and after the intervention group was not statistically significant (P=0.144). A baseline	Factors such as patient characteristics that had not been controlled for may have limited the conclusions that could be drawn.

DRAFT FOR FIRST CONSULTATION

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						comparison of patients who had skin lesions excised showed that the patients of intervention and control group doctors differed significantly in several ways.	
SIGN, Cutaneous melanoma: A National Clinical Guideline, 2003		The guidelines recommended that: targeted education can enhance health professionals' ability to diagnose melanoma (recommended best practice).					

Table 10 SKIN: delay

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Betti et al, 2003	Italy	Consecutive patients referred to an Italian hospital with cutaneous melanoma between September 1994 and December 2000 were interviewed by a trained dermatologist. The questionnaire included demographic, tumour and behavioural data.	216 patients	Only patients agreeing to be subjects were enrolled.	Patients who were not able to respond accurately to the questionnaire	<p>Mean patient delay was 6.11 months (range \pm 9.75 months), and mean medical delay was 1.53 months (range \pm 5.34 months). There were no differences among causes of patient delay and mean age, anatomic site of lesions, level of education, knowledge of the problem, civil status or pigmentation. 51% of the patients delayed the consultation of a physician because of anxiety, fear, or lack of no time or being too busy. They tended to have a longer patient delay and a higher Breslow thickness (0.99 ± 1.41) ($P < 0.001$).</p> <p>22 cases (10.19%) were observed in which the practitioner or the specialist delayed diagnosis or treatment. No correlation between physician delay and anatomic location of the lesion was observed. Pigmentation of the lesion significantly delayed the time of diagnosis by the physician (4 ± 9 months vs. 1.34 ± 5 months for the pigmented melanomas) ($P < 0.04$).</p>	
Blum et al, 1999	Switzerland	Patients were interviewed using a standardised questionnaire, the information obtained being merged with the data on tumour characteristics and case history contained in the medical records. Delay in melanoma diagnosis was defined as the time period between a patient's first observation of a suspicious skin lesion and definite tumour treatment.	429 patients	All patients with histologically confirmed cutaneous melanoma who had undergone surgical treatment at a Swiss hospital between 1993 and 1996. Only those patients with a melanoma diagnosis within the last 3 years were included	All patients with an initial diagnosis more than 3 years previously.	<p>The melanoma was detected in 67% of women and 45% of men by the patients themselves (inter-gender comparison: $P < 0.0001$). The tumour was detected in about 50% of the remaining patients by a physician. Earlier diagnosis and treatment of melanoma were not significantly related to prognostic tumour parameters such as Breslow thickness or Clark's level of invasion. Women were significantly more aware than men of the possible benefit of early treatment ($P = 0.004$). However, increased melanoma awareness was not associated with an earlier visit to a physician. Patients who detected the lesions themselves sought medical attention later than patients in whom attention had been called to their skin changes by other persons (median 122 vs. 59 days), and therefore were treated significantly later ($P < 0.01$). A misdiagnosis by the first physician visited was reported by 18% of patients, and 60% of these physicians were</p>	

DRAFT FOR FIRST CONSULTATION

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						<p>dermatologists. Misdiagnosis increased the period of time between first observation and treatment (median 122 vs. 31 days, $P < 0.0001$) as well as between the first visit to a doctor and treatment (median 61 vs. 28 days, $P < 0.0001$). When more than one physician omitted the diagnosis of melanoma (in 8% of all patients), there was a significant additional delay in treatment (median 303 vs. 89 days, $P < 0.001$).</p> <p>Multiple regression analysis revealed the following factors to be significantly related to delay in melanoma diagnosis: denial of melanoma diagnosis by the first physician visited ($P < 0.001$, regression coefficient = 0.192), invasive melanoma of the head and neck ($P < 0.05$, regression coefficient = 0.134), self detection of melanoma vs. detection by other persons ($P < 0.05$, regression coefficient = 0.129), and patient's knowledge about the induction of skin cancer by sun exposure ($P < 0.05$, regression coefficient = - 0.107). No correlation was found between delay in diagnosis/treatment and gender, age, Breslow tumour thickness, Clark's level of invasion and histological type of melanoma.</p>	
Brochez et al, 2001	Belgium	The aim of this study was to describe the diagnostic pathway for cutaneous melanoma in a Belgian community, to quantify both patient and physician delay and to define factors related to it. Patients were recruited both from a university hospital setting and from practices (population based melanoma register). patients were asked to complete in a questionnaire about delay in diagnosis.	131 completed questionnaires.	All patients with a diagnosis of cutaneous melanoma between January 1995 and December 1999 were included	--	<p>The time from the first noticing a new or changing lesion to consultation with a physician (patient delay) was a mean of 169 days (median, 61 days). Worried patients tended to have a longer patient delay, although the difference did not reach statistical significance. There was no difference in patient delay for lesions difficult to self-examine compared with lesions more easily self-examined such as head and neck, chest, abdomen, arms, extensor side of the legs. Colour change and itch were associated with longer patient delay (median 64 days vs. 24 days if no colour change, $P < 0.05$; and 137.5 days vs. 29 days if no itch, $P < 0.01$).</p> <p>Patient delay was not influenced by age, gender or socio-economic factors. General practitioners and dermatologists were the physicians most frequently involved in the first medical encounter</p>	

DRAFT FOR FIRST CONSULTATION

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						about a lesion (55 and 33% of all cases, respectively). Of the physicians who first observed the lesion, 34 of the 43 dermatologists suspected the lesion immediately, compared with 38 of 72 GPs ($\chi^2 = 7.95$, $P = 0.005$). There were significant differences in the time to excision if the physician took immediate action, referred the patient or took no immediate action.	
Carli P et al, 2003	Italy	The aim of this study was to investigate patterns of detection and variables associated with early diagnosis of melanoma in a population at intermediate melanoma risk. Each patient received a questionnaire about first identification of the lesion, the interval before diagnosis by a dermatologist or another specialist (patient's delay), and the interval before the lesion was removed (physician's delay). Patients were also asked about their knowledge of the criteria for early diagnosis of melanoma, their skin self-examination habits, and periodic medical consultation aimed to screen for melanoma. The main outcome measure was the relationship between patterns of detection and patients' and physicians' delays with melanoma thickness.	816 patients	Patients with cutaneous melanoma diagnosed in 2001, in 11 Italian clinical centres. Persons with newly diagnosed lesions were included in the study at the first visit after surgery.	--	Patterns of melanoma detection Most patients self-detected melanoma. Their spouse detected 12.5% of the lesions, while physicians first detected 38.7% of the lesions. The percentage of melanomas detected by a spouse differed according to sex (18.5% in male patients vs. 6.4% in female patients; χ^2 test, $P = .000$). More than half of the subjects (68.9%) waited no more than three months before obtaining a diagnosis. The main reasons for longer waiting were the feeling that it was not important (56%), fear about a possible diagnosis of cancer (10.1%), lack of time (7.3%), and the mistaken opinion that to remove a naevus is dangerous (5.6%). Fifty-two patients (21%) reported waiting more than three months because another physician, seldom the family physician, did not think it was really a lesion suggestive of being a melanoma. Effects on mean thickness A lower mean thickness was significantly associated with female sex, high educational level, and the habit of performing skin self-examination. Age older than 60 years was associated with a higher mean thickness, compared with age younger than 40 years. Paradoxically, a lower mean thickness was found in those patients who waited more than one month before surgery once a definite diagnosis of a lesion suggestive of a melanoma was established (adjusted mean thickness, 0.74 vs. 0.89 mm). Association with diagnosis of thin lesions A statistically significant association with early diagnosis was found for female sex (odds ratio [OR] for a lesion >1mm in	

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
						thickness, 0.70; 95% confidence interval [CI], 0.50-0.97), higher educational level (OR, 0.44; 95% CI, 0.24-0.79), and the habit of performing skin self-examination (OR, 0.65; 95% CI, 0.45-0.93). The association with age was of borderline statistical significance.	
Cassileth et al, 1988)	USA	In this study, consecutive patients with cutaneous malignant melanoma referred to two US hospital-based melanoma clinics by community physicians between 1984 and 1986 participated in the study. The authors conducted interviews with all the patients and also the physicians whom they had consulted regarding their suspicious lesions before their eventual referral to a melanoma centre. Histology data were obtained for all patients.	275 patients and 437 physicians	Charts of all patients diagnosed with superficial spreading melanoma at a university pigmented lesion clinic from 1972 through 1982. only data for patients over 17 years of age and with no prior primary melanomas were included.	----	A mean of six months elapsed (median one month) between the time that patients first noticed a new mark or a change in an existing lesion and the time that they became suspicious about it. The particular characteristics of lesions noted by patients did not influence length of time to suspicion. A mean of 2.6 additional months elapsed following suspicion until patients sought medical attention. The median delay during this period was one month. No lesion signs or characteristics were related to how quickly patients sought medical attention. The most common reason given by patients to explain this delay was that the lesion "did not represent an urgent problem". For the entire subject population, the mean time from the initial physician visit to the diagnosis of malignant melanoma was 3.9 months. Time from initial physician visit to diagnosis was shorter only for lesions with pigmentation (P = 0.002). No other lesion characteristic was associated with length of delay from initial visit to diagnosis. Physicians alerted primarily by the lesion's pigmentation and/or by its diameter or border, recalled having assessed the lesion clinically as a melanoma in 74% of patients. There was a significant relationship between correct identification of melanoma and physicians' specialty (chi square, P < 0.05). Surgeons and dermatologists were more likely than other physicians to have identified the lesion correctly. The relationship between self-rated knowledge and correct identification of melanoma did not achieve statistical significance. Physicians' actions in response to this initial evaluation were associated with type of specialty practice (chi square, P <	

DRAFT FOR FIRST CONSULTATION

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						<p>0.001). Internists were most likely to make an immediate referral to a melanoma clinic, and surgeons were least likely to do so. Lesion characteristics were not associated with melanoma referral. Half of physicians interviewed reported that they did not examine the patient's entire cutaneous surface. 52% of patients were seen by more than one physician prior to melanoma clinic referral. Patients who saw more than one physician were diagnosed as having melanoma a mean of 6.8 months after becoming suspicious about their lesions, compared to 4.1 months for patients who saw only one physician prior to melanoma clinic referral (Mann-Whitney U test, P= 0.006). Further, the interval from the initial physician appointment to diagnosis was greater for patients seen by more than one physician (5.8 months) than for patients seen by only one physician (1.8 months; P < 0.0001 by Mann-Whitney U test).</p> <p>Of all the demographic variables analysed (sex, occupation, education, marital status, health insurance, and age), only sex was significantly associated with delay. Men waited an average of 1.9 months and women an average of 3.3 months before seeing a physician after becoming suspicious about their lesions (P < 0.005 with the Mann-Whitney U test). Neither patients' self-rated awareness of body changes nor their scores on the preoccupation with appearance test were associated with any component of delay, with tumour thickness, or with level of invasion.</p>	
Montella et al, 2002	Italy	The study's aims were to test the relationship between tumour thickness and social and clinical variables (including diagnosis/treatment delay), and the relationship between delay and clinical variables. The authors undertook a retrospective study of consecutive patients who underwent surgery for histologically confirmed melanoma between January 1996 and December 2000 at a single Italian hospital.	530		Patients with an unknown primary site and metastatic tumour	<p>The most frequently reported symptoms were a lesion with increasing size (50.8%), bleeding (17.8%), colour change (15.2%), and itching (12.0%).</p> <p>Breslow thickness</p> <p>A larger proportion of females (72.1%) compared with males (64.4%) had a Breslow tumour thickness < 1.5 mm (OR = 1.8, 95% CI = 1.2-2.8, P = 0.005). A significant risk of having a Breslow tumour thickness ≥ 1.5 mm was noted in patients who had a low level of education (OR 3.0,</p>	

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
						<p>95% CI 1.9-5.0, p = 0.0001) or who were unemployed (OR = 1.7, 95% CI = 1.1-2.8, P = 0.001). A significant risk of Breslow tumour thickness \geq 1.5 mm was reported for patients who were examined by a physician other than a dermatologist (OR = 1.8, 95% CI = 1.2-2.8).</p> <p>Patient delay A greater than three month delay was observed for anatomic locations visible to patients (OR = 1.7, 95% CI = 1.1-2.6, P = 0.02). Anatomic site of the primary lesion was also related to patient delay: patients who had the primary lesion on an extremity were more likely to delay > three months (OR = 1.6, 95% CI = 1.1-2.5, P = 0.02), especially females (OR = 2.2, 95% CI = 1.3-3.7, no P value given).</p> <p>Medical delay A significant association was observed between medical delay and the physician who made the diagnosis: a delay > three months carried a higher risk (OR = 2.0, 95% CI = 1.2-3.4, P = 0.01) in patients examined by a dermatologist. A medical delay of one to three months placed at risk patients with a primary lesion in an extremity (OR = 1.8, 95% CI = 1.0-2.9, P = 0.03).</p> <p>None of the other variables studied (gender, age at diagnosis, education, and occupational status) were significantly associated with either patient or medical delay.</p>	
Oliveria et al, 1999		<p>The purpose of this large population-based case control study was to examine the relationship between patients' knowledge and awareness of the signs and symptoms of melanoma and delay in seeking medical attention for suspicious lesions.</p> <p>Personal interviews were conducted to obtain information on patient's knowledge of melanoma signs and symptoms, skin awareness, and delay in seeking medical attention.</p>	650	residents of Connecticut 18 years of age or older with cutaneous melanoma newly diagnosed between 1987 to 1989, who were part of a population-based control study	Patients who had their melanoma identified by a physician during a visit for an unrelated condition	<p>The mean delay time for patients seeking medical attention was two months with a range from 0.5 to 22 months. Overall, the results revealed an inverse relationship between both knowledge and awareness and delay in seeking medical attention for melanoma. The odds ratios for knowledge of melanoma characteristics and delay ranged from 0.42 to 0.81 after controlling for age, gender, prior history of cancer, and skin self-examination. Patients who were aware of skin changes and or abnormalities had a reduced likelihood of delay in melanoma diagnosis after adjusting for age, gender, prior history of cancer, and skin self-examination</p>	

DRAFT FOR FIRST CONSULTATION

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						practices (OR = 0.30, 95% CI = 0.12 – 0.71). The findings suggested that knowledge of two or more signs or symptoms of melanoma reduces the likelihood of a delayed diagnosis (OR = 0.34, 95% CI = 0.13-0.88). Skin awareness was associated with a reduced thickness (OR = 0.50, 95% CI = 0.28-0.89). Increased knowledge of melanoma signs and symptoms also decreased the likelihood of being diagnosed with a thick tumour (≥ 0.75 mm). The odds ratio ranged from 0.69 to 0.95 for the knowledge variables (except for larger diameter and abnormal shape, odds ratios = 1.17 and 1.14 respectively).	
Rampen et al, 1989	Netherlands.	The aim of the study was to relate possible delay factors to the most important prognostic features at the time of diagnosis (the clinical stage of the disease for all patients, and the maximal tumour thickness). The study comprised consecutive patients with cutaneous melanoma presenting with primaries or metastases to 12 Dutch hospitals. All patients were interviewed shortly after diagnosis using a detailed questionnaire about the patient's history, tumour characteristics, treatment particulars, and pathology.	284 patients	Consecutive patients with cutaneous melanoma presenting with primaries or metastases, registered between January 1981 and the end of 1983	Patients with non-invasive (Clark level 1) melanoma, patients who refused taking part in the study, and patients who were mentally unsuitable for the enquiry	The interval between the onset of signs and the first visit to a doctor tended to increase with age ($P = 0.055$). Females presented with less advanced disease than males, particularly in stage I disease ($P = 0.004$). Visibility of the primary lesion had no impact on the stage of the disease. The average interval between the appearance of the first signs and doctor's consultation was similar in males and females. For both sexes, the interval was considerably longer for the easily visible melanomas than for the more hidden ones ($P < 0.001$, adjusted for sex). If patients suspected they had cancer, this tended to have a favourable impact on the stage of the disease (for the microstage $P = 0.079$, for the clinical stage $P = 0.049$). There was no evidence that patients in the higher socio-economic class have a better knowledge of the malignant nature of their disease ($P = 0.076$). Even if patients were aware of the possible malignant character of the growth, they often displayed a delay of more than one month before they consulted a doctor (54% of cases, $N = 63$). The reasons given for this delay were a feeling that the situation was not pressing in 41, lack of time in 24, fear of cancer in 15, aversion of going to the doctor in ten, and miscellaneous reasons in nine patients (many patients gave more than one reason).	

