

NCC-PC

The National Collaborating Centre for Primary Care

REFERRAL GUIDELINES FOR SUSPECTED CANCER IN ADULTS AND CHILDREN.

**PART ONE
CHAPTERS 1 - 12**



**University of
Leicester**

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Preface

As a practicing GP, I will see seven or eight new patients with cancer in a year, but may see hundreds of patients who have a possible diagnosis of cancer. Diagnosis is relatively straightforward when the presentation is obvious but when symptoms are vague or inconclusive – as is often the case – it becomes much more difficult. In such cases, I know that I would find it helpful to have information that would help me decide which patients to refer for further investigation and what clinical priority to accord.

Whilst greater vigilance is needed, it is important not to routinely over-investigate or make inappropriate referrals. The role of the GP¹ is to *‘tolerate uncertainty, explore probability and marginalise danger’*. In contrast, the role of the secondary care specialist¹ is to *‘reduce uncertainty, explore possibility and marginalise error’*.

Almost one million people visit their GP every day in the UK and making an accurate diagnosis can often be difficult. It is one of the strengths of general practice that uncertainty is managed so effectively. The RCGP² in its seminal document *The Future General Practitioner* says, *“A correct diagnosis is a crucial achievement which opens the way to prognosis and treatment.”* Delayed or missed diagnosis is the most common reason for medico-legal claims in general practice³.

Improvements in medical practice are therefore needed and indeed possible. However, the solutions sometimes proposed are too simplistic. But these guidelines are in a different league. They clearly understand the culture of general practice.

¹ Marinker M Looking and Leaping. In *Clinical Futures*. Marinker M, Peckham

² RCGP. 1972. *The Future General Practitioner: Learning and Teaching* BMJ Books London

³ http://www.rcgp.org.uk/quality_unit/insaferhands/ISH6.pdf

I therefore welcome these referral guidelines. They offer a practical way forward to improve cancer diagnosis. I liked the emphasis on support for patients, learning and peer review, communication and consulting skills, the appropriate use of investigations and the section dealing with children.

I commend these referral guidelines to primary health care teams and urge primary care organisations to implement them comprehensively.

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- Association of Clinical Biochemists, The
- Association of Coloproctology of Great Britain and Ireland
- Association of Surgeons of Great Britain and Ireland
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS)
- AstraZeneca UK Ltd
- Aventis Pharma
- Bard Limited
- Baxter Oncology
- Bayer PLC
- Beating Bowel Cancer
- Bedfordshire & Hertfordshire NHS Strategic Health Authority
- Birmingham Heartlands & Solihull NHS Trust
- Bournemouth PCT
- Breakthrough Breast Cancer
- Breast Cancer Care
- Brighton & Sussex University Hospitals Trust
- British Association of Dermatologists, The
- British Association of Head and Neck Oncologists
- British Association of Oral and Maxillofacial Surgeons

- British Association of Oral Surgeons
- British Association of Otolaryngologists, Head & Neck Surgeons
- British Association of Urological Surgeons (BAUS)
- British Committee for Standards in Haematology
- British Dental Association
- British Dietetic Association
- British Gynaecological Cancer Society
- British National Formulary (BNF)
- British Nuclear Medicine Society
- British Paediatric Neurology Association
- British Psychological Society, The
- British Psychosocial Oncology Society
- British Society for Haematology
- British Society of Gastroenterology
- British Society of Oral Medicine
- British Society of Paediatric Radiology
- British Thoracic Society
- British Thyroid Association
- BUPA
- Cancer and Leukaemia in Childhood (UK)
- Cancer Black Care
- Cancer Research UK
- Cancer Services Co-ordinating Group
- Cancer Voices
- CancerBACUP
- Chartered Society of Physiotherapy
- Chelsea & Westminster Healthcare NHS Trust
- City Hospitals Sunderland
- Cochrane Oral Health Group
- Community District Nurses Association
- Department of Health
- Eisai Limited

- Eli Lilly and Company Ltd
- E-Z-EM Ltd
- Faculty of Dental Surgery
- Faculty of Public Health
- Fibroid Network Charity
- General Practice Airways Group Limited
- Gorlin Syndrome Group
- Help Adolescents with Cancer
- Independent Healthcare Association
- Independent Healthcare Forum
- Leukaemia Research Fund
- Lewisham Hospital
- Link Pharmaceuticals
- Lymphoma Association
- Macmillan Cancer Relief
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- National Alliance of Childhood Cancer Parent Organisations
- National Cancer Alliance
- National Cancer Network Clinical Directors Group
- National Cancer Research Institute (NCRI) Clinical Studies Group
- National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
- National Kidney Research Fund, The
- National Public Health Service
- NHS Information Authority, (PHSMI Programme)
- NHS Modernisation Agency, The
- NHS Quality Improvement Scotland
- Novartis Pharmaceuticals UK Ltd
- Prostate Cancer Charity, The
- Queen Elizabeth Hospital NHS Trust
- Roche Products Limited
- Rotherham Primary Care Trust

- Roy Castle Lung Cancer Foundation
- Royal College of General Practitioners
- Royal College of General Practitioners Wales
- Royal College of Nursing (RCN)
- Royal College of Obstetricians & Gynaecologists
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians of London
- Royal College of Psychiatrists
- Royal College of Radiologists
- Royal College of Speech and Language Therapists
- Royal College of Surgeons of England
- Royal National Orthopaedic Hospital NHS Trust
- Royal Pharmaceutical Society of Great Britain
- Sanofi-Synthelabo
- Sarcoma UK
- Schering Health Care Ltd
- Scottish Executive Health Department
- Scottish Intercollegiate Guidelines Network (SIGN)
- Sheffield Teaching Hospitals NHS Trust
- Society and College of Radiographers
- Society of British Neurological Surgeons
- Society of Cardiothoracic Surgeons
- South Birmingham Primary Care Trust
- Sue Ryder Care
- Tameside and Glossop Acute Services NHS Trust
- Teenage Cancer Trust, The
- Tenovus Cancer Information Centre
- The Association of Breast Surgery at BASO
- The Leukaemia Society UK
- The Neurofibromatosis Association
- The Royal Society of Medicine

- The Royal West Sussex Trust
- UK Breast Cancer Coalition
- UK Childhood Leukaemia Working Party
- UK Children's Cancer Study Group
- University College Londons Hospital NHS Trust
- Walthamstow, Leyton & Leytonstone PCT
- Wandsworth Primary Care Trust
- Welsh Assembly Government (formerly National Assembly for Wales)
- Welsh Cancer Services Coordinating Group
- Wirral Hospital
- Women's Health Concern

Glossary of Terms

Equivocal: A symptom and/or sign that has more than one equally plausible explanation, or in which the explanation is uncertain.

Odds Ratio (OR): The odds of an event among an exposed population to the odds among the unexposed.

Persistent: 'Persistent' as used in the recommendations in this guideline refers to the continuation of specified symptoms and/or signs beyond a period that would normally be associated with self-limiting problems. The precise period will vary depending on the severity of symptoms and associated features, as assessed by the health professional. In many cases, the upper limit the professional will permit symptoms and/or signs to persist before initiating referral will be 4-6 weeks.

Progressive: Getting worse over a long or short period of time.

RCT: Randomised controlled trial.

Recurrent: A symptom and/or sign that resolves then returns at least once.

Relative risk (RR): Ratio of the risk of an event among an exposed population to the risk among the unexposed.

Trigger for referral: A symptom or sign that is sufficient to indicate the need for either urgent or non-urgent referral.

Watch and wait: A strategy that may sometimes be employed when the symptom(s) and/or sign(s) suggest a benign condition, although do not rule out the possibility of cancer. It is important to review the patient at intervals until the possibility of cancer is ruled out, to limit the duration of the watch and wait policy to a predetermined period, and to refer if the patient's condition

changes or if the predetermined period expires without a resolution of the patient's problem.

Unexplained: When used in a recommendation, unexplained refers to a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any).

Urgency of referral

Immediate/emergency: an acute admission or referral occurring within a few hours, or even more quickly if necessary.