DRAFT FOR FIRST CONSULTATION

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						<p>Patients who had waited until their symptoms became severe enough to seek medical care by themselves, had a more advanced clinical stage of the disease than those who had been persuaded by someone else to go to the doctor, or than those whose melanoma had been discovered by chance (P = 0.018). Patients who presented their melanoma secondary to another reason for visiting the doctor had a more favourable clinical stage and the primary melanomas were considerably thinner (P < 0.001).</p> <p>When doctors found a primary melanoma by chance, the microstage appeared to be much more favourable than when patients themselves had noticed a suspicious lesion (P < 0.001). Patients with amelanotic melanomas had more unfavourable microstages than those with melanotic primaries (P < 0.006). Melanoma suspicion was highest for melanotic and lowest for amelanotic tumours (P = 0.049).</p>	
Richard et al, 2000a	France	<p>This paper evaluates the role of a patient in contributing to delay in diagnosis of skin cancer. Consecutive patients referred for cutaneous melanoma to 18 French dermatological departments of the public hospital system participated in the study conducted between 1995 and 1996. All patients were examined and interviewed by a specially trained dermatologist in each centre. The questionnaire addressed patients' characteristics such as age, sex, residence, social level, and education level, amongst others.</p>	590	<p>Patients at least 12 years of age, histological confirmed diagnosis of melanoma, and interview within 12 weeks after melanoma resection. Patients were included only when the report forms were completed, when a histological slide was available, and when two experts confirmed the diagnosis.</p>	<p>Those that did not fulfil the inclusion criteria.</p>	<p>42.4% of the sample were males and 57.6% females. Tumour thickness in coincidentally diagnosed melanoma was significantly lower than in self-diagnosed melanoma (median 0.93 mm vs. 1.30 mm, P < 0.001). Median tumour thickness was significantly lower when the lesion was first detected by the patient than when it was detected by the family (1.22 mm vs. 1.40 mm, P < 0.001, Kruskal-Wallis test).</p> <p>Reasons for delay according to the patient</p> <p>Patients delayed presentation to a physician beyond two months in 48.1% of cases. The reasons given were: innocent appearance of the lesion together with the absence of systemic signs in 39.3%, absence of awareness about the urgency in 34.8%, occupational reasons in 20.4%, familial reasons in 16.9%, fear of diagnosis in 9.4%, passivity until family urged consultation in 5.5%, negligence in 4.5%, and absence of pain in 1.0%.</p> <p>Comparison of the self-detected and the</p>	

DRAFT FOR FIRST CONSULTATION

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						<p>coincidentally diagnosed melanoma Melanomas were more often self-detected by women than by men: 74.1% vs. 66.8%, respectively (χ^2 test, $P = 0.053$). The patients with a self-detected melanoma had a significantly higher educational level than the patient with a coincidentally diagnosed melanoma (53.1% vs. 65.7%, χ^2 test, $P = 0.03$). The patients with a coincidentally diagnosed melanoma lived more frequently in the countryside than the patient with a self-detected melanoma (29.6% vs. 20.3%, χ^2 test, $P = 0.02$). Previous history of melanoma was more frequent in the patients with a coincidentally diagnosed melanoma than in the patients with a self-detected melanoma (27.9% vs. 16.5%, $P < 0.001$). The degree of awareness about skin, sun, and cancer was higher in patients who later detected their melanoma themselves than in those whose tumour was coincidentally detected.</p> <p>Analysis of factors influencing delays and tumour thickness in self-detected melanoma Univariate analysis. People older than 65 years sought medical attention more quickly than people younger than 50 years ($P = 0.003$), but they tended to develop thicker tumours ($P = 0.51$). Gender did not influence significantly any component of the delays, although Breslow thickness was higher in men than women ($P < 0.001$). Delays did not differ in patients with high and low level of education, although those with low education level had thicker tumours ($P < 0.001$). There was no difference in the socioeconomic profile of the patients in regard to delays or Breslow thickness. Delays or tumour thickness were not influenced by marital status. People living in the countryside, although seeking medical attention more rapidly ($P = 0.003$), developed thicker tumours ($P = 0.045$). Awareness and information about melanoma did not have any significant impact on patient delay. Tumour thickness was significantly</p>	

DRAFT FOR FIRST CONSULTATION

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						<p>thinner when the patient had already heard about melanoma and was previously aware of the early signs of melanoma.</p> <p>Multivariate analysis. None of the candidate variables related to patient delay significantly predicted independently patient delay in multivariate analysis. In a stepwise multiple linear regression using all variables influencing tumour thickness, three variables were predictive of a high Breslow: ulceration, the fact that the patient said that raising was the reason for consultation, and nodular histological type.</p>	
Richard et al, 2000b	France	<p>The purpose of the study was to assess all doctor-related components in the delay before melanoma resection. Consecutive patients referred for cutaneous melanoma to 18 French dermatological departments of the public hospital system participated in the study conducted between 1995 and 1996.</p> <p>All patients were examined and interviewed by a specially trained dermatologist in each centre. The questionnaire investigated patient characteristics and habits, tumour clinical features, circumstances of melanoma detection, causes of delay in diagnosis, and doctors attitudes before removal. Physician delay was defined as the interval between the date the lesion was first examined by a physician and the date when a physician first proposed resection.</p>	590	<p>Inclusion criteria were: at least 12 years of age, histological confirmation of diagnosis of melanoma, and interview within 12 weeks after melanoma resection. Patients were accepted only when the report forms were completed, when a histological slide was available, and when two experts confirmed the diagnosis.</p>	<p>Persons that did not fulfil the inclusion criteria.</p>	<p>The median delay before the doctor proposed tumour resection was 0 (mean 103, range 0-5,783) days. For comparison, the median delay under patient responsibility was 912 (mean 3,829, range 0-25,261) days.</p> <p>Attitude of the physician The first advice from the first doctor was considered to be appropriate in 85.8% of cases.</p> <p>Factors influencing medical delays and tumour thickness Univariate analysis. The delay to propose resection was much longer when the attitude of the first physician was inappropriate than when removal was proposed at the first visit (median 109 days vs. 0 days, $P < 0.001$). Although there was a higher tumour thickness when the attitude was inappropriate (median 1.40 vs. 1.15 mm, mean 3.15 vs. 2.00 mm), the difference was not significant ($P = 0.99$).</p> <p>Tumour thickness was significantly lower when first seen by a dermatologist than by another physician (median 0.94 mm vs. 1.50 mm, mean 1.88 mm vs. 2.82 mm, respectively; $P < 0.001$). The delay to propose removal was significantly shorter when the first physician was a dermatologist than when he or she was a general practitioner or another specialist (median 0 vs. 25 days, mean 60 vs. 153 days, respectively; $P < 0.001$).</p>	

DRAFT FOR FIRST CONSULTATION

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						<p>In self-detected tumours, doctors proposed removal significantly later for acrolentiginous melanoma, amelanotic melanomas, and melanomas of the hand and foot than for other tumours. Multivariate analysis.</p> <p>In a stepwise multiple linear regression, the most predictive factors influencing physician delay were histoclinical type and the ability of the first physician seen to recognise melanoma. The shorter delays were observed with lentigo melanoma and melanomas first seen by dermatologists. In a stepwise logistic regression, the factor most predictive of a long physician delay (> 30 days) remained the specialty of the first physician (other physicians vs. dermatologists; coefficient 2.27, SE 0.32, OR 9.7, 95% CI 5.16-18.2, P< 0.001).</p>	
Schmid-Wendtner et al, 2002	Germany	The aim of the study was to investigate the extent and consequence of patient and professional delay in diagnosis and treatment of cutaneous melanoma. The interview investigated melanoma-associated symptoms, the site and features of the cutaneous melanoma, time intervals, and reasons for delay in diagnosis.	233 patients	Patients with primary cutaneous melanomas diagnosed and treated at a university hospital between January 1999 and January 2001.	Not mentioned.	<p>Patients with knowledge about melanoma presented with a median tumour thickness of 0.7 mm, whereas patients without knowledge had a median tumour thickness of 2.1 mm (P < 0.0001). Knowledge about melanoma was associated with the educational status of patients. More than 90% of patients with a high or medium educational status had knowledge about melanoma, and less than 10% had no knowledge about melanoma (P < 0.001). In contrast, only 71% of patients with low educational status were knowledgeable about melanoma.</p> <p>Medical attention was sought within 1 month of noticing the appearance of a new lesion or the onset of changes in a pre-existing lesion by 15.5% of patients. Longer periods of patient delay were not associated with greater tumour thickness. The majority of patients asked about the reasons for delay had initially thought that the pigmented lesion was benign or not important (63.5%). A smaller group of patients did not delay the consultation of a physician (12.0%), 9.9% of patients were afraid of the physician's diagnosis, 8.1% of patients could not detect the lesions themselves because of its anatomical</p>	

DRAFT FOR FIRST CONSULTATION

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						site, and 6.9% mentioned that they were too busy to consult a physician. In 3% of patients the reasons for delay remained unclear.	
Silfen et al, 2002		In this authoritative review, the authors investigated the role of the physician and the patients in diagnostic delay of melanoma				<p>Physicians Tumour characteristics have an important effect, a shorter medical delay occurring for nodular and lentigo melanoma than for acrolentiginous melanoma. Longer diagnostic delays have also been associated with tumours deriving from nevi compared with de novo melanomas.</p> <p>Patients In one case-control study, monthly skin self-examination was associated with a 63% reduction in mortality from melanoma. However, although people may report conducting a thorough examination of their study, on closer questioning, only a few have actually done so (quoted in the review).</p>	

Table 11 HEAD and NECK: signs and symptoms, including risk factors

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Beaty et al, 1998	USA	A retrospective review of the medical records of patients who had undergone tonsillectomy at a US hospital	453	Patients 18 years old or older undergoing palatine tonsillectomy at the University of Iowa Hospitals and clinic between January 1985 and September 1995.	--	<p>There was a strong statistical association between the presence of risk factors and malignancy ($P < .0001$). Features postulated as predictive of a diagnosis of tonsillar malignancy included a prior history of head and neck cancer $P < .0001$; tonsillar asymmetry $P < .0001$; palpable firmness or visible lesion of the tonsil $P < .0001$, neck mass $P < .0001$; unexplained weight loss $P < .0001$; and constitutional symptoms including fatigue, night sweats, fevers and anorexia $P = .003$. These risk factors were correlated with the pathologic diagnosis in the reviewed cases.</p> <p>Of the 453 patients included, 25 had a tonsillar malignancy confirmed histopathologically. Patient age ranged from 18 to 72 years, with a mean age of 29.8 years. The mean age was 28.4 years for patients with benign lesions, and 54.4 years among those with malignant lesions. This difference was statistically significant ($P < .0001$). There were 210 (49%) men and 218 (51%) women with benign disease. There were 17 (68%) male and 8 (32%) female patients with malignant lesions, (not a statistically significant difference). Of the 428 patients with benign disease, 87 (20%) identified themselves as tobacco smokers. Among the 25 patients with malignant pathology, 10 (40%) identified themselves as smokers. Tobacco smoking was significantly associated with the diagnosis of malignancy ($P < 0.05$).</p> <p>No patient without the postulated features was found to have malignancy. Of the 25 patients with malignant tonsillar pathology, 23 had two or more features, and two patients had one feature only. Tonsillar asymmetry, found in 20 of the 25 cases was the sign most frequently associated with malignancy. Of the 453 patients, 70 had at least one of the features identified during their preoperative assessment. Of this group, 25 had malignant tonsillar lesions. Of the remaining 383 patients with no features identified, none had histologically</p>		

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						<p>demonstrable malignancy. The same statistical protocol was used to analyse the patient group excluding those with a prior history of cancer because this group may have included some patients with recurrent or persistent disease rather than a primary malignancy. The chi-square and Fisher's Exact tests resulted in p values of 1) history of cancer P<.0001; 2) tonsillar asymmetry P<0.001; 3) palpable firmness or visible lesion of the tonsil P<0.0001; 4) neck mass P<0.0001; 5) unexplained weight loss P= 0.0004 and 6) constitutional symptoms P=0.03. No patients with three or more features had benign tonsillar pathology. Modelling analyses that included all patients in the study indicated that advanced age, tonsillar asymmetry, history of cancer, and presence of a neck mass yielded a predictive model for malignancy with an R of 0.772. Patients' smoking or alcohol history or sex was not significantly correlated with malignancy. 29 patients (6.8%) among the 428 with benign lesions were identified as alcohol abusers. Among the 25 with malignancy, 11 (44%) had a history of alcohol abuse; this difference was significant (P,0.001).</p>		
British Thyroid Association / Royal College of Physicians, 2002		The remit of the guideline group was to develop evidence based guidelines of best current practice for management of thyroid cancer in adults. The guidelines were developed from the Northern Cancer Network Guidelines through a process of literature review, discussion by the multidisciplinary guideline group and external peer review. Evidence was graded Ia to IV, and recommendations graded A to C.				The guideline recommendations on diagnosis and referral were concerned with the symptoms or signs that warrant an investigation (thyroid cancer usually present with a lump in the neck), symptoms needing urgent referral (e.g. thyroid lump in a patient with a family history of thyroid cancer), physical examination (the patient should have a full examination focussing on inspection and palpation of the neck), who to refer to		
DiLeo et al, 1996	USA	Patients with primary nasal septal squamous cell carcinoma of three university affiliated hospitals were identified from tumour registries and medical records. A meta-analysis was performed to evaluate predictors of survival.	16	Only primary tumour series giving individual patient stage, treatment, survival, and disease status were included in the analysis. Only those patients for whom chart notes, surgical reports, or	--	The 12 male and four female patients had a mean age of 62 years (range: 45 to 88 years). The time from first symptom to presentation averaged 12 months (range: 0-48 months), and the most common initial symptom was a nasal mass. The time from the initial physician visit to the diagnosis of squamous cell carcinoma of the nasal septum averaged six months (range: 0-48 months). On physical examination, the most	Histology	

DRAFT FOR FIRST CONSULTATION

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				pathologic descriptions clearly identified the tumour as a primary squamous cell carcinoma of the nasal septum were entered into the study		common findings were nasal ulcerations, masses, septal perforations and skin changes. A history of heavy smoking was reported in 15 of the 16 patients.		
DoH Referral Guidelines for Suspected Cancer, 2000						Recommendations were made for urgent referral; Hoarseness persisting for >six weeks Ulceration of oral mucosa persisting for > three weeks Oral swellings persisting for > three weeks All red or red and white patches of the oral mucosa Dysphagia persisting for three weeks Unilateral nasal obstruction particularly when associated with purulent discharge Unexplained tooth mobility not associated with periodontal disease Unresolving neck masses for > three weeks Cranial neuropathies Orbital masses Additionally the level of suspicion is increased further if the patient is a heavy smoker or heavy alcohol drinker and is over 45 years and male.		
Hoare et al, 1993	UK	Case series in which information was collected about patients referred to a hoarse voice clinic in Birmingham. All patients with a hoarse voice for four weeks were referred by general practitioners who were asked to make a presumptive diagnosis of laryngeal cancer, vocal cord palsy, laryngitis or other conditions.	271 patients	The first 300 patients.	--	When seen in the clinic, 102 (34%) had normal voices and larynxes. Thirty-nine patients (14%) were admitted for direct laryngoscopy and biopsy under general anaesthetic. Ten (3.3%) were found to have laryngeal cancer of which eight were early lesions. All of those with cancer were current or past smokers. Although 40% of the study population were men, 80% of those with cancer were men. A hoarse voice for four or more weeks was regarded in this study as a symptom requiring specialist assessment. It was feasible to offer this service without appointments to patients with persistent hoarseness. There were six cases of cancer among the 25 patients in whom general practitioners diagnosed malignancy. They did not diagnose malignancy in seven other cases of cancer or dysplasia. This gave a sensitivity and specificity for general practitioner diagnoses of 46% and 24%		

DRAFT FOR FIRST CONSULTATION

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						respectively. The mean duration of symptoms before initial general practitioner consultation was 14 weeks and the time between this consultation and attendance at the hoarse voice clinic was three weeks. This study indicated that the diagnosis of the cause of prolonged hoarseness without visualising the larynx was unreliable. Symptoms were insufficient to make an accurate diagnosis.		
Holmes, 2003	USA	Case series in which clinical information about patients with newly diagnosed oral or oropharyngeal squamous cell carcinoma were collected through patient interview and chart audit	51 patients	Only patients with squamous cell cancers of the oral cavity or oropharynx.	Patients with second primaries or recurrences were excluded, as were patients with lesions discovered during the evaluation of neck mass.	Thirty-six patients had squamous cancer of the oral cavity and 15 had cancer of the oropharynx. The mean age of the study population was 62.2 years (range 29 to 88 years). Seventy-six percent of patients had a smoking history, and 67% admitted to occasional or heavy use of alcohol. Three patients had a family history of squamous cancer of the mouth or throat. The average clinical size of the lesions was 2.7cm. Detection of a lesion during an office visit for an unrelated reason or routine office visit (non-symptom-driven detection) occurred in 18 cases. Detection during these non-symptomatic driven examinations took place in dental offices (N=15), a dentist's office (N=1), and in oral and maxillofacial surgeons' offices (N=2). Lesions detected during a non-symptom driven examination were of a statistically significant lower average clinical and pathologic stage (1.7 and 1.6 respectively) than lesions detected during a symptom directed examination (2.6 and 2.5 respectively). Lesion (symptom-driven detection) occurred in 33 cases during appointments made by patients. Symptom driven examinations took place in dental offices (N=18), primary care offices (N=7), oral and maxillofacial surgeons' offices (N=4), and otolaryngologists' offices (N=4). Detection of a lesion during a non-symptom driven examination was associated with a significantly smaller lesion clinically (2.2; SD, 1.1 cm) than one detected during a symptom-directed examination (3.0; SD, 1.2cm).		
Lewin et al, 1998	Sweden	The aim of this case controlled study was to investigate the association between tobacco smoking and alcohol consumption, and squamous cell	605 males 756 controls	Males aged 40-79 living in two geographic regions selected by stratified	Cancers occurring outside the study base	Among those who were tobacco smokers at the time of the study, the relative risk of head and neck cancer was calculated at 6.5% (95% confidence interval, 4.4-9.5%). After		

DRAFT FOR FIRST CONSULTATION

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		carcinoma of the head and neck. males living in two geographic regions were studied in addition to controls.		random sampling from population registries		<p>cessation of smoking, the risk gradually declined, and no excess risk was found after 20 years. The results suggested that tobacco smoking and alcohol intake had a strong interactive effect on the risk of squamous cell carcinoma of the head and neck. Moderate alcohol intake (10-19 grams per day) had little or no effect among non-smokers. For different intensities of smoking, the RRs were 6.1 (95% CI =4.0-9.5) for men smoking <15 grams per day, 6.1 (95% CI =4.0-9.3) for men smoking 15-24 grams per day, and 6.6 (95% CI = 3.4-12.7) for men smoking 25 grams per day, suggesting little or no impact of mean smoking intensity. Nevertheless, smoking cessation and the duration of smoking each had a decisive impact on risk. The cancer subsites in the cases were: the oral cavity in 128 , the pharynx in 138 (75 oropharynx and 63 hypopharynx), the larynx (mainly glottic) in 157, and the oesophagus in 123 cases. Analysis by cancer subsite showed similar results, although the relative effect of smoking was more pronounced for cancers of the pharynx and larynx than for cancers at the other subsites. For current smokers, the RR (with 95% CI) were as follows: for cancer of the pharynx, 8.5 (4.0-18.2); larynx 7.5 (3.9-14.2); oesophagus 5.2 (2.6-10.3); and oral cavity 4.9 (2.6-9.2). For men who had smoked 45 years or longer: pharynx, RR =10.1 (4.6-22.1); larynx, relative risk =7.6 (3.9-14.7); oesophagus, RR =5.4 (2.7-11.0); and oral cavity, RR =6.3 (3.2-12.4).</p> <p>There was a gradual increase in the risk of cancer of the head and neck with increasing alcohol intake. However, moderate alcohol intake (10-19 grams per day) had little or no impact on the risk of cancer in ex-smokers and in men who had never smoked.</p>		
Lo Muzio et al, 1998	Italy	A total patients affected by oral lichen planus were followed between 1986-1996 in order to determine how many developed cancer. This study also investigated the clinical aspects of cases of oral squamous cell carcinoma affecting patients with oral lichen planus	263 patients	The criteria for inclusion were 1) clinical diagnosis of OLP; 2) confirmation of the diagnosis by oral biopsy.	--	Fourteen cases (5.3%) developed oral squamous cell carcinoma: ten (3.8%) in an area of pre-existing oral lichen planus, three (1.1%) in other sites, and in one case the diagnoses of oral lichen planus and squamous cell carcinoma were synchronous (0.4%). Three patients were positive for anti-HCV antibody.		

DRAFT FOR FIRST CONSULTATION

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						Of the 263 patients with oral lichen planus, 156 (59.3%) were in females. Age ranged from 22 to 80 years, with a mean of 55.5 years; 57.2 years for women and 54.7 years for men. The follow up period ranged from two to ten years, with a mean of 5.7 years. 74 (28.13%) patients were smokers. Nine of the fourteen patients who developed squamous cell carcinoma were male (64.3%) and five were female (35.7%); at the time of squamous cell carcinoma diagnosis the patients' ages ranged from 25 years to 66 years, with a mean age at presentation of 53 years (52.7 years for males and 53.4 years for females). Three aetiological theories were possible: 1) oral lichen planus transforms into squamous cell carcinoma, thus being truly premalignant; 2) the altered surface epithelium could be more susceptible to carcinogens, viruses or chemical irritants; 3) a carcinoma could appear coincidentally in the area affected by oral lichen planus.		
Musholt et al, 2000	Germany	<p>A meta-review of the literature on familial papillary thyroid carcinoma (FPTC) was undertaken to identify the characteristics of families with frequent occurrence of papillary thyroid carcinoma (PCT) or multinodular goitre (MNG) or both.</p> <p>A database of patients with thyroid cancer was searched for potential FPTC families at the Hannover University Medical School. Clinical examinations were performed in six of 12 Hannover kindreds identified and blood samples of all family members were collected for genetic analyses. Based on the meta-review and the team's own experience, predictive criteria to identify families at risk were developed.</p>	six Hannover kindreds			<p>Primary criteria for susceptibility to FPTC were identified as 1) papillary thyroid carcinoma in two or more first-degree relatives and 2) MNG in at least three first or second-degree relatives of a papillary thyroid carcinoma patient. Secondary criteria included diagnosis in a patient younger than 33 years, multifocal or bilateral papillary thyroid carcinoma, organ exceeding tumour growth (T4), metastasis (N1, M1), and familial accumulation of adolescent-onset thyroid disease. A hereditary predisposition to papillary thyroid carcinoma was considered if both primary criteria or one primary criterion plus three secondary criteria were present.</p> <p>From 1958 to 1999 a total of about 160 kindreds with two or more relatives suffering from papillary thyroid carcinoma (with or without MNG in family members) were identified in the literature search. Patient age at the time of diagnosis of malignant thyroid disease ranged from 8 to 66 years but was often below 33 years. Approximately one-third of patients presented with organ-exceeding tumours. Bilateralism, tumour multifocality, or both were seen in about 40%</p>		

DRAFT FOR FIRST CONSULTATION

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						<p>to 50% of cases. There was early metastatic spread to loco-regional lymph nodes in a considerable number of patients and distant metastases in up to 5% of patients. In addition, even small multifocal tumours presented with lymph node metastases. Characteristic features of FPTC were outlined as early onset, a more aggressive biologic behaviour than that of sporadic papillary thyroid carcinomas, tumour in multiple thyroid sites, and metastasis even in micro- papillary thyroid carcinomas. A high incidence of MNG developing at a young age, and adolescent-onset thyroid disease such as hypo/hyperthyroidism, immunothyroiditis, or adenoma were identified as common features of blood relatives of FPTC patients.</p>		
Office for National Statistics, 2001						<p>Laryngeal cancer is rare in males aged under 40 but rates rise quickly after this age, reaching a peak in the 75-79 age group (27 per 100,000 in 1997) There were just under 600 deaths in males from laryngeal cancer in England and Wales in 1999. As with incidence, mortality from laryngeal cancer is rare in the under 40s but rises steeply thereafter. The most affluent groups have the lowest rates; mortality in the most deprived groups is approximately four times that in the most affluent groups. The steeper gradient with deprivation in mortality than in incidence suggests that survival is worse in the more deprived groups.</p> <p>There is a north-south divide in the incidence of laryngeal cancer. Incidence was substantially higher in the Northern and Yorkshire and North West regions with a rate around 30% above the average for England and Wales. The incidence in Anglia and Oxford, South Thames, Trent, South West and West Midlands is below average. The regional variation in mortality is generally similar to that for incidence. Survival from cancer of the larynx in England and Wales was rated as moderately good with one-year relative survival of 83% and after five years of 64% for patients diagnosed in 1991-93. Five year relative survival decreases with increasing age at diagnosis, from 75% in the</p>		

DRAFT FOR FIRST CONSULTATION

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						youngest age group (15-39) to just over 50% in the oldest (80-99).		
Oral cancer awareness group, 2000		This review was prepared by the Scottish Oral Cancer Awareness Group to provide guidance to primary health care teams				In providing advice on prevention, the guidance highlighted the risk factors of tobacco, alcohol, nutrition (a diet high in fruit and vegetables was recommended), sunlight exposure, human papilloma viruses, oncogenes, and pre-existing mucosal abnormalities including leukoplakia, erythroplakia and speckled leukoplakia. Primary health care professionals were encouraged to help patients reduce their level of risk with an emphasis on smoking cessation and sensible drinking. The early symptoms of oral cancer were described as a (i) non-healing ulcer or sore, (ii) any lump or thickening, (iii) any white or red patch, (iv) persistent soreness. Late symptoms were described as (i) difficulty chewing or swallowing, (ii) difficulty moving the tongue or jaw, (iii) numbness of the tongue or other area of the mouth, (iv) swelling of any part of the mouth which may cause dentures to fit poorly or become uncomfortable, (v) a lump in the neck. Common presenting signs were described as (i) red patch, (ii) white and red patch, (iii) ulceration or erosion, (iv) induration, (v) fixation to surrounding tissues, (vi) lymphadenopathy.		
Talamini et al, 1994	Italy	An early detection programme for cancer of the head and neck was conducted from January 1991 to January 1993. high-risk individuals were referred to a research nurse by 21 general practitioners	212	Patients above 35 years of age, who reported habitual smoking and intake of more than half a litre of wine or equivalent per day	--	Head and neck cancer was found in 5 (2.4%) subjects (i.e. one cancer of the oral cavity, one of the pharynx, two of the larynx and one of the oesophagus, which was suspected because of saliva residues in the hypopharynx); precancerous lesions were detected in 15 (7.1%) additional subjects. Female had a 2.4-fold higher odds of non-compliance with the offered examination than males. Acceptance tended to be lower in younger age groups (OR of non compliance in individuals below age 45 as compared to those aged 65 or above=2.1). The presence of upper aerodigestive tract symptoms (6.2% of the overall group) exerted a significant influence on compliance with the programme, making attendance at the ENT examination 2.4-fold more frequent than in the absence of symptoms.		

DRAFT FOR FIRST CONSULTATION

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						With respect to major risk factors for head and neck cancer, current smokers were more reluctant to attend the ENT examination (OR in current smokers vs. non smokers = 3.4, 95% CI 1.8-6.3). Drinkers and former drinkers were particularly likely to accept the invitation. It was concluded that the response of targeted patients to the invitation to undergo an ENT examination was low and the most important risk factor of smoking for head and neck cancer onset, was associated with a significantly lower compliance.		

Table 12 HEAD and NECK: investigations

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
British Thyroid Association / Royal College of Physicians, 2002		A recommendation about initial investigations in primary care of patients with thyroid nodules.				Appropriate investigations pending hospital appointment (B) Thyroid function tests should be requested by the general practitioner. Euthyroid patients with a thyroid nodule may have thyroid cancer and should be referred to a member of the multidisciplinary thyroid cancer team. Patients with hyper- or hypothyroidism and a nodular goitre should be referred routinely to an endocrinologist. Initiation of other investigations by the general practitioner, such as ultrasonography or isotope scanning, is likely to result in unnecessary delay and cost in making the diagnosis of cancer (Iib, B).		
Caplan et al, 2000	USA	A one-year retrospective chart review of patient records. A table was constructed to record the use of fine-needle aspiration (FNA), cytology, radionuclide scanning and thyroid ultrasonography by primary care physicians (non specialists) evaluating thyroid nodules	49 primary care 81 thyroid nodules	Patients evaluated for thyroid nodules at a medical centre in 1996.	--	it was concluded that FNA cytology was a safe and accurate test. The study concluded that fine-needle aspiration cytology, adopted as the initial test for diagnosing thyroid nodules reduced the use of imaging studies and substantially decreased the cost of thyroid nodule management.		
Epstein, 1997		A review involving a search of Medline and Cancerlit 1990 to 1995. Evidence was sought on diagnostic tools to assist in biopsy site selection and subsequent diagnosis of patients at risk for oral cancer	Not stated.	All articles identified from a Medline and Cancerlit search from 1990 to August 1995.	--	The identified studies indicated that there was consensus that oral examination of patients at risk for oral squamous cell carcinoma should be conducted on a regular basis. Toluidine blue has been shown to be useful as an adjunct to the clinical examination when used by experienced clinicians. Exfoliative cytology was not currently used as a routine measure for the evaluation of lesions of the oral mucosa, but further development and the application of biologic markers to cytologic specimens may increase its value. Fluorescent imaging of malignant lesions of the oral mucosa has been shown to be sensitive and specific in animal models but thus far has been reported in only one human trial. The sensitivity and specificity of these techniques when used by general practitioners have not been assessed. Further, none of the above procedures		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						has yet been shown to be a cost-effective public health measure in screening for oral cancer.		
Johnson, 1998		Toluidine blue staining as a screen for oral cancer was evaluated by systematically reviewing the evidence from trials (from 1964 to 1997). The trials were divided into those using a single application of the stain and those using a second application of the stain or a period for resolution of transient inflammatory lesions	Single application: 17 trials and a total of 2948 patients Second application: five trials and 924 patients.	--	--	It was concluded that the sensitivity and specificity of toluidine blue as a test for early detection of oral cancer was adequate, but it must not be seen as a replacement for a detailed visual and digital examination. The use of a second test 14 days later was recommended, as was mandatory biopsy of clinically suspicious lesions/areas even if staining is negative. For clinicians in primary care settings specific training is required for correct application of the test and correct interpretation of the results.		
Lawrence, 2002	USA	A informal review	50 references	--	--	Fewer than 5% of all adults will have a palpable thyroid nodule, but this is still a large number of individuals who require evaluation. Important aspects of history taking with a patient in whom a thyroid nodule has been noted include age, gender, family history of thyroid cancer, dysphagia, and presence of symptoms of hypermetabolism. Key features of evaluation by physical examination are the size and location of the thyroid abnormality, the degree of firmness of the nodule, the presence of other nodules in the thyroid, palpable cervical lymph nodes, vocal cord paralysis, and tachycardia and/or tremor. The major categories of thyroid abnormality in such patients include cysts, adenomas, thyroiditis and cancer. Fine needle aspiration biopsy (FNAB) has proved to be the most efficient diagnostic tool.		
Warnakulasuriya, 1998	Asia	The efficacy of 1% toluidine blue (TB) in the identification of oral malignancies and potentially malignant oral lesions was evaluated among a group of Asian patients with undiagnosed oral lesions and conditions The study involved patients who had all been referred to, or had attended specialist centres with unconfirmed oral mucosal lesions.	102 patients	Patients who had all been referred to, or had attended specialist centres with unconfirmed oral mucosal lesions. The consultant dental surgeon in each centre approved the appropriateness of each included case.	--	86 clinically detected lesions, dye retained or not, were biopsied. Microscopy diagnosis and, where relevant, degree of dysplasia were recorded independently by two experienced histopathologists blinded to the dye results. When there was disagreement, concordance was reached following consultation. All the histopathologically confirmed malignancies (N=18) demonstrated stain uptake and there were no false negatives, yielding a test sensitivity of 100% for the		In view of the small size of the study, caution is required in generalising from the findings.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						detection of invasive carcinoma. Eight of 39 oral epithelial dysplasias were toluidine blue-negative, giving a false negative rate of 20.5% and a sensitivity of 79.5% for oral epithelial dysplasias		

Table 13 HEAD and NECK: diagnostic difficulties

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Canto et al, 2002	USA	A qualitative descriptive study on physicians' knowledge, opinions and practices about oral cancer examination was undertaken in Maryland. The methods used included one focus group with ten physicians, and nine one-to-one interviews		Primary selection criteria: 1) general physicians, family physicians or internists practicing in the Baltimore Metropolitan area or the Eastern shore Region, and 2) physicians who were serving a population with a racial/ ethnic mix. Secondary selection criteria: 1) physicians who were working at least 20 hours per week, and 2) diverse practice settings including private (solo or group practice), hospital outpatient clinic, and managed care organisations.		Physicians were not surprised that they detected more lesions than dentists, although most did not provide oral examination on a routine basis. Patients were more likely to see physicians than dentists because US health insurance coverage did not include dental care. Also, physicians' opinions indicated that patients were afraid of going to a dentist and only associated them with pain in their teeth or gums. Patients also consulted the doctor about the tongue or buccal mucosa. Patients consulted physicians for other medical problems that enabled them to raise additional issues such as a sore in their mouth or throat. There was a misconception that oral cancer was painless and asymptomatic, and that early lesions were small. Physicians needed more information about how to conduct a comprehensive oral cancer examination. Their knowledge about this examination was based on their variable medical training. It was related to whether or not physicians had completed an ENT or oncology rotation, or on their residency experience and the location where training was received.	
Clovis et al, 2002	Canada	Dentists in British Columbia and Nova Scotia were surveyed about their knowledge and opinions on oral and pharyngeal cancer	670 dentists	A systematic random sample of licensed dentists selected from the registrars' 1997 listing of licensees in British Columbia.		only 56.7% of dentists agreed that their knowledge of the subject was current. Most dentists correctly identified tobacco use (99.4%) and alcohol use (90.4%) as risk factors, but fewer correctly identified factors such as the use of spicy foods (57.0%) and poor oral hygiene (46.3%) as not being risk factors, a finding that was attributed to a high level of misinformation. Only 42.5% identified both erythroplakia and leukoplakia, in that order, as the conditions most likely to be associated with oral cancer. It was stressed that early detection and screening during routine examination was the single most critical intervention influencing survival. Fewer than half knew that familial clustering of cancer and poor-fitting dentures were not real risk factors. Only a small proportion knew that a family history of cancer was not in itself a risk factor for oral cancer. The procedure for complete examination of the tongue, the fact that early oral cancer is asymptomatic, and the appearance of early oral cancer lesions were correctly identified by large numbers of respondents. Just over half knew that most oral cancer was diagnosed at an advanced stage.	
Greenwood, 2001	UK	A prospective study in which a	420 doctors	Randomly selected general medical		dentists were more likely to have diagnosed cases of oral cancer than general practitioners (OR=2.68, 95% CI 1.6, 4.4). Important	The article did not provide details of how many cancer