Urgent: the patient is seen within the national target for urgent referrals (currently two weeks).

Non-urgent: all other referrals.

Prompt: This term has been occasionally used in the guideline in connection with referrals that are non-urgent, but delay should nevertheless be avoided. The upper limit for 'prompt' referrals will vary according to the particular case, but if delay beyond six weeks is likely, the primary care professional should discuss the case and the need for an early appointment with the specialist.

The category of 'soon' referral is no longer generally used and therefore is not used in this guideline.

Introduction

1.1 Guideline aims

Clinical guidelines are defined as “*systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances*”.(1) This guideline offers advice on the referral of patients with suspected cancer to specialist services. It updates previously published guidelines,(2) following a commitment in the NHS Cancer Plan(3) that these guidelines would be reviewed by NICE. The new guideline takes account of new research evidence and the findings of audits{969] undertaken since the publication of the previous guideline.

1.2 Referral of patients with suspected cancer

A key aim for the NHS is improvement in the care of people with cancer, including a reduction in mortality by 20% in people under 75 by 2010 in comparison with a 1995-97 baseline. Progress is being made towards this objective, and death rates are falling.{970} In England and Wales in 2003, 136,030 people died from cancer(4). The cancers causing most deaths are shown in *Table 1*.

Table 1 Deaths from cancer males and females, all ages, in England and Wales(4)

Cancer		Deaths in 2003, all ages
Trachea, bronchus and lung	M	17,141
	F	11,608
Colorectal cancers	M	7,498
	F	6,589
Breast	M	67
	F	11,219
Prostate	M	9,160
Oesophagus	M	4,138
	F	2,286
Pancreas	M	3,064
	F	3,177
Stomach	M	3,282
	F	2,008
Non-Hodgkin's lymphoma	M	2,210
	F	1,932
Ovary	F	3,979
Leukaemia	M	2,239
	F	1,685
Bladder	M	2,901
	F	1,507
Multiple myeloma and malignant plasma cell neoplasms	M	1,196
	F	1,141
Brain	M	1,699
	F	1,246
Liver, intrahepatic bile ducts, gallbladder and biliary tract	M	1,537
	F	1,228
Kidney	M	1,716
	F	1,107
Mesothelioma	M	1,373
	F	253
Lip, oral cavity, pharynx, and larynx	M	1,577
	F	738
Cervix uteri	F	953
Malignant melanoma of skin	M	834
	F	751

*Permission to reproduce being sought

Five-year survival rates for some cancers are increasing. For example, rates for breast cancer rose from 72.8% in the period 1991-5 to 77.5% in the period 1996-9; for colon cancer the improvement was from 42.1% in men and 42.8% in women to 46.9% in men and 47.9% in women over the same period. However, in cancers survival rates have been relatively unchanged, for example certain types of cancers of the bladder, brain, and cervix.(5)

Early referral has a role to play in the improvement of care for people with cancer, and in some cancers early referral may improve survival rates. In addition to its roles in prevention, support and long-term management of people with cancer, primary health care has particular responsibility for the early detection of cancer and the initiation of speedy referral to specialist services. To assist primary healthcare professionals identify people with suspected cancer as early as possible, the Department of Health issued guidelines on the topic in 2000.(2)

A recent report by the National Audit Office(6) on cancer services in England observed that patients in England tended to have more advanced cancer at the time of diagnosis than some other countries, at least for breast and bowel cancer. Older people and those from deprived areas were more likely to be diagnosed with cancer at a more advanced stage.

The national Audit Office accepted that more action was needed to reduce delay in the presentation of patients for treatment. Delay may be explained by the failure of some patients to seek help quickly, and by the difficulties general practitioners can face in identifying people with cancer. An electronic survey was circulated to the several thousand subscribers of a general practitioner information network. The survey attracted 814 responses, just under half of whom had read the Department of Health guidelines published in 2000 and found them useful. Some respondents reported that the guidelines had not added to their existing knowledge. A survey of consultants indicated that respiratory physicians reported that 80% of referrals from general practitioners were appropriate, but colorectal surgeons reported 50% that only were appropriate. The National Audit Office recommended that the updated

guidelines should be widely disseminated and acted upon, and that stronger joint working relationships between general practitioners and hospitals should be encouraged through the continued development of standardised referral procedures and feedback to general practitioners on appropriateness of referrals.

1.3 Principles underlying the guideline development

The key principles behind the development of this guideline were that it should:

- take full account of the perspective of the person with suspected cancer and their family and/or carers
- consider all the issues that are important in the primary care assessment and referral of people with suspected cancer
- base the recommendations on the published evidence that supports them, with explicit links to the evidence
- be useful and usable by all health care professionals dealing with people with suspected cancer
- indicate areas of uncertainty requiring further research.

1.4 Who should use this guideline

The guideline is intended for use by individual healthcare professionals in primary care, people with suspected cancer and their carers, the wider general public, and health care commissioning organisations and provider organisations.

Separate short form documents for people with suspected cancer and healthcare professionals are available without details of the supporting evidence. The guideline does not consider health promotion or education of the public about cancer.

1.5 Structure of guideline documentation

The guideline is divided into sections which cover in detail specific topics relating to twelve groups of cancers:

- lung
- upper gastrointestinal cancers
- lower gastrointestinal cancers
- breast cancer
- gynaecological cancers
- urological cancers
- haematological cancers
- skin cancers
- head and neck including oral cancers
- brain/central nervous system cancers
- bone and sarcoma, and
- children's and young people's cancers.

In each section, the symptoms, signs and risk factors relevant to initial assessment in primary health care are considered. The role of investigations in primary care is then addressed, and the sections conclude with consideration of factors related to delay and difficulties in diagnosis.

Two additional sections are included at the beginning of the guideline. The first deals with the needs of patients with suspected cancer at the time of referral. The second considers the process followed by healthcare professionals in reaching an initial diagnosis, and interventions to help healthcare professionals improve their ability to identify patients who should be suspected of having cancer.

Important general methodological issues are flagged up as appropriate. Where appropriate, full details of the papers reviewed are presented in the evidence tables (see Appendix A and B).

1.6 Guideline limitations

The guideline documentation and recommendations are limited to the detection of people who may have cancer in primary care, and do not address the assessment or investigation of patients after referral. The guideline will be

relevant to professionals in general practice, walk-in centres, accident and emergency departments and other open access services that may be consulted by patients with symptoms or signs caused by undiagnosed cancers.

1.7 Scope

Guideline title

Referral guidelines for suspected cancer.

Short title

Referral guidelines for suspected cancer.

Background

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework is to be published. The statements in each NSF reflect the evidence that was available at the time the Framework was prepared.

The National Institute for Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Primary Care to develop referral guidelines for suspected cancer for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The guideline will be an update of previously published guidelines,(2) following a commitment in the NHS Cancer Plan that these guidelines would be reviewed by NICE. The new guideline will take account of new research evidence and the findings of audits undertaken since the publication of the previous guideline.

Both the Department of Health and the Welsh Assembly Government have introduced policies on the urgent referral of patients with suspected cancer.

Clinical need for the guideline

Cancer was responsible for a quarter of all deaths in England and Wales in 1997, and for over half of all deaths among women between 45 and 55 years of age.(7) The incidence of new cases of cancer increased by 12% in males

and 28% in females between 1960 and 1997. For some cancers, mortality rates in the UK compare unfavourably with those in other countries.

Delays of three to six months between the onset of symptoms and diagnosis are associated with worse survival rates in breast cancer.(8) However, evidence about the influence of relatively short delays in other cancers is less clear. The initial symptoms of some cancers can be difficult to distinguish from the symptoms of other more common disorders,(9) and delays can occur between the first presentation and referral for suspected cancer. In a study of the time between presentation and treatment of six common cancers in general practice, the median number of days between presentation of the first symptom or sign and initiation of referral was 0 days for breast, 28 days for large bowel, 31 days for lung, 84 days for oesophageal, 20 days for prostate and 66 days for stomach cancer.(10)

Survival rates for some cancers are lower than elsewhere in Europe, and patients in the UK may have more advanced disease at the time of diagnosis or treatment.(11;12)

The guideline

The guideline development process is described in detail in three booklets that are available from the NICE website (see 'Further information').

The Guideline Development Process – Information for Stakeholders describes how organisations can become involved in the development of a guideline.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider.

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups and categories that will be covered

Patients in all age groups suspected of having one of the cancers covered by the guideline will be included.

The guideline will cover the following cancers:

- lung
- upper gastrointestinal cancers
- lower gastrointestinal cancers
- breast cancer
- gynaecological cancers
- urological/renal cancers
- haematological malignancies
- skin cancers
- head and neck including oral cancers
- brain/central nervous system malignancies
- sarcomas
- children's and young people's malignancies.

Groups and categories that will not be covered

The guideline will not cover:

- the organisation or effectiveness of screening schemes for cancer
- the tests undertaken after referral, therefore definitive diagnosis will not be covered
- referral for suspected recurrence or metastases in previously diagnosed cancer, or referral for palliative care.

Healthcare setting

The guideline will cover the care received from primary healthcare professionals who have direct contact with, and make decisions concerning, the referral of people with suspected cancer.

The guideline will address care in primary care prior to referral for specialist assessment, but will not address care after referral in secondary and tertiary centres.

The guideline will also be relevant to healthcare professionals in secondary care who suspect a patient they are managing for another condition also has cancer, and in whom referral to another specialist would be indicated.

The guideline will also be relevant to the work, but will not cover the practice, of those working in:

- accident and emergency departments
- walk-in centres
- NHS Direct
- voluntary sector
- occupational health
- other health professionals who may encounter patients with symptoms of cancer, for example allied health professionals, dentists, clinicians in secondary care and pharmacists.

Clinical management

The guideline will address:

1. the symptoms, signs and other factors that should prompt consideration of the need for referral, taking into account variation in risk by age and ethnic group
2. the initial investigations that contribute to the assessment of patients prior to, or in association with, urgent referral for suspected cancer
3. interventions intended to help healthcare professionals appropriately identify patients needing urgent referral for suspected cancer
4. the need for urgent referral, and the consequences of delay in referral
5. the information and support needs of patients who are referred for suspected cancer and their families
6. the monitoring of patients after referral but before the first specialist assessment will be considered in the guideline

Audit support within guideline

The guideline will include review criteria and advice.

2 Methods

2.1 Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the National Institute for Clinical Excellence (the Institute) in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (available at: <http://www.nice.org.uk>).

2.1 The developers

The National Collaborating Centre for Primary Care (NCC-PC)

The National Collaborating Centre for Primary Care (NCC-PC) is hosted by the Royal College of General Practitioners (RCGP), and involves the following partners: Royal College of General Practitioners, Royal Pharmaceutical Society of Great Britain, Community Practitioners and Health Visitors Association, and the Clinical Governance Research and Development Unit (CGRDU), Division of General Practice and Primary Health Care, Department of Health Sciences, University of Leicester. The Collaborating Centre was set up in 2000, to undertake commissions from the National Institute for Clinical Excellence to develop clinical guidelines for the National Health Service in England and Wales. The two partners – University of Leicester and the RCGP unit – undertake this work on behalf of the NCC-PC.

This guideline was developed by the Clinical Governance Research and Development Unit (CGRDU), Department of Health Sciences, University of Leicester.

The methodology team

The methodology team was led by the Director of the NCC-PC Leicester, Professor of Quality in Health Care (the project lead). Other members of the team were the Deputy Director of the NCC-PC Leicester, a clinical lecturer, a

systematic reviewer, an information librarian and a health economist. Where appropriate, the advice and opinion of the Chief Executive of the NCC-PC, the appointed Chair of the Guideline Development Group (GDG, see below) and members and co-opted experts of the GDG was sought. Editorial responsibility for the guideline rested solely with the methodology team.

2.3 The Guideline Development Group

Nominations for group members were invited from various stakeholder organisations who were selected to ensure an appropriate mix of health care professionals and delegates of patient groups. In view of the number of organisations who needed to contribute to the guideline it was decided that there should be two groups: nominated members of the Guideline Development Group (GDG) and co-opted experts. Each nominated member was expected to serve as an individual expert in their own right and not as a representative of their parent organisation, although they were encouraged to keep their nominating organisation informed of the process. The co-opted experts contributed to aspects of the guideline development. For each group of cancers two experts were identified: one a specialist in the field and the other a general practitioner with a particular interest in that group of cancers. These experts were sent copies of the evidence reviews, were invited to sit within the GDG and entered fully into any discussion. Details of the experts can be found in the preface to the guideline. Group membership details can be found in the preface to the guideline.

The GDG met at six weekly intervals for 18 months to review the evidence identified by the methodology team, to comment on its quality and completeness and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the GDG.

All GDG members made a formal “Declaration of Interests” at the start of the guideline development and provided updates throughout the development process.

2.4 *Developing key clinical questions (KCQs)*

The first step in the development of the guideline was to refine the guideline scope (see chapter 1) into a series of key clinical questions (KCQs) which reflected the clinical care pathway for adults and children with symptoms and signs suggestive of suspected cancer seen in primary care. These KCQs formed the starting point for the subsequent systematic reviews and as a guide to facilitate the development of recommendations by the GDG.

The KCQs were developed by the GDG, with input as appropriate from co-optees and with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs) by the methodology team and these EBQs formed the basis of the literature searching, appraisal and synthesis.

The methodology team and the GDG agreed that a full literature search and critical appraisal process could not be undertaken for all of these KCQs due to the time and resource limitations within the guideline development process. The methodology team, in liaison with the GDG, identified those KCQs where a full literature search and critical appraisal were essential. Reasons for this included awareness that the evidence was conflicting or that there was a particular need for evidence-based guidance in that area. The KCQs prioritised for detailed searching were the symptoms and signs of cancers presenting in primary health care, primary care investigations, and diagnostic difficulties leading to delay in primary health care.

2.5 *Identifying the evidence*

Literature Search Strategy

The aim of the literature review was to seek to identify all available, relevant published evidence in relation to the key clinical questions generated by the GDG. The prioritised KCQs were turned into EBQs by the project lead and systematic reviewer. Literature searches were conducted using generic

search filters and modified filters, designed to best address the specific question being investigated. Searches included both medical subject headings (MeSH terms) and free-text terms. Details of all literature searches are available from the NCC-PC, University of Leicester and an example can be seen in Appendix D.

The information librarian developed a search strategy for each question with the assistance of the systematic reviewer and the project lead. Searches were re-run at the end of the guideline development process, thus including evidence published up to the end of June 2004.

Depending on the clinical area, some or all of the following databases were searched: Cochrane Library (up to Issue 2, 2004) was searched to identify any relevant systematic reviews, and for reports of randomised controlled trials, MEDLINE (for the period January 1966 to June 2004, on the OVID interface), EMBASE (for the period January 1980 to June 2004, on the OVID interface), the Cumulative Index of Nursing and Allied Health Literature (for the period January 1982 to November 2003, on the Dialog DataStar interface), PsycINFO (for the period 1887 to June 2004, on the OVID and the Dialog DataStar interfaces), the Health Management Information Consortium database (HMIC), the British Nursing Index (BNI), and the Allied and Complementary Medicine Database (AMED). Searches for non-systematic reviews of the literature were limited to 1997 – June 2004. This was a pragmatic decision that draws on the search strategies used by the North Of England Evidence Based Guideline Development Project. No systematic attempt was made to search 'grey literature' (such as conference proceedings, abstracts, unpublished reports or trials, etc.).

Existing systematic reviews and meta-analyses relating to referral for suspected cancer were identified. Recent (last six years) high quality reviews of referral for suspected cancer were also identified. New searches, including identification of relevant randomised controlled trials (RCTs), were conducted in areas of importance to the guideline development process, for which existing systematic reviews are unable to provide valid or up to date answers.

The search strategy was dictated by the exact EBQ the GDG wished to answer. Expert knowledge of group members was also drawn upon to corroborate the search strategy.