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
		questionnaire was sent to primary care clinicians (half dentists and half doctors) to assess the knowledge of both groups in examining patients with oral cancer		and dental practitioners from family health service authority lists in and around Newcastle upon Tyne and on Teeside.		differences arose between the groups in terms of risk factor knowledge and clinical examination techniques. One explanation was that general practitioners had received less training in oral pathology than dentists and therefore might be expected to have less knowledge of oral cancer and related issues. Dentists were more likely to list alcohol as a risk factor than general practitioners (OR+6.9, 95% CI3.9, 12.1). The proportion of dentists and doctors identifying smoking as a risk factor was 93.7% and 90.7% respectively. This difference was not significant (OR =1.5, 95% CI 0.6, 3.6). Dentists were significantly less likely to state they would examine all sites in the mouth than general practitioners (OR=0.5, 95% CI 0.3, 0.8). Dentists showed a preference for examining areas relating to the tooth bearing or potential denture bearing tissues, rather than for some of the more high risk sites, for example, the floor of the mouth. Dentists were more likely to identify various presentations of oral cancer and premalignant disease than general practitioners (OR+13.6 and 25.7 respectively).	cases were successfully identified by dentists and general practitioners.
Kamal, 1999	Jordan	A retrospective study was undertaken to highlight some of the presenting features of nasopharyngeal carcinoma as seen in a large hospital over a period of 20 years.	91 cases of nasopharyngeal carcinoma	All relevant data available to the department of Pathology and Otolaryngology, as well as medical records at the Jordan university hospital.		Tumours were detected at an advanced stage with 34% having metastasised most frequently to bone. Data collected during the period revealed that nasopharyngeal carcinoma accounted for 1% of all malignant tumours with an age range from six to 89 years, and a mean of 39.5 years. A high incidence of childhood nasopharyngeal carcinoma was also noticed (two percent of all childhood malignant tumours). The tumours were frequently symptomless or initially evoked symptoms that were common to other minor clinical conditions, and consequently did not attract serious patient attention. Some of these silent tumours were overlooked on clinical examination in the early stages. Seventy patients (77%) presented with a single complaint and 21 (23%) presented with multiple complaints. The most common single presenting symptom was neck swelling (45.5%). In 37 patients (41%) carcinoma affected one site of the nasopharynx, most frequently a lateral wall. Thirty-five patients (38%) had multifocal malignant involvement of the nasopharynx. In 19 patients (21%) the nasopharynx appeared normal and no site of involvement could be seen at the time of first diagnosis. Difficulties in early diagnosis by general practitioners included the small size of tumours, near normal appearance of nasopharyngeal mucosa or the inherent presence of massive lymphoid tissue obscuring the underlying lesions.	The findings of this study should be treated with caution since it was undertaken in Jordan where the incidence of this cancer is relatively high and the patient population was different to England and Wales. Consequently, the significance of the findings of this study to general practice in England and Wales is uncertain.

Table 14 HEAD and NECK: delay

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Allison et al 1998		Review of diagnostic delays and prognosis of oral cancer				Focuses mainly on factors that affect the diagnostic process, and the consequences that diagnostic delay has on the prognosis of oral cancer patients.	Narrative review that notes lack of evidence
Allison et al, 1998b	Canada, Secondary care	The aim of the study was to investigate the relationship between patient and professional diagnostic delays, and patient prognosis in a group of upper aerodigestive tract cancer patients. Patients were interviewed and data elicited on socio-economic and demographic variables, information concerning the cancer development and symptomatology, health care professionals consulted and the period of time taken for each stage in the diagnostic process.	188 patients	Patients diagnosed with squamous cell carcinoma of oral cavity sites, oro-, naso- and hypopharynx, and larynx.	Not explicitly mentioned	77% of the sample presented initially to a family physician and 16.5% consulted a dentist. Patients under the age of 65 years have a significantly increased risk of being diagnosed with late stage disease when compared with those 65 years and older (OR=1.91, 95% CI= 1.07-3.41). Gender and education were not associated with disease stage. The risk of late stage disease appears to be increased among those who live alone, although the significance of this is marginal (OR=1.97, 95% CI= 0.93-4.17). The general health status indicators of comorbidity and dental status at the time of diagnosis were not associated with disease stage. Those subjects who had a mucosal lesion or voice change as their presenting symptom had a significantly reduced risk of being diagnosed with late stage disease when compared with those subjects presenting with a swelling. Subjects with a pharyngeal cancer had odds of being diagnosed with late stage disease eight times those of subjects with oral cancer. No association was found between increased patient delay and risk of late	Multivariate analysis. Questionnaire was validated by randomising a subset, and checking their responses against primary physician or dentist and hospital charts. No particular pattern for laryngeal cancers was found throughout the analysis, probably as a result of categorising all laryngeal cancers together (instead of categorising them as supraglottic, glottic and subglottic cancers). Small sample. Delay data is largely dependent upon subject recall, although the authors' random validity check for professional delay demonstrated 100% accuracy. However, misclassification of the patient delay information may have led to a decreased statistical association between this variable and late stage. Good overall quality. Retrospective observational study. Grade III.

DRAFT FOR FIRST CONSULTATION

						<p>stage disease. However, there was a pattern of increased odds for late stage disease with increased professional delay, with these odds being three times greater among those subjects delayed more than 3 months compared to those with less than 1 month's professional delay. (p for trend 0.03). Those subjects who first consulted a dentist, rather than a family physician, had a reduced risk of late stage disease of borderline significance. Stepwise multiple logistic regression demonstrated that: (i) pharyngeal cancers have nine times the odds of oral or laryngeal cancers for late stage disease; (ii) professional delay > 1 month has approximately twice the odds for late stage of professional delay < 1 month; (iii) older patients (>65 years) have approximately half the odds for late stage cancer of those < 65 years). The type of primary health care professional first consulted no longer remained a significant predictor of disease stage in the multiple regression analysis.</p>	
Cooke BED and Tapper-Jones L, 1977	UK, Secondary Care	The study is an attempt to analyse the factors underlying delay between the patient's first symptom and the institution of treatment. The authors examined the case histories of patients attending a teaching hospital to ascertain information on factors underlying delay in diagnosis (patient and	50 patients (all with squamous cell carcinoma). 84% of the patients were 60 years of age and above.	Patients suffering from oral cancer	Patients whose case studies failed to reveal detailed information prior to their diagnosis of oral cancer	The most common reason given by the patient for failing to see early advice was that the lesion did not hurt. The major presenting symptom was ulceration (60%) and only 10 per cent of patients experienced pain. 50% of patients were referred from general medical practitioners and 30% from general dental practitioners. There was only a degree of urgency in the	Small size study, mainly descriptive without analysis of causation. No enough socio-demographic variables were included in the study. Inclusion bias likely, doubts remain on quality of information extracted from case histories. Old study, dynamics of society and communications/transport greatly transformed since. Retrospective observational study. Grade III.

DRAFT FOR FIRST CONSULTATION

		professional delay).				referral letter or card for these patients from 56% of the GPs and 53% from the general dental practitioners. The delay in patients being referred to hospital for confirmation of diagnosis is mainly caused by a low degree of suspicion, it appeared as if the general medical practitioner did this more often than the general dental practitioner.	
Elwood JM and Gallagher, 1985	Canada, Secondary Care	The authors aimed to examine the factors associated with stage at time of diagnosis and with interval between recognition of the first symptom and histologic diagnosis. The study was a consecutive series of patients with newly diagnosed cancer of the oral cavity seen at cancer centre. Data was obtained from the admission history and the patients' records, and from patients' interviews (structured questionnaire). Patient variables assessed were alcohol consumption and smoking, life-time occupational history (socio-economic classification), and dental care.	160 patients (90% of those eligible for the study)	Patients with primary epithelial tumours of the oral cavity.	Not explicitly mentioned	Of the 160 patients 55% had stage I or II disease. The factor most strongly associated with differences in stage distribution was regular dental care (70% of patients who had regular dental care had stage I or II tumours, compared with 40% of those who did not have regular dental care, p=0.0002). Socio-economic status and alcohol consumption were also related to differences in stage distribution (60% of patients with high socio-economic status and 65% of patients who drank less than 9 oz of alcohol per week had stage I or II tumours). The association of stage of disease and socio-economic status became non-significant once controlling for the effects of the other two variables The interval between recognition of the first symptom and diagnosis was not significantly related to these factors, but it was shorter for men. There was no association between this interval and age, marital status, smoking history, diet and religion. There was a tendency for tumours on more easily visible surfaces to be diagnosed earlier. The	Clear definition of methods, validated questionnaire. Appropriate use of statistical tests. Information relating to interval between the recognition of the first symptom and the histologic diagnosis was not available for 26 patients. It is impossible to determine whether dental attendance and alcohol consumption are associated with disease stage as indicators of patient, professional or tumour behaviour. It is not possible either to say which aspect of the total diagnostic delay is longer for women. Retrospective observational study. Grade III.

DRAFT FOR FIRST CONSULTATION

						interval between recognition of the first symptom and histologic diagnosis did not differ significantly with the site of the tumour. These relations were specific to the patients with cancer of the oral cavity, not being seen in those with other head and neck tumours.	
Guggenheimer J et al, 1989	Unclear (presumably USA, Secondary care)	The study was undertaken to identify possible bases for patient and/or professional delays and to determine whether or not these delays were related to tumour stage at diagnosis. In addition, the authors also assessed the relationship between delay and several other variables. Delay was compared against age, gender, education, alcohol consumption, and tumour T stage at the time of diagnosis. A personal interview questionnaire was administered by three of the investigators.	149 patients (out of 151 eligible)	Patients with oral and oropharyngeal squamous cell carcinoma.	Not explicitly mentioned	Delay by doctors occurred in 30% of cases. Neither short nor long delays had a statistically significant relationship to tumour T stage at time of diagnosis. The length of patient delay was also not related to age, gender, amount of education, or history of alcohol consumption. Physician delays were most often associated with base of tongue and tonsil primaries. Tongue and floor of mouth tumours accounted for the major share of dentist's misdiagnoses.	Patient delay was determined by the patients recollection of the approximate dates of events. Appropriate use of statistical tests. Setting of study is not described by the authors, questionnaire is not available for inspection either. Methods not described clearly enough, including eligibility criteria Retrospective observational study. Grade III.
Jones TM et al, 2002	UK, Secondary care	The authors undertook an audit of the management of patients with suspected head and neck malignancy, referred by GPs to an ENT hospital department. Their aim was to compare the authors' local services with the nationally stipulated targets, and to identify any specific problem areas during the diagnosis and treatment of head and neck cancer patients. Data were recorded from case-notes and hospital and GP records.	75 consecutive patients attending for post-treatment follow-up	Patients with a solid head and neck malignancy	Not explicitly mentioned	Thirty-seven patients presented with hoarseness, 15 with a neck lump, 14 with pain, three with haemoptysis and two with a visible ulcerative lesion. The longest delay was due to late presentation of the patient (mean waiting time = 4.9 months, range = 1-20), and late referral by the GP (mean waiting time = 5.1 weeks, range = 2-12).	Retrospective observational study. Poor description of methods and data analysis, small sample for quantitative analysis. Insufficient demographic data to address question, purely descriptive analysis of delays in diagnosis without analysis of causality. Poor presentation results. Very likely inclusion bias. Poor quality study. Grade IIIC evidence.
Kantola S et al, 2001	Finland, Primary Care	The study aim was to investigate the detection of tongue cancer in primary care and to examine the	75 patients (78%) with a diagnosis of tongue cancer	Patients with a new diagnosis of tongue cancer detected in the period 1974-	Patients with a premalignant oral lesion that underwent a cancerous change	At the initial visit, the tongue cancer patient was correctly referred for further examinations in 49 (65%)	Definition of measurable outcomes, multivariate analyses. Sample small with limited statistical power. Generalisability may be limited

DRAFT FOR FIRST CONSULTATION

		<p>consultation prevalence of oral symptoms in primary care. The authors identified all patients who lived in an area and who had been diagnosed for tongue cancer from population databases. They then recorded detailed data on the first medical visit from the patient medical files (primary health centres, private medical or dental practitioners), and finally collected data on demographic and clinical variables from the cancer centre.</p>	<p>(out of 108 initially eligible)</p>	<p>1994.</p>	<p>during the hospital follow up (10), cases discovered incidentally at the tertiary centre (2), and patients whose primary care patient files were missing (21)</p>	<p>cases. In 12 (16%) of cases the patient was not referred but was scheduled for a follow-up visit, and was neither referred nor followed up in 14 (19%). When compared with the referred patients the median professional delay was somewhat longer for the unreferred but increased dramatically if no follow up was arranged (0.6 months, range=0.1-2.4; versus 1.2, range=0.3-2; versus 5.2, range=0.7-18.2; p<0.001). Adjusted relative hazards of death were significantly increased for those non-referred followed up patients (1.4), and the non-referred/non-followed up patients (6.3). The high-risk patients included those who sought an early professional evaluation, those who made the appointment for a completely different reason and only mentioned the symptom suggestive of cancer incidentally, those that had a small ulcerative lesion, those with an inability to live alone at home, rural domicile, and blue-collar workers (low occupational status, P=0.009). There were no statistically significant differences in the ability to refer cancer patients correctly between physicians and dentists. The referred patients tended to have exophytic tumours located on the marginal edge of the tongue, which are more readily visible (p=0.02). The lesions suspected to be cancer tended to be palpated</p>	<p>because of patients having been drawn from a relatively small geographical area. Information on the initial visit was not available for all patients, which gives rise to the possibility of small selection bias. Only cancer cases were recorded (no information available on overdiagnoses or false positive rates)</p> <p>Retrospective sample, observational study, good overall quality. Grade III.</p>
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DRAFT FOR FIRST CONSULTATION

						more often than the unsuspected ones (p=0.04).	
Kerdpon D and Sriplung H, 2001	Thailand, Secondary Care	The purpose of the study was to identify the factors related to the patient and professional delay in diagnosis of oral squamous cell carcinoma in southern Thailand. The authors interviewed all participants using a structured questionnaire. Interview questions covered demographic variables (age at diagnosis, area of residence, occupation, marital status and religion) amongst other factors underlying patient and professional delay. Demographic variables were confirmed with the hospital record before filling in the questionnaire.	161 patients	Patients with squamous cell carcinoma of the lip and oral cavity sites (with histopathological confirmation)	Not explicitly mentioned.	Patient delay mean was 90.6 days, professional delay 51.2 days and total delay 141.8 days. About half of the patients who sought professional consultation had proper management by biopsy or were referred to a higher level hospital. 82.6% of patients sought consultation from doctors, 15.5% from dentists and 1.9% from community health workers. Out of all the variables examined (sex, age, marital status, tumour size, lymph node metastasis, TNM stage, religion, area of residence, occupation, initial sign or symptom, site of lesion, type of health care professional, treatment-seeking before professional consultation, traditional herbal medication received before professional consultation and habit of smoking, alcohol drinking and betel quid chewing) only traditional herbal medication was a significant predictor for patient delay. Those who received traditional herbal medication before health care professional consultation had a longer patient delay (HR 0.46, 95% CI 0.28-0.76). There was no significant association between any of the variables investigated and professional delay. Total delay was significantly influenced by religion and traditional herb medication. Buddhists had less total delay than Muslims (HR 0.68, 95% CI 0.49-0.95). Patients who used traditional herb medication had a longer	Non-validated questionnaire. Multivariate analyses. Positive findings cannot be extrapolated to western countries population because of different cultural beliefs and different health care systems. Extrapolation of negative findings requires caution for same reason. Small sample. More investigation is needed to identify the factors associated with a longer delay in Muslims. Retrospective observational study. Grade III.