The National Research Register (NRR), National Guidelines Clearinghouse (NGC), New Zealand Guidelines Group (NZGG) and the Guidelines International Network (GIN) were searched to identify any existing relevant guidelines produced by other organisations. The reference lists in these guidelines were checked against the methodology team's search results to identify any missing evidence.

The titles and abstracts of records retrieved by the searches were scanned for relevance to the GDG's clinical questions. Any potentially relevant publications were obtained in full text. These were assessed against the inclusion criteria and the reference lists were scanned for any articles not previously identified. Further references were also suggested by the GDG. Evidence submitted by stakeholder organisations that was relevant to the GDG's KCQs, and was of at least the same level of evidence as that identified by the literature searches, was also included.

2.6 Health economics

A separate systematic literature review was conducted to assess the state of the economic evidence, given that in the main searches this evidence was limited. The systematic reviewer and the health economist carried out these searches for health economics evidence. Economic search filters were used - including the one developed by the Centre for Reviews and Dissemination - in the following bibliographic electronic databases MEDLINE, PreMEDLINE, EMBASE, PsycINFO, CINAHL, the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Review of Effectiveness (DARE), the Cochrane Controlled Trials Register (CCTR) and the NHS R&D Health Technology Assessment Programme and special health economic databases Office of Health Economics – OHE - Health Economic Evaluations

Database (HEED) and NHS Economic Evaluation Database (NHS EED) were searched.

Given the limited economic evidence in the area it was decided to perform a broad search for evidence that was designed to identify information about the costs or resources used in providing a service or intervention and /or the benefits that could be attributed to it. No criteria for study design were imposed a priori. In this way the searches were not constrained to RCTs or formal economic evaluations. Papers included were limited to studies of referral for suspected cancer published after 1990, written in English, and reporting health economic information that could be generalized to UK.

2.7 Review of clinical audits

The Centre for Reviews and Dissemination (CRD) has undertaken a review of clinical audits(13) to assess the implementation and effectiveness to the two week waiting time referral system to inform the cancer referral guideline. The summary findings relating to each group of cancers are outlined in each chapter of the guideline.

The review included audits undertaken following the adoption of the two week standard and the publication of the Department of Health's guidelines in 2000. Audits were identified by direct contact with all NHS Trusts, a detailed search of relevant internet sites, and by a search of electronic bibliographies. This broad strategy was required because many audits would not have been published in medical journals. The audits identified were assessed for quality, and data were extracted into a database. The findings were reported in relation to each cancer site.

Two hundred and forty-one audits met the inclusion criteria. The majority of the audits were poorly reported, and only 44% provided sufficient detail on methods for the audit to be reproducible. Less than 20% provided an action plan outlining recommended changes to service delivery, or how changes

would be implemented. In the review, only the findings from the 173 most reliable audits were presented in detail.

The reviewers found that under the two week wait system, there was wide variation in the proportion of referrals seen within two weeks for each cancer site, and in the proportion of referrals that were found to be in accordance with the symptoms listed in the guidelines.(2) Improved reporting of audits was recommended, and it was suggested that the methods and reporting of cancer referral audits should be standardised across the NHS.(13)

Despite these qualifications about the quality of the audits, the findings do indicate that the proportion of patients referred under the two week wait system who turn out to have cancer is often low. Moreover, a variable proportion of patients who have cancer are not diagnosed after a two week referral. The explanations for these findings will vary according to the cancer concerned, for example some cancers may be more likely to be diagnosed following acute admission or in screening programmes. Nevertheless, guidelines appear to have a role to play in informing decisions about referral for suspected cancer.

2.8 Reviewing and grading the evidence

General

The studies identified following the literature search were reviewed to identify the most appropriate evidence to help answer the KCQs and to ensure that the recommendations were based on the best available evidence. This process required four main tasks: selection of relevant studies; assessment of study quality; synthesis of the results and grading of the evidence.

The searches were first sifted by the information librarian and systematic reviewer to exclude papers that did not relate to the scope of the guideline. The abstracts of the remaining papers were scrutinised for relevance to the EBQ under consideration. Initially both the systematic reviewer and project

lead reviewed the abstracts independently. This proved impractical as the guideline progressed and the task was delegated to the systematic reviewer. The project lead was asked to review the abstracts in cases of uncertainty.

One of the challenges in this guideline was defining inclusion and exclusion criteria for retrieved studies. There were very few studies in which presenting symptoms and signs of suspected cancer were assessed prospectively or in a primary care setting. In addition, there was concern about the applicability and generalisability of studies conducted in countries other than the UK to the NHS in England and Wales. Therefore, a pragmatic, inclusive approach was adopted so the GDG were able to consider a wider body of evidence than if a stricter, more exclusive approach had been taken. The GDG then considered the evidence within the context of primary care in the NHS.

The papers chosen for inclusion were obtained and were assessed for their methodological rigour against a number of criteria that determine the validity of the results. These criteria differ according to study type and were based on the checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN). Critical appraisal was carried out by the systematic reviewer. Further appraisal was provided by the GDG members at the relevant GDG meeting.

The data were extracted to a standard template on an evidence table. The findings were summarised by the systematic reviewer into a series of evidence statements and an accompanying narrative review. The project lead independently assessed the accuracy of the derived evidence statements. None of the EBQs required the preparation of a quantitative synthesis (meta-analysis) by the project team.

The evidence statements were graded by the project lead according to the established hierarchy of evidence table presented in section 0 of this chapter. This system reflects the susceptibility to bias inherent in particular study designs.

The type of EBQ dictates the highest level of evidence that may be sought. For questions relating to therapy/treatment the highest possible level of evidence is a systematic review or meta-analysis of RCTs (evidence level Ia) or an individual RCT (evidence level Ib). For questions relating to prognosis, the highest possible level of evidence is a cohort study (evidence level IIb). For diagnostic tests, the highest possible level of evidence is a test evaluation study using a quasi-experimental design that uses a blind comparison of the test with a validated reference standard applied to a sample of patients who are representative of the population to whom the test would apply (evidence level IIb). For questions relating to information needs and support, the highest possible level of evidence is a descriptive study using either questionnaire survey or qualitative methods (III).

For each clinical question, the highest level of evidence was selected. If a systematic review, meta-analysis or RCT existed in relation to an EBQ, studies of a weaker design were ignored.

Summary results and data are presented in the guideline text. More detailed results and data are presented in the evidence tables (Appendices A and B).

A number of KCQs could not appropriately be answered using a systematic review, for example, where the evidence base was very limited. These questions were addressed by the identification of 'published expert' narrative reviews by the project team and/or GDG, which formed the basis of discussion papers written either by the project lead or a member of the GDG. This approach has been used on the sections dealing with "breaking bad news", how primary care practitioners should make a diagnosis and patient information and support needs. Systematic reviews or expert narrative reviews were also used to summarise the risk factors for each of the groups of cancers.

2.8.1 Details of levels of evidence and grading of recommendations

Table 2 Levels of evidence

Hierarchy of evidence	
Ia	Systematic review or meta-analysis of randomised controlled trials
Ib	At least one randomised controlled trial
IIa	At least one well-designed controlled study without randomisation
IIb	At least one well-designed quasi-experimental study, such as a cohort study
III	Well-designed non-experimental descriptive studies, case-control studies, and case series
IV	Expert committee reports, opinions and/or clinical experience of respected authorities
NICE	NICE guidelines or Health Technology Appraisal programme

Table 3 Grades of recommendation

Grading of recommendations	
A	Based directly on level I evidence
B	Based directly on level II evidence or extrapolated from level I evidence
C	Based directly on level III evidence or extrapolated from level I or level II evidence
D	Based directly on level IV evidence or extrapolated from level I, level II, or level III evidence
A NICE	Recommendation taken from NICE guideline or Technology Appraisal
GPP	Good practice point based on the clinical experience of the GDG

Table 4 Levels of evidence for studies of the accuracy of diagnostic tests

Levels of evidence	Type of evidence
Ia	Systematic review (with homogeneity) [†] of level-1 studies [‡]
Ib	Level-1 studies [‡]
II	Level-2 studies [§] Systematic reviews of level-2 studies
III	Level-3 studies ^{§§} Systematic reviews of level-3 studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research or 'first principles'.

[†]Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

[‡]Level-1 studies are studies:

that use a blind comparison of the test with a validation reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply

[§]Level-2 studies are studies that have only one of the following:

narrow population (the sample does not reflect the population to whom the test would apply)

use a poor reference standard (defined as that where a 'test' is included in the 'reference', or where the 'testing' affects the 'reference')

the comparison between the test and reference standard is not blind

case-control studies

^{§§}Level-3 studies are studies that have at least two or three of the features listed above[§]

(from the NICE Technical Manual, and adapted from The Oxford Centre for Evidence-based Medicine Levels of Evidence(14) and the Centre for Reviews and Dissemination Report Number 4(15))

Table 5 Classification of recommendations for studies of the accuracy of diagnostic tests

Class	Level of evidence (see Table 4)
A (DS)	Studies with level of evidence Ia or Ib
B (DS)	Studies with level of evidence II
C (DS)	Studies with level of evidence III
D (DS)	Based on studies with level of evidence IV

(DS – diagnostic studies).

2.8.2 The role of risk factors in decisions about referral for suspected cancer

Risk factors are often included in reviews of the presenting features of cancers, and the guideline group considered the role of selected risk factors in decisions about referral for suspected cancer. However, the place of risk factors in making decisions about referral for suspected cancer was found by the guideline group to be unclear. The guideline group recognised that in a patient with symptoms or signs suggestive of cancer, the presence or absence of risk factors was usually irrelevant to the referral decision. The following paragraphs outline the issues taken into account by the guideline group in considering the place of risk factors in referral decisions.

2.8.3 What is a risk factor?

Risk factors are generally viewed as factors that increase the likelihood of development of a disease or condition. One definition is ‘those patient characteristics associated with the development of the disease in the first place’.(16) For example, regular smoking increases the risk of lung cancer, cardiovascular disease, and so forth. Prognostic risk factors are also sometimes described, and these are defined as ‘patient or study participant characteristics that confer increased or decreased risk of a positive or adverse outcome’.(16)

However, a rather different question is relevant in the context of identifying people who have cancer, namely does the presence of certain features in a

person presenting to primary care with certain symptoms and signs increase the likelihood of cancer? The risk factor of increasing age for breast cancer illustrates the issue.

Figure 1 Incidence of breast cancer among females, in England and Wales, 1997(17)

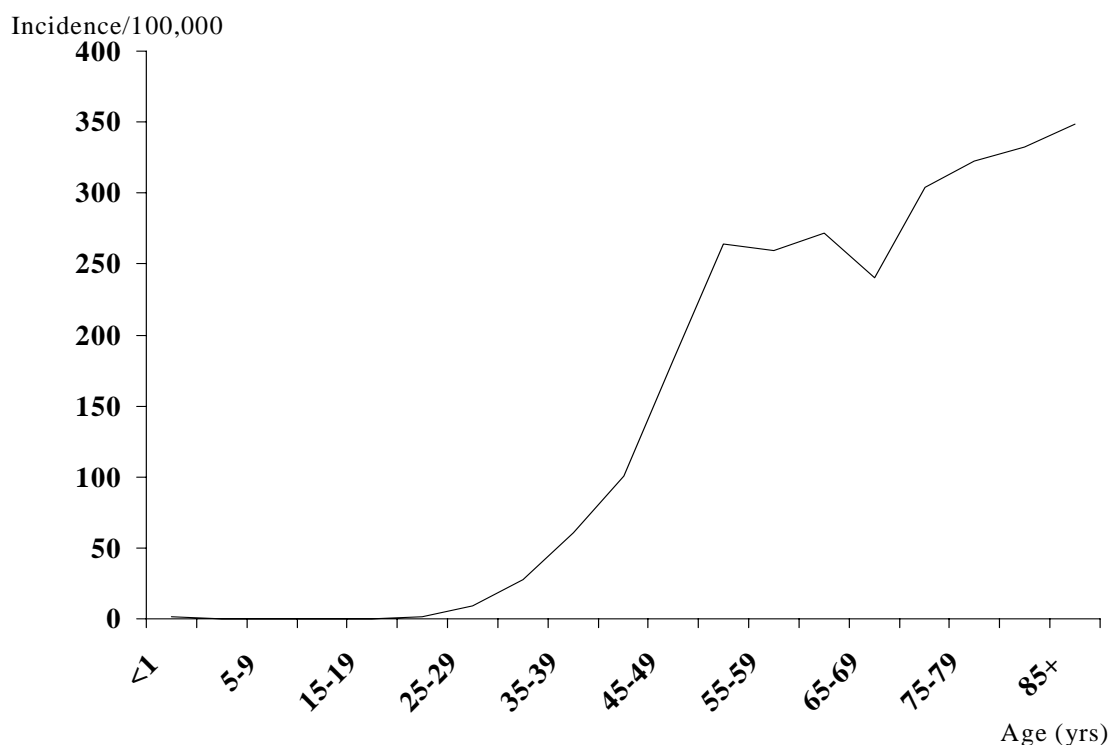


Figure 1 shows the risk of breast cancer to be around 50/100,000 at age 35, and around 275/100,000 at age 55. However, the data do not indicate the proportion of breast lumps at different ages that will be cancer, since they do not include information about the total numbers of patients presenting in primary care with benign lumps. Consequently, the guideline group required judgement in interpreting the breast cancer incidence data. Because breast lumps are 'common' in the 30-35 age group, but cancer uncommon, then referral of all patients below aged 30 cannot be recommended. However, cancer was judged by the group to be not only more common at age 55, but also to constitute a greater proportion of those cases presenting with breast lumps.

2.8.4 When is a risk factor relevant to a referral decision?

Relative risk (RR) is the 'ratio of the risk of an event among an exposed population to the risk among the unexposed'. Is the RR of conditions occurring when a risk factor is present helpful in making referral decisions?

Although age has been taken into account in making recommendations about referral in some cancers, small increments in age do not confer high relative risks. However, the fact that cancer is rare below a certain age was regarded by the group as important. The group has not found information about risk factors with low RRs helpful. In the case of haematological cancers, Epstein-Barr virus was found to have a RR for Hodgkin's disease of 2.4,(18) high birth weight had an RR of 1.7 for ALL,(19) and farm labourers had a RR of 1.8 for myeloma.(20) The group considered these findings as irrelevant to the referral decision.

Risk factors with high RRs are not necessarily helpful either. It is uncommon for patients to have such risk factors, and the absence of the risk factor in someone who presents with symptoms and signs does not mean that cancer is ruled out.

2.8.5 Specificity of the symptoms and signs

If the symptoms and/or signs are reasonably specific for the condition, the presence of an additional risk factor would be unlikely to be helpful in making a referral decision. Thus, in a patient aged 60 with weight loss, change in bowel habit, rectal bleeding and a palpable abdominal mass, a past history of ulcerative colitis will not influence the referral decision. However, if the symptoms and/or signs are less specific, risk factors might be considered relevant. Thus, it could be argued that in a patient of 48 who incidentally reports 7lbs weight loss only, a past history of ulcerative colitis might be taken into account in decisions about further investigation, although probably not referral in the first instance.

2.8.6 Patient concern

The presence of a risk factor could increase patient concern, even though it does not increase the likelihood that the presenting symptoms and signs could be explained by cancer. In this case, the primary care practitioner may or may not be able to provide adequate reassurance. Referral decisions should involve patients, and therefore patient concern was accepted as appropriate by the guideline group as a factor that would contribute to the decision on referral.

The guideline group concluded that for the majority of symptoms and/or signs or initial investigations suggestive of the need for referral for cancer, risk factors other than age are not helpful to the decision to refer or the urgency of referral. If an individual has a risk factor indicating a substantially increased risk of a particular cancer, this may increase the health care professional's index of suspicion of cancer, but in the majority of symptomatic cases it should not influence referral decisions or the urgency of a referral if made. For example, a family history of breast cancer or parity would not be factors that would influence the referral decision in the case of a woman presenting with a breast lump. In assessing the significance of risk factors, the guideline group decided to seek good quality reviews rather than undertake primary searches for studies of risk factors, most of which would have no bearing on referral decisions.