DRAFT FOR FIRST CONSULTATION

<p>Kowalski LP et al, 1994</p>	<p>Brazil, Secondary Care</p>	<p>The study analyses the importance of various pre-treatment factors such as demographic and socio-economic factors and lateness of case referrals. Prior to any medical treatment patients were submitted to a structured questionnaire-based, standardised interview. Variables included were socio-economic and demographic, history of tobacco smoking and alcoholic beverage consumption.</p>	<p>336 patients</p>	<p>Patients with newly diagnosed carcinomas of the oral cavity and oropharynx.</p>	<p>Lesions that could not be accessible to self-examination (not on the lip, other parts of the oral cavity, tonsillar fossa and posterior wall of the oropharynx). Also patients with malignant neoplasms of minor salivary glands, related structures such as bone and soft parts or cases of base of the tongue and vallecula. Patients who had difficulty in communication due to pain or speech problems.</p>	<p>total delay. There was no delay on the referral to a head and neck service of 59 patients (17.6%). The patient was only responsible for the delay in reaching a head and neck service in 196 cases (58.3%). A medical doctor delayed the referral for a median of 12.3 months in 19 cases (5.7%), a dentist for 6.5 months in 11 cases (3.3%), a pharmacist or drug store clerk for 3.5 months in 13 cases (3.9%). In 38 cases (11.3%) there was a delay for 8.5 months because patients were seen by more than one health professional. Duration of symptoms and patient and professional delays were not associated with the risk of advanced disease in unifactorial analysis. The risk of having advanced disease was moderately lower in females (RR=0.45, 95% CI=0.24-0.86), marginally lower in older patients (RR=0.54, 95% CI=0.27-1.08), and not dependent upon family income and educational levels. Alcoholism was not associated with the stage of disease at diagnosis. A significant reduction in risk for advanced stage was seen when a painful ulcer as the first symptom (RR=0.24, 95% CI=0.13-0.45). A substantial increase in risk was observed in cases with odynophagia and/or dysphagia (RR=4.52, 95% CI=1.99-10.26). Tumours on less visible surfaces or oral cavity or oropharynx tended to be advanced at time of diagnosis.</p>	<p>Prospective study. Multivariate analyses. Clear definition of methods and measurable outcomes. The absence of correlation between income and educational levels is probably because the study includes few patients of high income and educational levels and the effects of these variables could not be fully appreciated. Grade III.</p>
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DRAFT FOR FIRST CONSULTATION

<p>Pitiphat et al, 2002</p>	<p>Greece, Secondary Care</p>	<p>The authors attempted to evaluate factors associated with delay in the diagnosis of oral cancer by interviewing patients attending three teaching hospital-based clinics (structured, pre-tested questionnaire). Risk factor data included demographic and socio-economic characteristics, information on tobacco use, alcohol drinking, family history of cancer, intra-oral status, and weight change. Tumour size and TNM stage at time of diagnosis were also assessed. The authors recorded the time interval from the self-reported date when oral cancer signs and/or symptoms were first noted to the date of definite diagnosis</p>	<p>105 respondents</p>	<p>Patients aged 26 to 91 years, with no prior history of oral cancer, who were diagnosed with histopatholog. confirmed squamous cell oral or pharyngeal cancer</p>	<p>Not explicitly mentioned</p>	<p>The time from initial diagnosis to definitive diagnosis ranged between 0 and 780 days, with a median of 30 days. Fifty-five patients exhibited a delay of 21 days or more (52.4%). Length of delay was significantly longer among single patients, non-smokers, or those with stage IV tumours. There was no significant association between age and diagnostic delay. The authors found no association between gender and delay in diagnosis. Surrogate measures for socio-economic status, such as education level and unemployment, were found not to affect the timing to diagnosis. Findings suggest a strong association between history of sexually transmitted disease and delay in diagnosis. There was no significant association between delay in diagnosis and alcohol use.</p>	<p>Case-control study. Clear definition of methods and measurable outcomes. Univariate and multivariate analyses. No distinction between the different types of delay (patient or professional delay), difficulty on inferring the true causes of observed delays as a result. Residual confounding for socio-economic status cannot be ruled out. Residual confounding and limited statistical power may have also influenced association of delay with history of sexually transmitted disease. Assessment of the time to diagnosis depended on patients' recollection of their first symptoms (limitation). Reflective discussion with good overview of findings from other published papers.</p> <p>Good overall quality. Grade III.</p>
<p>Shira RB, 1976</p>	<p>Denmark, Secondary Care</p>	<p>The purpose of the study was to outline the two time factors (patient and professional delay) that intervene in reaching a diagnosis of oral cavity malignancy. The authors surveyed 34 patients who had been referred to a Department of Oral Surgery, additional information was extracted from the patients' hospital records. Parameters evaluated in the study were: sex, age, referral from physician or dentist, symptoms, referral diagnosis, time lapse from first symptoms until consultation with physician or dentist, time lapse from</p>	<p>34 patients (20 patients had squamous cell carcinomas)</p>	<p>Patients suffering from malignant tumours of the oral cavity</p>	<p>Not explicitly mentioned</p>	<p>The tumours occurred more often in men than in women, and most often in the group aged 50 to 70 years. Twenty-four patients consulted a physician or dentist within 3 months after the appearance of the first three symptoms. The average period from the time that the patient first observed the symptoms until he consulted a physician or dentist was 4.9 months. Twenty of 32 patients were referred within 3 months, the average period for all patients was 5.6 months.</p>	<p>Small sample. As with previous studies, patients' own recollection of time elapsed between first symptoms until contacting a physician or dentist may lead to underestimates. A purely descriptive analysis that does not examine causal relationship between delay in diagnosis and patient or health professional characteristics.</p> <p>Retrospective observational study. Grade III.</p>

DRAFT FOR FIRST CONSULTATION

		the first consultation with physician or dentist to referral and final diagnosis, previous treatment, localisation, bone involvement, final treatment, control period, survival period.					
Wildt J et al, 1995	Denmark, Secondary care	The purpose of the study was, firstly, to assess and describe the importance of the different elements of the delay. Secondly, to investigate the possible correlation between the delay and some tumour and patient factors, and thirdly, to examine whether the delay can be used as an independent prognostic factor. The authors examined patient delay, professional delay, and total delay.	167 patients with an oral squamous cell carcinoma. Ratio of men to women was 1.5:1 and the median age was 66 years.	All patients with an oral squamous carcinoma seen at a hospital clinic between 1 January 1986 and 1 November 1990	Not explicitly mentioned	The patient's choice of primary medical contact was a GP in 45% of cases, ENT specialist (14%), dentist (35%) and others (7%). The median total delay was 4 months, of which 71 days was patient delay. Tumour size correlated significantly with the professional delay but not with the patient delay, the proportion of patients with a professional delay above the median value (45 days) increased with decreasing tumour size. Tumour site, STAGE grouping and histological score did not correlate significantly with either patient delay or professional delay. The patient delay did not correlate significantly with any of the patient-related factors. In contrast, the professional delay was significantly correlated with sex as women had a longer professional delay than men ($r=0.26$). It also correlated with age, as the oldest age groups had the longest professional delay ($r=0.19$). The professional delay was not significantly related to the type of professional advice sought, be it GP, ENT specialist or dentist.	The only two patient socio-demographic factors were age and sex. Relies on patients' account to estimate patient delay, data must be interpreted cautiously. Professional delay correlates were the products of series of univariate analyses and, although the correlations were statistically significant, they were weak. The use of Spearman's rank correlation test with a nominal variable such as gender is inappropriate. Prospective observational study. Grade III.

Table 15 BRAIN: signs and symptoms, including risk factors

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Ambulatory Sentinel Practice Network, 1987	USA and Canada	The clinical characteristics of patients making consecutive visits for headache and the therapeutic strategies employed by the doctors in primary care practices were investigated. . Data were recorded between November 1982 and December 1983 about each consultation at which headache was discussed, investigated or treated.	3847 patients 38 primary care practices.			Tension headaches and vascular heachaches were the most frequent diagnoses (30.4% and 23.8% respectively). (31.6%) of visits were for headaches associated with a variety of other causes such as sinusitis, influenza, trauma and mass lesions. (47.2%) were for headaches which were new or changed in character. (13.7%) were for headaches associated with febrile illnesses. Vascular headache was more likely to be diagnosed in patients who had unilateral symptoms, or if nausea or aura accompanied their headaches than in patients with none of these symptoms. Of 690 patients who made a second visit only 56.4% presented with the same combination of symptoms on both occasions. (27.0%) of the 37 patients with all three migraine like symptoms at the first visit who made a second visit, and 30.4% of the 92 patients who initially presented with two migraine like symptoms, had none of these symptoms when they returned. Headache intensity changed for 42.9% of the 690 patients making a second visit. Changes in diagnosis accompanied these symptom changes.		Investigation of headache was limited to history and physical examination. Only a small minority of headache patients underwent an x-ray examination (4.5%), electroencephalogram (1.1%) or computerised tomographic scan (3.0%). The rate of computerised tomographic scanning was greater at second and third visits than first visits (3.8% and 4.5% vs. 2.2%). Referral to consultants and hospitalisation were also infrequent. Nearly three quarters of patients (71.0%) had no investigations at any visit and were never referred to consultants or hospitalised. Only 35.9% of patients were advised to make a return visit; half of these did so.
Becker et al, 1988	US and Canada	The study aimed to examine the clinical characteristics of new headaches and document the diagnostic and management strategies employed by primary care clinicians.	120 primary care physicians in 38 practices. The final study group consisted of 1,331 patients			A total of 332,818 office visits were recorded during the period, of which 0.4% were fist visits for new headaches. At first visit, most patients (76.6%) were managed without diagnostic tests. Drugs were prescribed for 73.6%, and advice was given for 58.6%. Only 2.0% of patients had computerised tomographic scanning ordered at first visit. Of persons with a new headache		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						<p>presenting at first visit, 23.8% were diagnosed as having tension and 12.8% as having vascular headaches. Nearly one half (47.8%) were classified as having headaches other than tension or vascular. A total of 15.3% were undiagnosed. Patients with vascular headaches were more likely than those diagnosed as having tension headaches to report occurrence of aura (24.7% vs. 1.3%), nausea or vomiting (46.5% vs. 18.9%) and unilateral focus (50.0% vs. 13.2%). These differences were significant ($p < .05$). Headache severity was related to the ordering of CT scan ($P < .001$) and x-ray examinations ($P < .007$) at first visit. X-ray examinations were ordered most frequently for patients with other or undiagnosed-mixed headaches ($P < .006$); CT scan and blood tests were also used mostly ($P < .0001$) for patients with undiagnosed-mixed headaches.</p> <p>Patients with disabling headaches at first visit were more likely to be hospitalised ($P < .001$); referral was not related to headache intensity. Patients were 2.05 times as likely to be referred at the second visit than the first ($P < .05$), and the percentage of those hospitalised similarly increased (2.0%).</p> <p>Primary care clinicians in this study were two thirds as likely to order an x-ray examination as were physicians. Expensive tests were seldom ordered at first or subsequent visits, even when headaches were classified as severe or disabling.</p>		
Christiaans et al, 2002		A prospective study to assess the diagnostic value of neurologic evaluation in cancer patients with new or changed headache in	68 patients.			<p>The mean age of the patients was 57 years (range 24-88 years; standard deviation ± 13.3 years). Breast carcinoma was the primary tumour in 32 patients (47.1%) and lung carcinoma was the primary</p>	MRI of the brain within 1 week of the neurologic examination.	

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
		identifying intracranial metastases. All patients referred by their general practitioners and specialist to a department of neurology underwent a structured history and neurologic examination.				tumour in 12 patients (17.6%). MRI scans demonstrated intracranial metastases in 22 patients (32.4%). An association was found between intracranial metastases and seven variables: interval between headache onset and neurologic consultation of ≤10 weeks (odds ratio [OR] of 11.2; 95% confidence interval [95% CI], 1.4-91.1), emesis (OR of 4.93; 95% CI, 1.6-15), pain not of tension type (OR of 5.7; 95% CI, 1.8-17.7), Mini-mental state examination score of ≤ 23 (OR of 11.0; 95% CI, 1.1-105.9), apathy (OR of 10.0; 95% CI, 1.0-95.7), coordination disturbance (OR of 3.43; 95% CI, 1.1-4.3), and Babinski sign (OR of 6.47; 95% CI, 1.1-36.6). In multiple regression, three variables were found to be significant independent predictors: headache duration of ≤10 weeks (OR of 11.0; 95% CI, 1.1-108.2), pain not of tension type (OR of 6.7; 95% CI, 1.8-25.1), and emesis (OR of 4.0; 95% CI, 1.1-14.3). When at least one of the three predictors were present, all patients with intracranial metastases could be identified. If this rule had been applied, 12 MRI scans (26%) could have been omitted in patients without intracranial metastases. As a single predictor, emesis predicted one of the 22 cases of metastases (5%) and there were no negative MRI findings. As a single predictor, a headache duration of ≤10 weeks predicted four of the 22 positive MRI scans (18%) (with metastases) and 19 of 46 negative MRI scans (41%). The combined presence of the predictors of emesis and headache of a duration ≤10 weeks predicted five of the 22 positive MRI scans (23%) and seven of 46 negative MRI scans (15%). The		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						combined presence of pain not of tension type and a headache duration of ≤ 10 weeks predicted 6 of the 22 cases of metastases (27%) and three of 46 negative MRI scans (7%). The combined presence of emesis and pain not of tension type predicted none of the 22 positive MRI scans and one of 46 negative MRI scans and one of 46 negative MRI scans (2%).		
Counsell and Grant 1998		The incidence of intracranial tumours was investigated in a review of studies identified in a search from Medline (1966-1995).	20 studies			The studies included over 20,000 primary tumours. Higher incidences of primary tumours were found in studies that: used many methods to identify cases (OR 1.92); included a higher percentage of asymptomatic patients (OR 2.03); and did not require histologic confirmation of the diagnosis (OR 1.69). Studies from the 1980s onwards reported higher incidences than in previous decades (OR 1.51), a finding assumed to be due to improved methodology of diagnosis.		
DoH, Referral Guidelines for Suspected Cancer, 2000								
Hoffman et al, 1999		A structured literature review was undertaken of studies identified from Medline searches (1966-1996) on the aetiology, prognosis and diagnostic evaluation of dizziness.		Studies that presented original data on at least ten dizzy or vertiginous patients 18 years of age or older with diagnostic test results comparable with a gold standard or applied to a control group		The most common aetiologies for dizziness were peripheral vestibulopathies (35% to 55% of patients) and psychiatric disorders (10% to 25% of patients). Cerebrovascular disease (5%) and brain tumours (<1%) were infrequent. The history and physical examination were stated as leading to a diagnosis in about 75% of patients. The most common central nervous system cause of dizziness in primary care patients was cerebrovascular ischemia or infarction (median 5%, range 2%		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						to 10%); tumours were found in <1% of dizzy patients. Tumour rates were higher (2% to 3%) in older patients referred to neurologists. Acoustic neuromas typically presented with gradual hearing loss. Nonetheless, investigators have reported normal hearing in 7% of patients with acoustic neuromas smaller than 1cm in diameter. For acoustic neuromas between 1cm and 3cm, normal hearing was found in 3%; no patients with tumours greater than 3cm had normal hearing.		
Kroenke, 2000		A Medline search between 1966 and 1996 identified studies of the presentation of dizziness in consecutive patients	12 studies			Dizziness was attributed to peripheral vestibulopathy in 44% of patients, a central vestibulopathy in 11%, psychiatric causes in 16%, other conditions in 26%, and an unknown cause in 13%. Certain serious causes were relatively uncommon including cerebrovascular disease (6%), cardiac arrhythmia (1.5%), and a brain tumour (<1%). Dizziness was ascribed to vestibular or psychiatric problems in more than 70% of cases. Brain tumour was detected in 32 patients (0.7% of the 4,536 patients assessed). Seven studies reported one or more cases whereas five studies reported no tumours. Other central vestibular explanations were reported in 57 patients (1.2%), including 18 patients with abnormal examination findings (vertical nystagmus, abnormal brain stem evoked potentials) without a specific diagnosis, 17 with cerebellar atrophy, seven with migraine, six with multiple sclerosis, three with epilepsy, and six with other diagnoses.		Since only two studies were primary care based, it was difficult to draw precise conclusions about the frequency of various causes of dizziness in unselected patients in the primary care setting.
Office of National Statistics,						The majority of malignant brain tumours are gliomas, including astrocytoma, oligodendroglioma,		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
2001						<p>and ependymoma. The other most common histological types, meningiomas and neuromas, are predominantly benign. The disease was more common in males than females. The male:female ratio in the age standardised rates were in the region of 1.5:1. There is a bimodal age distribution in tumours of the brain with a small peak in children under 10 and a much larger peak in adults at ages 55 to 80. Most tumours are gliomas (85%): 30% (of all brain cancer cases) are astrocytomas, 22% glioblastomas, 3% oligodendroblastomas, and 30% other or unspecified gliomas; the remainder were of poor histological specification.</p> <p>The incidence of brain tumours is 25%-30% higher in affluent groups compared to the most deprived groups, but no consistent regional variation was reported, although the incidence and mortality rates are higher in developed countries. Survival from brain cancer was poor. One year relative survival rates were approximately 30% in men and women diagnosed in 1991-93, and five year survival was in the region of 13%. Survival fell rapidly with age. Five year relative survival was above 40% for men and women aged 15-39, but fell to 20% in men and 23% in women aged 40-49. Survival was 3% or less in adults aged 60 or over at diagnosis.</p> <p>Regional variation in survival was not marked. One year survival was 4% points higher in the most affluent group diagnosed in 1986-90 compared with the most deprived group, but there was no difference across the deprivation categories in five year survival.</p>		