2.8.7 Health economics

Identified titles and abstracts from the economics searches were reviewed by the health economist and full papers obtained as appropriate. The full papers were critically appraisal by the health economist using a standard validated checklist. A general descriptive overview of the studies, their qualities, and conclusions was presented and summarized in the form of a short narrative review. The economic evidence was not summarized in the form of meta-analyses given the limited evidence found.

The GDG identified the economics of referral of people with suspected lower gastrointestinal cancer as an important area where further analysis was needed. This area was chosen because there is a high prevalence of the primary symptoms of bowel cancer in the community (rectal bleeding, changes in bowel habit and abdominal pain) relative to the low incidence of bowel cancer. The results of this analysis are presented in Appendix C.

2.9 *Developing recommendations*

For each KCQ, the recommendations were derived from the evidence statements presented to the GDG. The link between the evidence statement and recommendation was made explicit. The GDG were able to reach their agreed recommendations through a process of informal consensus.

Each recommendation was graded according to the level of evidence upon which it was based using the established grading of recommendations table presented in section 12 of this chapter. For questions relating to therapy/treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) would equate to a grade A recommendation. For questions relating to prognosis and diagnostic tests, the generally appropriate level of evidence (a cohort study) would equate to a grade B recommendation. For questions relating to information needs and support, the generally appropriate level of evidence (descriptive study) would equate to a grade C recommendation. It is important that the grading in such areas is not treated as inferior to those of therapy as it the existence of relevant evidence.

Many recommendations in this guideline are graded C or D. This is an inevitable consequence of the focus in the guideline on symptoms and signs rather than clinical interventions, and it would be inappropriate to infer from the grade given to most of the recommendations in this guideline that the recommendations are not important. The relevant studies have usually described the presenting symptoms and signs in patients with the cancer of interest, and some studies have compared the findings among patients who

were subsequently found to either have or not have cancer. It is essential to note that the guideline group has been able to use this evidence to make recommendations it regards as highly important.

2.10 External review

The guideline has been developed in accordance with the Institute's guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline, the first draft of the full and short form guideline and the final draft of the guideline. In addition, the first draft was reviewed by nominated individuals with an interest in cancer and an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented anonymously for consideration by the GDG. All comments were considered systematically by the GDG and the project team recorded the agreed responses.

3 Key Priorities for implementation

Making a Diagnosis

- The primary care professional should recognise that the diagnosis of any cancer on clinical grounds alone can be difficult.
- Primary healthcare professionals should be familiar with the typical presenting features of cancers, and be able to readily identify these features when patients consult with them.
- Primary healthcare professionals must be alert to the possibility of cancer when confronted by unusual symptom patterns or when patients who are thought to not have cancer fail to recover as expected. Discussion with a specialist should be considered if there is uncertainty about the interpretation of symptoms and signs, and whether a referral is needed. This may also enable the primary care professional to communicate their concerns and a sense of urgency to secondary healthcare professionals when symptoms are not classical.
- Cancer is uncommon in children, and its detection can present particular difficulties. Primary healthcare professionals should recognise that parents are the best observers of their children, and should listen carefully to their concerns. Professionals should also be willing to reassess the initial diagnosis or to seek a second opinion from a colleague if a child fails to recover as expected.

Investigations

- In patients with features typical of cancer, investigations in primary care should not be allowed to delay referral. In patients with less typical symptoms and signs that might, nevertheless, be due to cancer, investigations may be necessary but should be undertaken urgently to avoid delay. If specific investigations are not readily available locally, an urgent specialist referral should be made.

The need for support and information

- When referring patients with suspected cancer, primary healthcare professionals should assess the patient's need for continuing support whilst awaiting a specialist opinion, and should provide appropriate information about the possible diagnosis, what to expect from the service the patient will be attending, and how to obtain further information or help prior to the specialist appointment.
- In assessing the need of the patient for support, the primary healthcare professional should take account of the needs of people from different cultural groups, social factors, including family circumstances or isolation, and the needs of people of different ages.

Continuing education for health professionals

- Primary healthcare professionals should take part in education, peer review and other activities to improve or maintain the clinical consulting skills they need to identify patients who may have cancer at an early stage and should be aware of the methods of communicating the possibility of cancer to the patient. Current guidance for advising patients and breaking bad news should be followed (taking into account the personal characteristics of the patient).

4 Executive Summary

4.1. Support and Information needs of people with suspected cancer at the time of referral

Number		Grade
1	Patients should be able to consult a primary healthcare professional of the same sex if preferred.	D
2	Primary healthcare professionals should discuss with patients (and carers as appropriate, taking account of the need for confidentiality) their preferences for being involved in decision-making about referral options and further investigations (including their potential risks and benefits), and ensure they have the time for this.	D
3	When cancer is suspected in a child, the referral decision and information to be given to the child should be discussed with the parents or carers (and the patient if appropriate).	D
4	Adult patients who are being referred with suspected cancer should normally be told by the primary healthcare professional that they are being referred to a cancer service, but if appropriate they should be reassured that most people referred will not have a diagnosis of cancer, and alternative diagnoses should be discussed.	D
5	Primary healthcare professionals should be willing and able to give the patient information on the possible diagnosis (both benign and malignant) in accordance with the patient's wishes for information. Current advice on communicating with patients and/or their carers and	D

breaking bad news⁴ should be followed.

6 The information given to patients, family and/or carers as **D** appropriate by the primary healthcare professional should cover, among other issues:

- where patients are being referred to
- how long they will have to wait for the appointment
- how to obtain further information about the type of cancer suspected or help prior to the specialist appointment
- who they will be seen by
- what to expect from the service the patient will be attending
- what type of tests will be carried out, and what will happen during diagnostic procedures
- how long it will take to get a diagnosis or test results
- whether they can take someone with them to the appointment
- other sources of support, including those for minority groups.

7 When referring a patient with suspected cancer to a **D** specialist service, primary healthcare professionals should assess the patient's need for continuing support while waiting for their referral appointment. This should include inviting the patient to contact the primary

⁴ *Improving communication between doctors and patients*. A report of the working party of the Royal College of Physicians (1997) www.rcplondon.ac.uk/pubs/brochures/pub_print_icbdp

healthcare professional again if they have more concerns or questions before they see a specialist.

- 8** Consideration should be given by the primary healthcare professional to meeting the information and support needs of parents and carers. Consideration should also be given to meeting these particular needs for the people for whom they care, such as children and young people, and people with special needs (for instance, people with learning disabilities or sensory impairment). **D**
- 9** The primary healthcare professional should be aware that some patients find being referred for suspected cancer particularly difficult because of their personal circumstances, such as age, family or work responsibilities, isolation, or other health or social issues. **D**
- 10** Primary healthcare professionals should provide culturally appropriate care, recognising the potential for different cultural meanings associated with the possibility of cancer, the relative importance of family decision-making and possible unfamiliarity with the concept of support outside the family. **D**
- 11** The primary healthcare professional should be aware that men may have similar support needs to women but may be more reticent about using support services. **D**
- 12** If the patient has additional support needs because of their personal circumstances, the specialist should be informed (with the patient's agreement). **D**
- 13** All members of the primary healthcare team should have **D**

available to them information in a variety of formats on both local and national sources of additional support for patients who are being referred with suspected cancer.

- 14** In situations where diagnosis or referral has been delayed, or there is significant compromise of the doctor/patient relationship, the primary healthcare professional should take care to assess the information and support needs of the patient, parents and carers, and make sure these needs are met. The patient should be given the opportunity to consult another primary healthcare professional if they wish. **D**
- 15** Primary healthcare professionals should promote awareness of key presenting features of cancer when appropriate. **D**

4.2. The Diagnostic Process

Number		Grade
1	Diagnosis of any cancer on clinical grounds alone can be difficult. Primary healthcare professionals should be familiar with the typical presenting features of cancers, and be able to readily identify these features when patients consult with them.	D
2	Cancers usually present with symptoms commonly associated with benign conditions. The primary healthcare professional should be ready to review the initial diagnosis in patients in whom common symptoms do not resolve as expected.	D
3	Primary healthcare professionals must be alert to the possibility of cancer when confronted by unusual symptom patterns or when patients thought not to have cancer fail to recover as expected. In such circumstances, the primary healthcare professional should systematically review the patient's history and examination, and refer urgently if cancer is a possibility.	D
4	Cancer is uncommon in children, and its detection can present particular difficulties. Primary healthcare professionals should recognise that parents are usually the best observers of their children, and should listen carefully to their concerns. Primary healthcare professionals should also be willing to reassess the initial diagnosis or to seek a second opinion from a colleague if a child fails to recover as expected.	D

- 5** Primary healthcare professionals should take part in continuing education, peer review and other activities to improve and maintain their clinical consulting, reasoning and diagnostic skills, in order to identify at an early stage, patients who may have cancer, and to communicate the possibility of cancer to the patient. **C**
- 6** Discussion with a specialist should be considered if there is uncertainty about the interpretation of symptoms and signs, and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals when symptoms are not classical (for example, by telephone or email). **D**
- 7** There should be local arrangements in place to ensure that letters about non-urgent referrals are assessed by the specialist, the patient being seen more urgently if necessary. **D**
- 8** There should be local arrangements in place to ensure a maximum waiting period for non-urgent referrals, in accordance with national targets and local arrangements. **D**
- 9** There should be local arrangements in place to identify those patients who miss their appointments so that they can be followed up. **D**
- 10** The primary healthcare professional should include all appropriate information in referral **D**

correspondence, including whether the referral is urgent or non-urgent.

- 11** The primary healthcare professional should use local referral proformas if these are in use. **D**
- 12** Once the decision to refer has been made, the primary healthcare professional should make sure that the referral is made within 1 working day. **D**
- 13** A patient who presents with symptoms suggestive of cancer should be referred by the primary healthcare professional to a team specialising in the management of the particular type of cancer, depending on local arrangements. **D**
- 14** In patients with features typical of cancer, investigations in primary care should not be allowed to delay referral. In patients with less typical symptoms and signs that might, nevertheless, be due to cancer, investigations may be necessary, but should be undertaken urgently to avoid delay. If specific investigations are not readily available locally, an urgent specialist referral should be made. **D**

4.3. Lung Cancer

Number **Grade**

General recommendations

- 1** A patient who presents with symptoms suggestive of lung cancer should be referred to a team specialising in the management of lung cancer, depending on local arrangements. **D**

Specific recommendations

- 2** **An urgent referral for a chest X-ray should be made when a patient presents with:** **D**

- haemoptysis, or
- any of the following unexplained persistent (that is, lasting more than 3 weeks) symptoms and signs:
 - chest and/or shoulder pain
 - dyspnoea
 - weight loss
 - chest signs
 - hoarseness
 - finger clubbing
 - cervical and/or supraclavicular lymphadenopathy
 - cough with or without any of the above
 - features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin).

A report should be made back to the referring primary healthcare professional within 5 days of referral.

Number		Grade
3	An urgent referral should be made for any of the following: <ul style="list-style-type: none">• persistent haemoptysis in smokers or ex-smokers who are aged 40 years and older• a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation).	D
4	Immediate referral should be considered for the following: <ul style="list-style-type: none">• signs of superior vena caval obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)• stridor.	C
	Risk Factors	
5	Patients in the following categories have a higher risk of developing lung cancer: <ul style="list-style-type: none">• are current or ex-smokers• have smoking-related chronic obstructive pulmonary disease (COPD)• have been exposed to asbestos• have had a previous history of cancer (especially head and neck). An urgent referral for a chest X-ray or to a team specialising in the management of lung cancer should be made as for other patients (see 1.3.1 above) but may be considered sooner, for example if symptoms or signs have lasted for less than 3 weeks.	C

Number		Grade
	Investigations	
6	Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems should prompt an urgent referral for chest X-ray.	D
7	If the chest X-ray is normal, but there is a high suspicion of lung cancer, patients should be offered an urgent referral.	D
8	In individuals with a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms, lung cancer should be considered and a chest X-ray arranged. If this indicates a pleural effusion, pleural mass or any suspicious lung pathology, an urgent referral should be made.	C

4.4. Upper Gastrointestinal Cancer

Number		Grade
	General recommendations	
1	A patient who presents with symptoms suggestive of upper gastrointestinal cancer should be referred to a team specialising in the management of upper gastrointestinal cancer, depending on local arrangements.	D
	Specific recommendations	
2	An urgent referral for endoscopy or to a specialist with expertise in upper gastrointestinal cancer should be made for patients of any age with dyspepsia ⁵ who present with any of the following: <ul style="list-style-type: none">• chronic gastrointestinal bleeding• dysphagia• progressive unintentional weight loss• persistent vomiting• iron deficiency anaemia• epigastric mass• suspicious barium meal.	C
3	In patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, an urgent referral for endoscopy should be made.	D

⁵ The definition of dyspepsia is taken from the NICE guideline on *Dyspepsia: management of dyspepsia in adults in primary care* (www.nice.org.uk/CG017). Dyspepsia in unselected patients in primary care is defined broadly to include patients with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting.

- 4** In patients aged less than 55 years, endoscopic investigation of dyspepsia is not necessary in the absence of alarm symptoms. **D**
- 5** In patients presenting with dysphagia (interference with the swallowing mechanism that occurs within 5 seconds of having commenced the swallowing process), an urgent referral should be made. **C**
- 6** *Helicobacter pylori* status should not affect the decision to refer for suspected cancer. **C**
- 7** In patients without dyspepsia, but with unexplained weight loss or iron deficiency anaemia, the possibility of upper gastrointestinal cancer should be recognised and an urgent referral for further investigation considered. **C**
- 8** In patients with persistent vomiting and weight loss in the absence of dyspepsia, upper gastro-oesophageal cancer should be considered and, if appropriate, an urgent referral should be made. **C**
- 9** An urgent referral should be made for patients presenting with either: **C**
- unexplained upper abdominal pain and weight loss, with or without back pain, or
 - an upper abdominal mass without dyspepsia.
- 10** In patients with obstructive jaundice an urgent referral should be made, depending on the patient's clinical state. An urgent ultrasound investigation may be considered if available. **C**

Risk Factors

- 11** In patients with unexplained worsening of their dyspepsia, an urgent referral should be considered if they have any of the following known risk factors: **C**
- Barrett's oesophagus
 - known dysplasia, atrophic gastritis or intestinal metaplasia
 - peptic ulcer surgery more than 20 years ago.

Investigations

- 12** Patients being referred urgently for endoscopy should ideally be free from acid suppression medication, including proton pump inhibitors or H₂ receptor antagonists, for a minimum of 2 weeks. **C**
- 13** In patients where the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be carried out in accordance with local arrangements. **D**
- 14** All patients with new onset dyspepsia should be considered for a full blood count in order to detect iron deficiency anaemia. **D**

4.5. Lower Gastrointestinal Cancer

Number		Grade
---------------	--	--------------

General recommendations

- | | | |
|----------|---|----------|
| 1 | A patient who presents with symptoms suggestive of colorectal or anal cancer should be referred to a team specialising in the management of lower gastrointestinal cancer, depending on local arrangements. | D |
| 2 | In patients with equivocal symptoms who are not unduly anxious, it is reasonable to use a period of 'treat, watch and wait' as a method of management. | D |
| 3 | In patients with unexplained symptoms related to the lower gastrointestinal tract, a digital rectal examination should always be carried out, provided this is acceptable to the patient. | C |

Specific Recommendations

- | | | |
|----------|---|----------|
| 4 | In patients aged 40 years and older, reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for 6 weeks or more, an urgent referral should be made. | C |
| 5 | In patients aged 60 years and older, with rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms, an urgent referral should be made. | C |

Number		Grade
6	In patients aged 60 years and older, with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding, an urgent referral should be made.	C
7	In patients presenting with a right lower abdominal mass consistent with involvement of the large bowel, an urgent referral should be made, irrespective of age.	C
8	In patients presenting with a palpable rectal mass (intraluminal and not pelvic), an urgent referral should be made, irrespective of age. (A pelvic mass outside the bowel would warrant an urgent referral to a urologist or gynaecologist.)	C
9	In men of any age with unexplained ⁶ iron deficiency anaemia and a haemoglobin of 11 g/100 ml or below, an urgent referral should be made.	C
10	In non-menstruating women with unexplained ⁶ iron deficiency anaemia and a haemoglobin of 10 g/100 ml or below, an urgent referral should be made.	C

⁶ 'Unexplained' in this context means a patient whose anaemia is considered on the basis of a history and examination in primary care not to be related to other sources of blood loss (for example, non-steroidal anti-inflammatory drug treatment or blood dyscrasia).