Table 16 BRAIN: investigations

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Becker et al Part 1 1993	US and Canada	A study to investigate the reasons for clinicians in primary care ordering CT scans and the results obtained.	58 practices 349 CT scans were ordered.			Most scans were ordered because the clinician believed that a tumour (49%) or a subarachnoid haemorrhage (9%) might be present. 59 were ordered because of patient expectation or medicolegal concerns. Of the 293 reports reviewed, 14 indicated a tumour, a subarachnoid haemorrhage, or a subdural haematoma. Two of the 14 (14%) were false positives. 44 (15%) of the reports noted incidental findings of questionable significance. It was concluded that because there are no clear guidelines for the use of CT for the investigation of headache, physicians must exercise good clinical judgement in their attempts to identify treatable disease in a cost-effective manner.		
Becker et al Part 2 1993		This study was undertaken to determine the incidence and presenting signs and symptoms of intracranial tumour, subarachnoid haemorrhage, and subdural haematoma in primary care settings, and to determine whether a more aggressive investigative strategy for patients with headache is justifiable. Weekly return cards and a chart audit were used to collect data over a 19 month period on every patient who had a new diagnosis of intracranial tumour, subarachnoid haemorrhage, or subdural haematoma				25 new tumours, 17 subarachnoid haemorrhages, and eight subdural haematomas were reported in 58 practices (a rate of 12/100,000 patients per year). Only half of these patients had headaches, and no abnormalities were found on neurological examination of many. Diagnosis was delayed in only four patients with headache caused by a brain tumour and in three patients with subarachnoid haemorrhages. Diagnosis was delayed in two of the latter because of false negative CT scans.		
Consensus Conference 1982		At the National Institutes of Health (NIH), the Consensus Development Conference brings together investigators in the biomedical sciences, clinical investigators, practising physicians, and consumer and special-interest groups to make a scientific assessment of technologies, including drugs, devices, and procedures, and to seek agreement on their safety and effectiveness				was concluded that CT should not be employed as a routine screening procedure when a low diagnostic yield is anticipated. In general, patients with headache should be considered for CT scanning only if the symptom is severe, constant, unusual, or associated with abnormal neurological signs. In infants and children, CT is useful as a primary diagnostic tool in the evaluation of intracranial haemorrhage and mass lesions. CT is not necessary in evaluating conditions of the majority of children with headaches because the occurrence of a surgically treatable lesion is extremely low. The clinical situation must, in each case, be considered individually.		
Larson et al 1980		A careful history and physical and neurological examinations were adequate screens to detect intracranial mass lesions or systematic disease associated with headache	161 patients			In patients with normal findings from neurological examination, no clinically important abnormalities were detected by CT, skull X-ray, angiography, or nuclide brain scan. The cost of finding a case of brain tumour was estimated to be at least \$1,265	A careful history and physical and neurological examinations were adequate screens to detect intracranial mass	

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						for patients with abnormalities on neurological examination and \$11,901 for patients with normal findings on neurological examination. Neurodiagnostic evaluation of headache patients with normal findings from neurological examination is expensive and was clinically unrewarding in this series.	lesions or systematic disease associated with headache	

Table 17 BRAIN: delay and diagnostic difficulties

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Becker et al 1993	USA and Canada	<p>The presenting signs and symptoms of intracranial disorders in primary care settings in the US and Canada were reported in this study to determine whether a more aggressive investigative strategy for patients with headache was justifiable.</p> <p>It aimed to study the signs and symptoms with which patients presented to primary care physicians and to estimate the extent to which a more aggressive investigation strategy for patients with headaches would have led to earlier diagnosis.</p> <p>Weekly return cards and a chart audit were used to collect data over 19 months on every patient who had a new diagnosis of intracranial tumour, subarachnoid haemorrhage, or subdural haematoma. Information was obtained concerning the severity and symptom characteristics of the headache, presence or absence of papilloedema, abnormalities on neurological examination, and presence or absence of other symptoms that could indicate the presence of intracranial problems (such as seizures, loss of consciousness, changes in strength, sensation, or neurological function, changes in headache pattern or severity that awakened the patient from sleep.</p>	58 practices			<p>A total of 25 new intracranial tumours, 17 new cases of subarachnoid haemorrhages, and 8 newly diagnosed subdural haematomas were reported during the recording period. Only 26 of the 50 patients with a subarachnoid haemorrhage, subdural haematoma, or tumour in this study reported a headache. Only one half of these patients had headaches, and no abnormalities were found on neurological examination of many. Many of the patients with headache had no abnormalities noted on neurological or fundoscopic examination. This was the case for nine (75%) of the patients with headache and intracranial neoplasms, five (45%) of those with a subarachnoid haemorrhage, and two of the three patients with an subdural haematoma. An additional three patients with tumours and three with subarachnoid haemorrhages had symptoms such as new seizures, or changes in function suggesting a neurological problem prior to their diagnosis. Three patients (one with a primary malignancy and two with benign tumours) had a change in headache pattern as their only ominous symptom.</p>	<p>This study based in primary care practices, did not identify a large number of patients for whom a clinically significant delay in diagnosis occurred. Instead, it revealed a highly selective clinical approach that correctly identified over 70% of the patients with headaches due to subarachnoid haemorrhage, tumour, or subdural haematoma.</p>
Husband 1998	UK	Study of the delay in presentation, diagnosis and treatment of malignant spinal cord compression	301 patients			<p>Unacceptable delay in diagnosis, investigation, and referral occurs in most patients with malignant spinal cord compression and results in preventable loss of function before treatment. Improvement in the outcome of such patients requires earlier diagnosis and treatment</p>	Prospective
Levack et al 2002	UK	o report details concerning symptoms (especially pain) preceding the development of malignant cord compression (MCC); delays between onset/reporting of symptoms and confirmed diagnosis of MCC; accuracy of investigations carried out	319 patients			<p>At diagnosis, most patients (82%) were either unable to walk or only able to do so with help. Pain was reported by nearly all patients interviewed (94%) and had been present for approximately 3 months (median=90 days). It was severe in 84% of cases, with the distribution and characteristics of nerve root pain in 79%. The site of pain did not correspond to the site of compression. Where reported, weakness and/or sensory problems had been noticed by the patient for some time before diagnosis (median intervals 20 and 12 days, respectively). Most patients reported early symptoms to their General Practitioner</p>	Prospective

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
						(GP) and diagnosis was established, following referral and investigation, approximately 2 months (median=66 days) later.	
Salander et al 1999	Sweden	A study of symptom development and obstacles to early diagnosis. A consecutive sample of patients with the diagnosis of malignant glioma and their spouses were interviewed about symptom development, help seeking and experiences of medical care in order to study the psychological aspects of brain tumour in patients	28 patients	Patients aged 17-80		Headache Seizure/falling Motor or sensory dysfunction Obstacles on the pathway to medical care	

Table 18 BONE and SARCOMA: signs and symptoms, including risk factors

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Bauer et al, 1999	Data from Norway Sweden and Finland.	This article summarised data from the Scandinavian Sarcoma Group Register for cases notified to the register 1986-1993.	3152			Among bone sarcomas, the commonest sites were the femur (34%), tibia (13%) and humerus (9%), and among soft tissue sarcomas the thigh (33%), trunk wall (15%) and lower leg (12%). 84% of patients with bone sarcoma and 58% of patients with soft tissue sarcoma had been referred to a sarcoma centre before open biopsy or surgical treatment.		
Bauer et al, 2001		Series of 1851 cases of adults (aged 16 or over) with soft tissue sarcoma of the limbs or trunk wall notified to the Scandinavian Sarcoma Group Register 1986-1997				The median age at diagnosis was 65 years. 41% of tumours were in the thigh, 14% the trunk wall, and 11% the lower leg. 32% were subcutaneous, 32% intramuscular, and 32% deep, extramuscular. The median recorded size was 7cm (six 6 cm among those under aged 40 increasing to 8cm in those aged over 80).		
DoH Referral guidelines 2000		Guidelines for referral of suspected cancer						Nationally recognised
Lawrence et al, 1987	USA	A national survey of the presentation of soft tissue sarcoma in adults (aged 18 or over).	Data from 504 hospital and involving 2355 patients. In the second study from 645 institutions and involving 3457 patients.			8.9% of the sarcomas were in the head and neck, 17.9% trunk, 13.1% the upper limbs, 46.4% the lower limbs, 12.5% retroperitoneal, and 1.3% in the mediastinum. The female to male ratio was 1.0:1.1 (the ratio in the entire US population was 1.0:0.95). 86% of patients were described as white, 10% black and 1% orientals (the same as the race distribution of the US population). Among this adult population, 20.7% were under 40 years, 27.6% 40-60 years, and 51.8% over 60. The major presenting symptom was the presence of a mass (64%); one third had pain or discomfort as the initial symptom. A family history of sarcoma occurred in 0.8% of patients, and a family history of other cancer was not unusually high in comparison with the general population.		
Rosenthal and Kraybill, 1999	USA	An authoritative review of soft tissue sarcomas in the context of primary care. The study examine a series of malignant soft tissue tumours treated in one centre in the years 1980-1989				24% of the tumours were malignant fibrous histiocytomas, 14% liposarcomas, 12% undifferentiated sarcomas, 8% leiomyosarcomas, 6% malignant schwannomas, 6% dermatofibrosarcomas, 5% synovial sarcomas, 5% fibrosarcomas, and 20% other. The review reported that soft tissue sarcomas usually present as an asymptomatic mass. Patients often wait an average of four months before seeking medical attention, and a definitive diagnosis may be delayed for another six months in 20% of patients. No one feature reliably indicates if a mass is a sarcoma. Two thirds are deep seated and larger than most		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						subcutaneous tumours. The physical examination may reveal a firm, non-tender mass that may seem well defined as a result of compression by surrounding tissues.		
Rydholm, 1997	Sweden	This article reported experience from a population-based case series of people with sarcoma. and the findings in patients with lipoma were compared to those with sarcoma.				Lipomas were almost non-existent in children, and in adults were uncommon in the hand, thigh, lower leg and foot. The median size of solitary subcutaneous lipomas was 3 cm, 80% being smaller than 5 cm. The annual incidence of lipoma was estimated at 1/1000. In comparing these findings with findings relating to the sarcoma case series, patient age and duration of symptoms did not differentiate patients with lipoma from those with sarcoma. The median sizes of subcutaneous and deep-seated sarcomas were 4 cm and 8 cm respectively. The solitary lipoma:sarcoma ratio was 150:1 for tumours <5 cm, 20:1 for tumours >5 cm, and 6:1 for tumours >10 cm. For deep-seated tumours, the lipoma:sarcoma ratio was 4:1. One third of the soft tissue sarcomas were in the thigh.		
Stefanovski et al, 2002	Italy		395	Patients treated for primary soft tissue sarcoma between 1985-1997 were identified using a cancer centre database.		The median age at diagnosis was 53 years (range 10-94 years). There were 172 females (43.5%) and 223 males (56.5%). The most common sites were lower limb (44.8%), upper limb (12.4%), and superficial trunk (12.2%). Fifty-nine % of the patients had lesions >5cm.		
Welsh Cancer Intelligence and Surveillance Network, 2002						Sarcomas are relatively rare cancers. The age-standardised incidence of primary bone cancer in Wales per 100,000 population in 2001 was 1.18 in males and 1.01 in females.		
Widhe and Widhe, 2000			102 patients with osteosarcoma and 47 patients with Ewing's sarcoma.	Patients aged up to 30 years old were identified from the Swedish cancer registry and records were obtained for those with osteosarcoma and with Ewing's sarcoma.		Eighty-six (58%) patients' first consultation had been with a general practitioner, and 42 (28%) with a doctor at an emergency ward. Eleven (7%) had presented to a school doctor, and eight (5%) a military doctor. Seventy-one (70%) patients with osteosarcoma and 34 (72%) with Ewing's sarcoma consulted because of regional pain. Twenty-six (25%) of those with osteosarcoma consulted with pain and a palpable mass, and seven (15%) of those with Ewing's sarcomas consulted with pain and a mass. Only four (4%) of those with osteosarcoma and five (11%) of those with Ewing's sarcoma did not report pain at the first medical visit. These patients all had a palpable mass only. Only twenty-one (21%) of those with osteosarcoma and nine (19%) of those with Ewing's sarcoma had pain at night. However, 87 (85%) of those with osteosarcoma and 30 (64%) of those with Ewing's sarcoma reported pain related to strain. Intermittent pain at rest was reported by 57 (56%) of		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						<p>those with osteosarcoma and 27 (57%) of those with Ewing's sarcoma.</p> <p>Forty-eight (47%) of patients with osteosarcoma and 12 (26%) of those with Ewing's sarcoma related the onset of symptoms to trauma occurring at about the time the symptoms began. The majority of the traumatic incidents were of a similar type and magnitude to those regularly experienced by participants in common sports.</p>		

Table 19 BONE and SARCOMA: investigations

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
American College of Radiology, 1999		Evidence review presented appropriateness criteria for imaging techniques for evaluating bone tumours. A routine X-ray was given the highest rating of appropriateness for investigation of patients with suspected bone lesions				When a classically benign-appearing lesion is detected on routine X-ray, additional studies may not be necessary unless surgical intervention is contemplated. When routine X-ray features are indeterminate or the lesion is more aggressive and considered to be potentially malignant, additional imaging studies are frequently required. MRI has been demonstrated to be superior to CT for staging bone tumours before treatment.		
Widhe and Widhe, 2000			102 patients with osteosarcoma and 47 patients with Ewing's sarcoma.	Patients aged up to 30 years old were identified from the Swedish cancer registry and records were obtained for those with osteosarcoma and with Ewing's sarcoma.		68 (67%) of patients with osteosarcoma and 28 (60%) of those with Ewing sarcoma had a radiograph organised at the first medical visit. However, the correct diagnosis was not established for all patients who had a radiograph. The radiograph was misinterpreted by the radiologist as normal or inconclusive for six (9%) of those with osteosarcoma and 12 (43%) of those with Ewing's sarcoma. When a radiograph was ordered at the first visit, the doctor's delay to diagnosis averaged eight weeks, compared to 19 weeks when a radiograph was not ordered (p <0.0001).		

Table 20 BONE and SARCOMA: delay

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Brouns et al, 2003		A retrospective review of patients with soft tissue sarcomas. The aim was to determine patient and doctor related delay in diagnosis and treatment of soft tissue sarcomas, as well as the reasons for this delay.	100	Consecutive hospital patients in Belgium referred for treatment of soft tissue sarcomas between May 1999 and May 2001. Only primary tumours were considered	Patients with sarcomas of the bone	<p>Patient delay 93 patients discovered the mass themselves: 53 % showed no delay, the median delay of the other 47 patients was 4 months (ranging from 1 to 240 months). Of the 93 patients, 16 had pain as a symptom: 31% (n = 5) of the patients who had pain as a symptom delayed, whereas 55% (n = 42) of the patients who had no pain delayed. No correlation with age or location was found.</p> <p>Doctor delay Doctor delay occurred in 27% with median of 6 months (range, 2 to 79 months). Most frequent reason for delay was misdiagnosis from the start, based only on clinical examination in 59%, on clinical examination and radiology (34%), or on biopsy (7%).</p> <p>Total delay Of the high-grade tumours, 85% were diagnosed within 6 months, 50% without delay. Low-grade tumours either had no delay (50%) or a delay longer than 6 months (45%).</p>	
Sneppen and Hansen, 1983			84 cases of osteosarcoma and 40 cases of Ewing's sarcoma	consecutive cases of osteosarcoma and consecutive cases of Ewing's sarcoma admitted to a specialist tumour centre in Denmark between 1962 and 1979	Parosteal osteosarcomas and extraskelatal osteosarcomas were primarily excluded	<p>In the osteosarcoma group, the total delay averaged 6.4 months, ranging from two weeks to three years. Total delay was not influenced by gender, or anatomical site. Total delay was shorter for patients under 20 years old (4.7 months vs. 9.1 months, p<0.001). For the Ewing's group the total delay averaged 9.6 months, ranging from four weeks to four years. Total delay was not influenced by gender or age. Tumours involving the upper limbs were diagnosed earlier than tumours involving the legs (2.6 months vs. 14.3 months, p=0.02-0.01).</p> <p>In both groups patients with constant pain had relatively short delay, although the difference was only significant for patients in the Ewing group (3 months delay vs. 12.6 months, p=0.05-0.02). The presence of a swelling was also associated with a shorter total delay both for osteosarcomas and Ewing's sarcomas (p=0.05-0.02, and p=0.10-0.05 respectively). Patients with a relatively long or relatively short delay had the same prognosis.</p>	

Table 21 CHILDREN: signs and symptoms, including risk factors

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Abramson et al 1998	Hospital. USA	Retrospective study to describe the presenting signs of retinoblastoma	1265 children	Children with a diagnosis of retinoblastoma		Thirty-two distinct presenting signs of retinoblastoma were identified, the most common of which were leukocoria (56.2%), strabismus (23.6%), poor vision (7.7%) and family history (6.8%). Leukocoria, the most common presenting sign, was associated with more advanced disease (p<0.005). Strabismus correlated strongly (p<0.005) with macular involvement. All eyes with strabismus proved to have either tumour in the macula or a retinal detachment at the macula. No statistically significant correlation was found between laterality, sex or race and any presenting sign or between survival and any intraocular presenting sign.		Retrospective. Very large study.
D0H, Referral guidelines for suspected cancer 2000		National guidelines based on expert opinions and consensus, after consideration of the limited evidence available				<p>Leukaemia: Often present with relatively short history (weeks) with pallor, fatigue, irritability, fever, bone pain and bruising/petechiae. 70% have hepatosplenomegaly; >50% have lymphadenopathy.</p> <p>Brain: headache (65-70%), vomiting (65-70%), changes in mood/personality (45-50%), squint (20-25%), deterioration in school performance (20-25%), growth failure (20%), or in infants, rapidly increasing head circumference</p> <p>Lymphomas: Hodgkin's disease: usually presents with non-tender cervical/supraclavicular lymphadenopathy. Natural history is long (months). Only minority have systemic symptoms. Non-Hodgkin's lymphoma: lymphadenopathy and/or disease in mediastinum or abdomen. Rapid progression of symptoms.</p> <p>Neuroblastoma: Majority have symptoms of metastatic disease. Infants <1yr may have localised abdominal or thoracic masses; very young infants (< 6 months) may have rapidly progressive intra-abdominal disease. Wilms' tumour (nephroblastoma)</p>		Nationally recognised guidelines, but no explicit link between the limited evidence base and the consensus recommendations

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						<p>Unilateral abdominal mass +/- pain. Haematuria (rare) Soft tissue sarcoma Mass at almost any site Bone tumours Limbs are most common sites. Persistent localised bone pain. Retinoblastoma Family history (in approximately 15% cases). White pupillary reflex. Squint Gonadal tumours Testicular/paratesticular masses can be difficult to differentiate – any non transilluminable mass associated with the testis is significant. Ovarian tumours can be associated with precocious puberty. abnormal blood count If reported as requiring urgent further investigation. Petechiae/purpura. Fatigue in a previously healthy child when combined with either of the following: generalised lymphadenopathy, hepatosplenomegaly. Bone pain especially if it is: diffuse or involves the back, persistently localised at any site, requiring analgesia, limiting activity. Lymphadenopathy: non tender, firm/hard and >3 cms in maximum diameter progressively enlarging associated with other signs of general ill health, fever and/or weight loss involves axillary nodes (in the absence of any local infection or dermatitis)or supraclavicular nodes seen as a mediastinal or hilar mass on chest x-ray (particularly if no evidence of previous local infection) Headache of recent origin with one or more of the following features increasing in severity or frequency noted to be worse in the mornings or causing early waking associated with vomiting associated with neurological signs (e.g. squint, ataxia)</p>		

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						associated with behavioural change or deterioration in school performance. Soft tissue mass: any mass which occurs in an unusual location particularly if associated with one or more of these: shows rapid or progressive growth -size > 3 cms in maximum diameter fixed or deep to fascia associated with regional lymph node enlargement		
Dobrovoljac et al 2002	Childrens' hospital. Switzerland	Retrospective study to identify factors related to delays in diagnosis	252 children	Children admitted with primary brain tumours		Initial symptoms were (in decreasing order of frequency) headache, nausea/vomiting, seizures, behavioural changes, ataxia, squint/diplopia, lethargy, hemiparesis/quadruparesis, head tilt, anorexia, growth failure, sleep disturbance, polyuria/polydipsia, visual loss, weight loss, facial nerve palsy, enlargement of the head, cranial neuropathies other than III, IV, VI, VII, gaze depression/separation of cranial sutures/bulging fontanelle, dizziness, nystagmus, papilloedema, amenorrhoea, proptosis. Symptoms and frequencies changed when analysed by age of the child		Retrospective. Large study. Symptoms at initial presentation described.
Farwell et al 1984	Community – regional tumour registry. USA	Retrospective study of CNS tumours in adolescents compared with younger children	144 adolescents	Children aged 13 to 19 yrs with diagnosis of CNS tumour (intracranial or intraspinal)		Presenting symptoms included those that resulted from increased intracranial pressure as well as those that were local effects of tumours. The most common symptoms were headache (N=65), nausea or vomiting (N=53) and diplopia (30). Visual disturbances such as blurred vision (N=18), dim vision or field deficits were next in frequency followed by ataxia (N=15) and then mental status change (N=8) or longstanding retardation. Less common symptoms included paresis (N=7) and vertigo (N=7). At the time of diagnosis, papilloedema was present in 41 patients.		Retrospective. Population based.
Farwell et al 1978	Community – regional tumour registry. USA	Retrospective study of intracranial neoplasms, including presenting symptoms	54 infants	Infants ≤18 months at diagnosis of intracranial neoplasm		Infants presented at diagnosis with vomiting (47%), increasing head size (32%), lethargy (19%), convulsions (13%), paresis (9%), cranial nerve palsies (9%) and ataxia (6%). The physical findings at diagnosis indicated that 20 patients had an increased head circumference. A bulging fontanelle was reported in 12		Retrospective. Population based.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						cases (27%). Eleven infants (25%) had cranial nerve palsies. Papilloedema (16%) and nuchal rigidity (16%) were each seen in seven instances. Two patients (4%) were comatose and another five (16%) had a diminished level of consciousness. Other findings included ataxia (7%), nystagmus (11%), hemiparesis (9%), hyperreflexia (16%), hypertonia (9%), irritability (6%), hyptonia (11%), extracranial masses (4%) and hyperalertness (6%). Vomiting was the only symptom, besides enlargement of the head that occurred in more than six children. The loss of a previously acquired skill such as rolling over, sitting or crawling was a symptom observed in seven patients, and in two of these, it was the only symptom in addition to abnormal growth of the head. The physical findings were more varied than the symptoms. Nearly half of the children had an increased head circumference, often accompanied by a bulging fontanelle or prominent veins over the scalp. Papilloedema was noted in two children. Cranial nerve palsies occurred in infants with tumours in all locations. However, nystagmus occurred in cerebral hemisphere or brain stem tumours only and was not found in cerebellar tumours.		
Flores et al 1986	University hospital;. USA	Retrospective study to compare time to diagnosis in children with primary brain tumours, Wilms' tumour, or leukaemia	79 children	Children diagnosed with primary brain tumours		Common presenting symptoms and signs in children with brain tumours were ataxia and abnormalities in gait observed in the zero to five year old patients. Headaches were described more frequently in the six to 20 year old age group. Seizures were observed in the six to 20 year old group, while none were recorded among children 0 to 5 years of age. Nausea and vomiting frequently occurred in all groups.		Retrospective
Golden and Feusner 2002	Children's hospital. USA	Retrospective study to give guidance on evaluation and diagnosis of malignant abdominal masses in children	150 children	Children diagnosed with malignancy of the abdomen		Of children either younger than one year or older than ten years, 26% (11/43) had normal abdominal examinations at diagnosis, compared with only 9% (7/78) of all the remaining children. The authors investigated how these masses were characterised on physical examination. Not all children had every aspect of their		Retrospective.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						masses described fully, but patterns could be identified: 70% (49/70) were distinguished as nontender, 79% (11/14) were recorded as being nonmobile, and at least 87% (61/70) were firm. Not all malignant masses were defined as nontender.		
Hasle 2001		Narrative review of malignancies in children with Down's syndrome				Overall risk of cancer was not significantly increased in individuals Down's syndrome. However, the distribution of tumour types in Down's syndrome differed from the pattern in non-Down's children. Leukaemia constituted 95% of cases of cancer in children with Down's but only 34% of non-Down's children.		Narrative review.
Honig and Charney 1982	Children's hospital. USA	Retrospective study to establish practice guidelines	105 children	Children with a final diagnosis of brain tumour		Headaches were occipital in location in 16 children (28%), unilateral in 13 (22%) and diffuse in 29 (50%). 32 children (67%) were either awakened from sleep by the pain or were in pain on arising. Eight of 61 children had unusually severe or prolonged headaches and 19 (31%) had changes in headache frequency or severity. Vomiting was described as intermittent in 26 of 72 (36%), daily in eight of 72 (11%) and pernicious in two of 72 (3%). The vomiting was described as intermittent in 26 of 72 (36%), daily in eight of 72 (11%) and pernicious in two of 72 (3%). The vomiting increased in frequency (four patients) or first began (11 patients) following the onset of the headaches in 15 of 72 children (21%). In nine of these 15, the change coincided with increased frequency or severity of the existing headache pattern. Five patients were vomiting prior to the onset of their headaches. 68 children (94%) with headaches had neurologic and/or ocular signs at the time of diagnosis. In 60 of these, signs developed following the onset of their headaches. Thirty-three of 60 (55%) had findings within two weeks and 51 (85%) had an abnormality on physical examination within two months of the onset of their headaches. Within four months, 53 of 60 (88%) had neurological and/or ocular signs. The numbers of		Retrospective.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						patients with ocular signs and symptoms were papilloedema (42), diplopia (11), decreased acuity (8), squint (9), nystagmus (5), optic atrophy (4), blurred vision (3), blindness (2), failure of upward gaze (2), anisocoria (1), optic atrophy on side of tumour and papilloedema of the opposite disc (1).		
Jonsson et al 1990	Children's medical centre. USA	Retrospective study to assess relationship between bone pain and haematological findings at diagnosis of acute lymphoblastic leukaemia (ALL)	296 children	Children diagnosed with ALL		Haematologic indices were relatively normal in patients presenting with musculoskeletal signs and symptoms as prominent presenting manifestation. Patients with prominent bone pain could experience diagnostic delay because haematological values appeared normal. Haemoglobin and platelets were higher, blast cell and leucocyte counts lower among children with severe bone pain. Statistically significant differences found between groups for haemoglobin concentration (p<0.001), leukocyte count (p=0.014), absolute neutrophil count (p=0.001), percentage circulating blast cells (p=0.009) and platelet count (p<0.001).		Retrospective. Not primary care population based. Large study.
Jooma et al 1984	Children's hospital. UK	Retrospective study to analyse cases of children with intracranial tumours	100 infants aged under 1 yr	Infants admitted with intracranial tumours.	Infants with posterior fossa dermoid tumours, and orbital tumours	Most common symptoms reported by parents were vomiting and alteration of psychomotor development. In 7 patients a febrile illness preceded more specific symptoms of raised intracranial pressure, whereas in 6 a head injury had recently occurred. A head tilt was noted in 7 infants with infratentorial tumours and in 2 each of the infants with hemispheric and axial lesions. Macrocrania and signs of raised intracranial pressure were recognised in a majority of the children. 10 patients with suprasellar tumours had rotary nystagmus or bizarre eye movements. Behavioural disturbances with irritability, somnolence and indifference to surroundings were commonly reported and were important if combined with loss of a previously acquired motor skill or arrest of development. The following signs were observed in infants: papilloedema (n=36), optic atrophy (n =10), nystagmus or abnormal eye movements (n =22), sixth		Retrospective.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						nerve palsy (n =17), seventh nerve palsy (n =13), altered limb tone (n =35), hemiparesis (n =16), truncal ataxia (n =10), abnormal neck posture (n =20), neck stiffness (n =9).		
Keene et al 1999	Children's hospital. Canada	Retrospective study to describe the clinical patterns associated with childhood brain tumours	200 children	Children aged under 18 years at diagnosis with primary intracranial neoplasm, and lived within the study catchment area		<p>Hemispheric tumours occurred in 52 patients. The presenting signs were seizures 60%, headache 37%, vomiting 23%, changes in behaviour or personality 11%, facial asymmetry 9% and visual difficulties 6%. Initial findings on examination included one or more of the following: no abnormalities (51%), hemiplegia 34%, signs of increased intracranial pressure 23%, cranial nerve dysfunction 3% and macrocrania 3%. Supratentorial axial or midline tumours occurred in 50 patients. The presenting signs for tumours arising from axial structures included one or more of the following: non-specific headache 60%, polyuria 35%, non-specific malaise 10%, short stature 10% and visual difficulties 5%. Initial examination at the time of diagnosis included signs of increased intracranial pressure 30%, visual field disturbances 25%, optic atrophy 15% and Parinaud's sign 15%.</p> <p>Cerebellar tumours were present in 74 patients. The presenting symptoms included vomiting, headache 62%, and incoordination 55%. The frequency of clinical signs included ataxia 69%, increased intracranial pressure 57%, nystagmus 31%, head tilt 14%, cranial nerve palsies 28% and macrocrania 10%. Brainstem tumours affected 19 children. Patients experienced gait difficulties 83%, squint 50%, headaches 25%, vomiting 25% and swallowing difficulties 8%. The initial examination included findings of cranial nerve VI dysfunction 67%, ataxia 50%, cranial nerve VII dysfunction 42%, nystagmus 33%, hemiplegia 33% and head tilt 33%.</p>		Retrospective. Large study.
Linet et al 2003		Review of risk factors for sarcomas, brain and haematological				See tables in full guideline		Narrative review, linked with evidence base

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
		cancers						
Mag et al 1999	University hospital. Malaysia	Retrospective study to describe presenting features and prognostic significance	78 children	Children ≤12 yrs admitted with new diagnosis of neuroblastoma		The main presenting signs and symptoms in decreasing order were pallor, fever, abdominal mass, weight loss and bone/joint pain. Weight loss was reported in 36% and bone or joint pain in 33% of patients. Other presenting symptoms or signs were bleeding, infection or sepsis, seventh nerve palsy and bilateral leg swelling.		Retrospective.
Mehta et al 2002	Paediatric neurosurgical centres. Canada	Retrospective and prospective study to determine the tiem required for diagnosis and important associated factors	104 children	Children ≤17 yrs diagnosed with brain tumour, and lived in the study area	Children referred from outside the region. Neoplastic lesions that involved the spinal cord/leptomeninges. Children with Neurofibromatosis Type I, and only an optic pathway tumour that did not need treatment	<p>9 children (66%) exhibited vomiting or nausea as a presenting symptom. Nine of those children did not experience associated headaches. Five of these nine patients experienced vomiting for more than one month. 66 of the children (63%) complained of headaches or exhibited behaviour that indicated its presence (such as clutching the head). 37% (seven of 19) children less than four years of age exhibited behaviour that could be positively confirmed as indicating headaches. Among older children, 76% (28 of 37 children) and 67% (31 of 46 children) of those four to eight and nine to 17 years of age respectively had complaints of headaches as one of their presenting symptoms.</p> <p>Among the 66 children with histories of headaches, 85% (56 of 66 children) exhibited evidence of either nausea or vomiting at some point during their histories.</p> <p>Many did not experience headaches that increased in intensity, duration or frequency. 23 patients (22%) did not exhibit evidence of headaches, nausea or vomiting. Among these 23 cases, 18 presented with either a seizure or a focal neurological deficit. The most common neurological findings were focal weakness and cranial nerve dysfunction.</p> <p>Behavioural changes, failure to reach certain milestones and incidental imaging findings were responsible for identification in the remaining five cases. Of the 104 children, 52 exhibited behavioural changes, which were most often described as changes in temperament.</p>		Some prospective element.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
Soule and Pritchard 1977	Selected review of cases from literature and personal practice (clinic based). USA	Retrospective study to describe clinicopathologic results in children with fibrosarcoma	110 children	Children with a diagnosis of fibrosarcoma with histological results	Children with revised histological diagnosis. Lesion located in the orbit, dura, or base of the skull	The primary symptom of most patients was that of a mass or swelling in the soft tissues. Most of the lesions were enlarging, and with the exception of the congenital tumours were known to have been present from a few weeks to four years. Four patients first complained of discomfort or pain before a tumour was apparent. In some the skin had become tense, shiny and red. One congenital lesion became ulcerated and exhibited partial destruction of the adjacent tibia and fibula by the 13th day of life.		Retrospective. Selected cases from literature.
Stiller 2002		Narrative review of the epidemiology of cancer in adolescents				<p>The risk of both acute lymphoblastic leukaemia and acute non-lymphocytic leukaemia throughout the age range 5-29 years among people with Down's syndrome is approximately 10 times that in the non-Down population. Down's syndrome also appears to be associated with an increased risk of germ cell tumours of the testis and brain and possibly of other sites but the risk of most other solid tumours is lower than in the general population. Neurofibromatosis carries an increased risk for central nervous system tumours and soft tissue sarcomas.</p> <p>The considerable variation in the incidence of Ewing sarcoma, with its extreme rarity among black and east Asian populations suggesting a strong genetic component to its aetiology.</p> <p>The risk of Hodgkin's disease in adolescents and young adults who have an affected sibling is approximately seven times that in the general population. Epstein-Barr virus has a role in the development of some cases, though its relations with histologic subtype, age and ethnic group are complex. Hodgkin's disease is more common among adolescents in populations of higher socio-economic status.</p> <p>The thyroid gland is especially sensitive to the carcinogenic effects of ionising radiation, with the highest risk for young age at exposure; the excess risk of thyroid cancer persists for at least 40 years after</p>		Narrative review,

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						irradiation.		
Thulesius et al 2000	Community - regional tumour registry. Sweden	Retrospective study to describe the diagnostic process of childhood malignancies, from initial symptoms until diagnosis and treatment.	68 children	Children with tumours reported to the regional tumour registry	Excluded if tumours could not be classified as malignant, disease was congenital, child diagnosed outside the study area, or incomplete records	Initial symptoms were for Leukaemia (in decreasing order of frequency) fatigue, upper respiratory tract infection, fever, abdominal pain, joint pain, lymphadenopathy, headache, anorexia Brain tumours (in decreasing order of frequency) headache, vomiting, visual problems, convulsions, other neurological symptoms		Retrospective. Small sample, But primary care perspective.
Tomita and McLone 1985	Children's hospital. USA	Retrospective study to describe the distribution of brain tumours, their presentation and results of treatment	100 infants	Infants diagnosed with intracranial tumours in the first 24 months of life		Approximately 50% of group 1 with either infratentorial or supratentorial tumours showed macrocephaly beyond the 95th percentile, whereas 25% of group 2 had macrocephaly. Approximately 72% of the anterior fontanelles of the patients harbouring either infratentorial or supratentorial tumours were full, bulging or tense. Hydrocephalus was almost invariably present in association with infratentorial tumours, but its incidence was less in cases with supratentorial tumours (62%). Papilloedema was infrequent despite the high incidence of hydrocephalus and macrocephaly. The incidence of papilloedema was 26.3% in the cases with infratentorial tumours and 18.4% in the cases with supratentorial tumours in group 1, and was 52.6% and 25.0% respectively in group 2.		Retrospective
Wdhe and Widhe 2000	Community – national cancer registry. Sweden	Retrospective study to identify early symptoms of osteosarcoma and Ewing's sarcoma	149 individuals	People ≤30 yrs with diagnosis of osteosarcoma or Ewing's sarcoma	People with tumours in the skull or ribs	Most patients consulted because of regional pain alone or in combination with a palpable mass. A palpable mass was reported at the first visit in 40 (39%) of the patients with osteosarcoma and 16 (34%) of those with Ewing's sarcoma. Four patients with osteosarcoma and five with Ewing's sarcoma did not report pain at the first medical visit and had a palpable mass only. 21 (21%) of the osteosarcomas and nine (19%) of the Ewing's sarcomas caused pain at night. 87 (85%) of the patients with osteosarcoma and 30 (64%) of those with Ewing's sarcoma reported pain related to strain. Intermittent pain at rest was reported by 57 (56%) and 27 (57%) patients respectively. 48 (47%) of the patients with osteosarcoma and 12		Retrospective. Population based

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Gold Std	Quality
						(26%) of those with Ewing's sarcoma related the onset of symptoms to trauma occurring at about the time the symptoms began that were of a similar type and magnitude as those experienced regularly in common sports. Tendinitis was the most common initial misdiagnosis for 32 (31%) of the osteosarcomas. Patients with Ewing's sarcoma often reported relapsing fever and periods of pain that were followed by few or no symptoms, which misled doctors into believing the condition, was resolving spontaneously.		
Wilson and Draper 1974	Community – national cancer registry. UK	Retrospective? study to describe the natural history and prognosis for neuroblastoma	487 children	Children <15yrs with diagnosis of neuroblastoma with histological confirmation		The signs and tumours were varied because they arose in a range of sites. Up to three symptoms were recorded for each case. Abdominal swelling was most commonly a symptom in the youngest age group, its frequency decreasing with increasing age. The same relationship was evident to a lesser extent for the symptoms of breathlessness and stridor. Conversely, pain was a relatively uncommon symptom in very young children. It was more often reported by older children though this was presumably partly due to the greater ease in eliciting this symptom. Those symptoms related to nerve involvement were also more often reported for older children. There was little difference between the two sexes in the type of symptom reported. The figures reflected the infrequent incidence of abdominal tumours (of the adrenal, abdominal sympathetic ganglia and liver) and thoracic tumours in the youngest age groups while those occurring in the spinal canal and brain were more frequent among older children.		Retrospective? Some of the analysis did include data on 152 children without histological confirmation

Table 22 CHILDREN: delay

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Butros et al 2002	Specialist cancer centre. USA	Retrospective study to identify reasons for delayed diagnosis of retinoblastoma	57 children	Children presenting with newly diagnosed retinoblastoma	Children with a family history of retinoblastoma.	77% of patients delayed seeking treatment. Primary care physicians delayed referral in 30% of cases (n=14); in all of these patients, parents stated that they reported the presenting signs to the child's physician, who reassured the parents of normalcy or made a diagnosis different from retinoblastoma, neither of which led to an immediate referral to ophthalmology; 13 (925) of these patients had a median delay of 3.75 months. No adverse consequence of delayed diagnosis could be clearly established, but a trend towards eye loss being associated with longer delays in patients with bilateral retinoblastoma was noted.	Retrospective.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Dobrovoljac et al 2002	Childrens' hospital. Switzerland	Retrospective study to identify factors related to delays in diagnosis	252 children	Children admitted with primary brain tumours		<p>The median age at diagnosis for all patients was 6.3 years (range 0.0-16.9 years). The median pre-diagnostic symptomatic interval was 60 days (range 0-3010 days) with a parental delay of 14 days (range 0-2310 days) and a doctor delay of 30 days (range 0-3010 days). Only 81 (32%) of the 252 brain tumours were diagnosed within 30 days of onset of signs/symptoms. Age had a statistically significant correlation with PSI (Pearson's correlation $r = 0.32$, $P < 0.0001$) with shorter PSI for younger children. The parental delay was significantly shorter for younger than older children (Pearson's correlation $r = 0.16$, $P < 0.05$). However, doctor delay did not correlate significantly with age. Patients with signs/symptoms of raised intracranial pressure had a statistically shorter PSI (median 60 vs. 152 days; $P=0.007$, Mann-Whitney test) and shorter doctor delays (median 20 versus 60 days; $P=0.02$, Mann-Whitney test) than children without increased intracranial pressure. However, the parental delays in these two groups of patients were similar. Gender did not correlate with PSI, parental delay or doctor delay. During the study period of 20 years, there were no statistically significant changes in the PSI or parental delay. However, doctor delay decreased significantly (Pearson's correlation $r = -0.26$, $P < 0.001$). In 75 (45%) patients, doctor delay was more than 30 days, indicating misinterpretation of initial signs and/or symptoms. Common diagnostic difficulties included the correct interpretation of headache, nausea/vomiting, seizures, behavioural changes and squint/diplopia.</p>	Retrospective. Large study.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Edgeworth et al 1996	Neurosurgical unit. UK	Retrospective study to identify where and how delay in diagnosis occurs	74 children	Children with primary brain tumours aged 0 to 16 yrs		<p>One month after symptom onset 68% had not at that stage been correctly diagnosed, and after 6 months 20% were still not diagnosed. The interval between symptom onset and diagnosis was shortest for children aged 0-2 years. The mean (SD) duration of signs and symptoms before parents consulted a health professional was 3.0 (13.4) weeks (range 0-104 weeks). In 92% of cases parents took their child to a doctor within one month of symptom onset. The mean (SD) duration of clinical history between initial consultation with a health professional and clinical diagnosis was 16.0 (24.4) weeks (range 0-130 weeks). One month after initial consultation 58% of children had not yet been diagnosed and 18% were yet to be diagnosed six months after initial consultation. Before diagnosis, there were a total of 257 (mean 4.6, range 1-12) consultations with professionals in the 56 children for whom this information was available. Of these, 45.5% were with a general practitioner and 9% with an accident and emergency department. 62% of children were seen on four or more occasions before the correct diagnosis was made. Doctors were unable to make a diagnosis in 19% of children and in a further 15% could find nothing wrong. Symptoms and signs were confused with those of migraine in 14 children. Vomiting occurred in 65% and headache in 64% of the children. There was no relationship between site of tumour or duration of clinical history and incidence of psychological difficulty for any age group. Some parents felt that poor communication between professionals (including opticians, psychologists and teachers) had contributed to the delay in diagnosis. Many parents reported that professionals looked at the presenting symptoms of each consultation in isolation.</p>	Retrospective

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Fajardo-Gutierrez et al 2002	City hospitals. Mexico	Retrospective study to assess time to diagnosis in children with cancer	4,940 children	Children with diagnosis of cancer	Records that were illegible	<p>The time to diagnosis for all types of cancer ranged from one to five months. The shortest was for leukaemia (median = one month) and the longest for Hodgkin's disease, retinoblastoma and unspecified malignant neoplasms (median = five months). The association between time to diagnosis and age at diagnosis was different. When grouped by age in years as < 1 (the reference age), 1-4, 5-9, and 10-14; the risk of a delayed time to diagnosis increased with age ($\chi^2 = 29.12$; $P = 0.0001$), the highest being for the 10-14 group (OR= 1.8; 95% CI = 1.4-2.3). Risk for masculine gender and delayed time to diagnosis was low (OR = 1.1; 95% CI = 1.0-1.3). Parental educational level also influenced time to delay, and there was risk of delayed time to diagnosis in the lower compared to the higher educational level group (OR = 1.4; 95% CI = 1.1-1.8 for fathers, and OR = 1.5; 95% CI = 1.2-2.1 for mothers). The population without National Social Security had greater risk of delayed time to diagnosis (OR = 1.3; 95% CI = 1.1-1.4). The risk of delayed time to diagnosis varied among the different cancer types, but in general, age at diagnosis was the variable with greatest influence.</p> <p>Extrapolation of results to a UK setting requires caution because of differences between health care systems. However, findings on influence of age in diagnostic delay support findings from other studies.</p>	Retrospective

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Flores et al 1986	University hospital, USA	Retrospective study to compare time to diagnosis in children with primary brain tumours, Wilms' tumour, or leukaemia	79 children	Children diagnosed with primary brain tumours		The mean interval from the appearance of symptoms to diagnosis in patients with brain tumours was 26 weeks, with a median of six weeks. Patients less than five years of age who had infratentorial tumours and patients with more severe grades of signs and symptoms were diagnosed earlier. For patients with acute leukaemia the mean time to diagnosis was 4.5 weeks. Of 123 patients with acute leukaemia, 100 (80%) were diagnosed within four weeks. Of the patients with Wilm's tumour, 38 (84%) were diagnosed within four weeks, and 25 (55%) in the first week. The mean duration of symptoms for patients with Wilm's tumour was 2.8 weeks. Of the three types of malignant neoplasms, the primary brain tumour had the longest delays in diagnosis (P<0.0001).	Retrospective
Goddard et al 1999	Hospital. UK	Retrospective study to establish the extent of diagnostic delay and associated risk factors	100 children	Children with retinoblastoma	Children with family history of retinoblastoma. Those with dysmorphic features noted before diagnosis, or lived outside the UK	Older children were referred more rapidly than younger children. In children who presented to a health visitor with a squint, there was a significantly greater delay in diagnosis. Delay was associated with parental distress and increased the risk of local tumour invasion.	Retrospective.
Haik et al 1985	Specialist centre. USA	Retrospective study to describe the diagnostic delays in diagnosis of retinoblastoma	250 children	Children with diagnosis of retinoblastoma	Insufficient data	Significant percentages of primary care physicians (47% for children with no positive family history, and 25% for children with positive family history) delayed referral for a significant period of time (19 weeks for both groups). The mean time from first symptom to seeking the opinion of a primary care physician was two weeks (range 1-8 weeks) for children with a positive family history, and five weeks (range 1-100 weeks) for children with a negative family history.	Retrospective

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Mehta et al 2002	Paediatric neurosurgical centres. Canada	Retrospective and prospective study to determine the time required for diagnosis and important associated factors	104 children	Children ≤17 yrs diagnosed with brain tumour, and lived in the study area	Children referred from outside the region. Neoplastic lesions that involved the spinal cord/leptomeninges. Children with Neurofibromatosis Type I, and only an optic pathway tumour that did not need treatment	The median time from symptom onset to diagnosis was 3 months. The mean time to diagnosis was 7.3 months (95% confidence interval [CI], 5.0-9.7 months), and only 41% of cases were correctly diagnosed within three visits to various physicians. At least 30% of children required more than seven visits to physicians. Time to diagnosis was not significantly affected by either sex or age. Tumours located in the brainstem required significantly longer times for diagnosis, compared with those located elsewhere (mean = 11.8 months [95% CI, 3.1 -20.4 months] versus 6.6 months [95% CI, 4.2 -9.0 months], P=0.014). Medulloblastomas as a group exhibited significantly shorter diagnostic times, compared with other pathological subtypes (mean = 3.8 months [95% CI, 2.0-5.6 months] versus 8.4 months [95% CI, 5.4-11.3 months], P = 0.006).	Some prospective element.

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Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Pollock et al 1991	Unclear. USA	Retrospective study to assess the relationship between delay in diagnosis and associated factors	2665 children	Children with newly diagnosed lymphomas or solid tumours who were treated using defined protocols	Children with no symptoms at diagnosis, symptom information was incomplete.	Median lag time ranged from a low of 21 days for children with neuroblastoma to a high of 72 days for those with Ewing's sarcoma. A statistically significant difference was found among tumour types ($P < 0.001$). Age was positively and significantly correlated with lag time ($P < 0.001$) for all tumour types except Hodgkin's disease ($P=0.58$); that is, as age increased, lag time increased. Gender was significantly associated with lag time only for non-Hodgkin's lymphoma ($P=0.02$), for which girls had longer lag times. Race was significantly associated with lag time only for osteosarcoma ($P=0.002$), for which white children had longer lag times. With the exception of the Hodgkin's disease group, age remained a significant independent predictor of lag time for all diagnostic groups ($P < 0.05$). Gender remained significantly associated with lag time for non-Hodgkin's lymphoma ($P=0.02$). The multivariate analysis also revealed a significant association between gender and lag time for Ewing's sarcoma ($P=0.02$). The association differed in these two tumour groups; girls had longer lag times in the non-Hodgkin's lymphoma group but shorter lag times in the Ewing's sarcoma group. Race also continued to have a statistically significant association with lag time only for osteosarcoma ($P=0.02$). Patients with shorter lag time for brain tumour had a 67% frequency of gait abnormalities and ataxia, compared with 59% for those with a longer lag time ($P=0.13$), but were similar with respect to other common symptoms of brain tumour. For neuroblastoma, abdominal masses were more common in patients with shorter lag times (31% vs. 19%; $P = 0.037$). Patients with shorter lag time for non-Hodgkin's lymphoma had a higher frequency of abdominal masses (13% vs. 5%; $P=0.06$) and of breathing difficulty and coughing (32% vs. 15%, $P=0.007$).	Retrospective

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Saha et al 1993	Childrens' hospital. UK	Retrospective study to examine the time to diagnosis and associated factors	236 children	Children aged 0 to 15 yrs with a diagnosis of cancer	There was no significant difference in the lag time between males and females. Age was a significant predictor for lag time, with older children having a longer lag time. The mean lag time varied from 2.8 weeks for nephroblastoma to 13.3 weeks in brain tumour. One way analysis of variance showed diagnostic group to be significant for length of lag time, (P <0.001). Both age and diagnostic group remained individually significant in a multivariate analysis. The difference in lag time for children with acute leukaemia was not significantly related to a presenting white cell count of $\geq 50 \times 1000^3/l$ compared to those presenting with a lower count. The difference in lag time between the stages in all diagnostic cancer groups was not significant either. The authors failed to find a positive correlation between lag time and outcome.		Retrospective
Sloper 1996	Specialist hospitals. UK	Study (interviews and questionnaires) to investigate parents' responses to a diagnosis and treatment of cancer in their child	98 families	Children with cancer aged <18yrs, living at home, diagnosed in part 6 months. Parents could speak adequate English. Family included a sibling aged between 8 and 16 yrs.		Over half the families (57%) reported a delay in diagnosis. There were differences in delay between different diagnostic groups: the mean interval was shortest for children with leukaemia (4.8 weeks); longer intervals were reported for lymphomas (17.4 weeks), solid tumours (19.4 weeks) and central nervous system tumours (24.2 weeks). There was a significant relationship between age of the child and reported delay, with older children experiencing more delay ($r = 0.243$, $p=0.018$, $n= 94$), but no significant associations with other demographic variables of social class or single parenthood. A common theme was the feeling that parents' own concerns and knowledge of their child were not listened to or accepted by health professionals. Parents also voiced concerns in cases where an initial misdiagnosis was made and this was not fully re-assessed in view of continuing or increasing symptoms.	Qualitative description. No link with clinical perspective.

DRAFT FOR FIRST CONSULTATION

Author	Setting	Description	No.	Inclusion	Exclusion	Results	Quality
Thulesius et al 2000	Community - regional tumour registry. Sweden	Retrospective study to describe the diagnostic process of childhood malignancies, from initial symptoms until diagnosis and treatment.	68 children	Children with tumours reported to the regional tumour registry	Excluded if tumours could not be classified as malignant, disease was congenital, child diagnosed outside the study area, or incomplete records	Mean age at diagnosis was 7.8 years. Leukaemia was the diagnosis in 25 children (39%), and brain tumours in 22 children (34%). Parent's delay was shorter than four weeks in 22 of 25 children with leukaemia, compared with nine of 20 children with brain tumours ($\chi^2 = 9.59$, $P = 0.002$). For two children with leukaemia, parent's delay was three months or more with a common feature of diffuse and gradually aggravating symptoms and signs such as fatigue, diarrhoea and upper respiratory tract infections. Doctor's delay was <two weeks for 17 of 25 children with leukaemia, compared with 7 of 21 children with a brain tumour ($\chi^2 = 5.50$, $P = 0.019$). Lag time was four weeks or less for 19 of 25 children with leukaemia, compared with 6 of 20 children with a brain tumour ($\chi^2 = 9.52$, $P = 0.002$). Median lag time also was 3 weeks ($r=0-15$) for children with leukaemia, and 9 weeks (range 1-199) for children with brain tumours (mean lag time was 3.8 [SD = 3.8] and 19.8 weeks [SD = 43.0], respectively). The mean number of visits to a general practitioner in the year prior to tumour diagnosis was 2.3 for the children with leukaemia and 1.5 for the children with brain tumour (visits leading to diagnosis were included), and 0.2 and 0.6, respectively, the year after diagnosis. In the control group, the mean number of visits to a general practitioner was 1.0 in both years.	Retrospective. Small sample, But primary care perspective.