Risk Factors

- 11** In patients with ulcerative colitis or a history of ulcerative colitis, a plan for follow-up should be agreed with a specialist and offered to the patient as a normal procedure in an effort to detect colorectal cancer in this high-risk group. **C**
- 12** There is insufficient evidence to suggest that a positive family history of colorectal cancer can be used as a criterion to assist in the decision about referral of a symptomatic patient. **C**

Investigations

- 13** In patients with equivocal symptoms, a full blood count may help in identifying the possibility of colorectal cancer by demonstrating iron deficiency anaemia, which should then determine if a referral should be made and its urgency. **C (DS)**
- 14** In patients for whom the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be in accordance with local arrangements. **D**
- 15** In patients for whom the decision to refer has been made, no examinations or investigations other than those referred to earlier (abdominal and rectal examination, full blood count) are recommended as this may delay referral. **D**

4.6. Breast Cancer

Number		Grade
General recommendations		
1	A patient who presents with symptoms suggestive of breast cancer should be referred to a team specialising in the management of breast cancer.	D
2	In most cases, the definitive diagnosis will not be known at the time of referral, and many patients who are referred will be found not to have cancer. However, primary healthcare professionals should convey optimism about the effectiveness of treatment and survival because a patient being referred with a breast lump will be naturally concerned.	C
3	People of all ages who suspect they have breast cancer may have particular information and support needs. The primary healthcare professional should discuss these needs with the patient and respond sensitively to them.	D
4	Primary healthcare professionals should encourage all patients, including women over 50 years old, to be breast aware ⁷ in order to minimise delay in the presentation of symptoms.	D
Specific Recommendations		
5	A woman's first suspicion that she may have breast cancer is often when she finds a lump in her breast. The primary	C

⁷ Breast awareness means knowing what your breasts look and feel like normally. Evidence suggests that there is no need to follow a specific or detailed routine such as Breast Self Examination, but women should be aware of any changes in their breasts. See <http://cancerscreening.org.uk/breastscreen/breastawareness.html> for further information.

healthcare professional should examine the lump with the patient's consent. The features of a lump that should make the primary healthcare professional strongly suspect cancer are a discrete, hard lump with fixation, with or without skin tethering. In patients presenting in this way an urgent referral should be made, irrespective of age.

- 6 In a woman aged 30 years and older with a discrete lump that persists after her next period, or presents after menopause, an urgent referral should be made. **C**
- 7 **Breast cancer in women aged younger than 30 years is rare, but does occur. Benign lumps (for example, fibroadenoma) are common, however, and a policy of referring these women urgently would not be appropriate; instead, non-urgent referral should be considered. However, in women aged younger than 30 years with:** **C / D**
- a lump that enlarges, **[C]** or
 - a lump that has other features associated with cancer (fixed and hard), **[C]** or
 - in whom there are other reasons for concern such as family history. **[D]**
- an urgent referral should be made.**
- 8 The patient's history should always be taken into account. For example, it may be appropriate, in discussion with a specialist, to agree referral within a few days in patients reporting a lump or other symptom that has been present for several months. **D**
- 9 In a patient who has previously had histologically confirmed breast cancer, who presents with a further lump or **C**

suspicious symptoms, an urgent referral should be made, irrespective of age.

- 10** In patients presenting with unilateral eczematous skin or nipple change that does not respond to topical treatment, or with nipple distortion of recent onset, an urgent referral should be made. **C**
- 11** In patients presenting with spontaneous unilateral bloody nipple discharge, an urgent referral should be made. **C**
- 12** Breast cancer in men is rare and is particularly rare in men under 50 years of age. However, in a man aged 50 years and older with a unilateral, firm subareolar mass with or without nipple distortion or associated skin changes, an urgent referral should be made. **C**
- Investigations**
- 13** In patients presenting with symptoms and/or signs suggestive of breast cancer, investigation prior to referral is not recommended. **D**
- 14** In patients presenting solely with breast pain, with no palpable abnormality, there is no evidence to support the use of mammography as a discriminatory investigation for breast cancer. Therefore, its use in this group of patients is not recommended. Non-urgent referral may be considered in the event of failure of initial treatment and/or unexplained persistent symptoms. **[B (DS)]**

4.7. Gynaecological Cancer

Number		Grade
	General recommendations	
1	A patient who presents with symptoms suggesting gynaecological cancer should be referred to a team specialising in the management of gynaecological cancer, depending on local arrangements.	D
	Specific recommendations	
2	The first symptoms of gynaecological cancer may be alterations in the menstrual cycle, intermenstrual bleeding, postcoital bleeding, postmenopausal bleeding or vaginal discharge. For a patient who presents with any of these symptoms, the primary healthcare professional should undertake a full pelvic examination, including speculum examination of the cervix.	C
3	In patients found on examination of the cervix to have clinical features that raise the suspicion of cervical cancer, an urgent referral should be made. A cervical smear test is not required before referral, and a previous negative cervical smear result is not a reason to delay referral.	C

- 4** Ovarian cancer is particularly difficult to diagnose on clinical grounds as the presentation may be with vague, non-specific abdominal symptoms alone (bloating, constipation, abdominal or back pain, urinary symptoms). In a woman presenting with any unexplained abdominal or urinary symptoms, abdominal palpation should be carried out. If there is significant concern, a pelvic examination should be considered if appropriate and acceptable to the patient. **D**
- 5** Any woman with a palpable abdominal or pelvic mass on examination that is not obviously uterine fibroids or not of gastrointestinal or urological origin should have an urgent ultrasound scan. If the scan is suggestive of cancer, or if ultrasound is not available, an urgent referral should be made. **C**
- 6** When a woman who is not on hormone replacement therapy presents with postmenopausal bleeding, an urgent referral should be made. **C**
- 7** When a woman on hormone replacement therapy presents with persistent or unexplained postmenopausal bleeding after cessation of hormone replacement therapy for 6 weeks, an urgent referral should be made. **C**
- 8** Tamoxifen can increase the risk of endometrial cancer. When a woman taking tamoxifen presents with postmenopausal bleeding, an urgent referral should be made. **C**

- 9** An urgent referral should be considered in a patient with persistent intermenstrual bleeding and a negative pelvic examination. **D**

Vulval cancer

- 10** When a woman presents with vulval symptoms, a vulval examination should be offered. If an unexplained vulval lump is found, an urgent referral should be made. **C**
- 11** Vulval cancer can also present with vulval bleeding due to ulceration. A patient with these features should be referred urgently. **D**
- 12** Vulval cancer may also present with pruritus or pain. For a patient who presents with these symptoms, it is reasonable to use a period of 'treat, watch and wait' as a method of management. But this should include active follow-up until symptoms resolve or a diagnosis is confirmed. If symptoms persist, the referral may be urgent or non-urgent, depending on the symptoms and the degree of concern about cancer. **C**

4.8. Urological Cancers

Number		Grade
	General recommendations	
1	A patient who presents with symptoms or signs suggestive of a urological cancer should be referred to a team specialising in the management of urological cancers, depending on local arrangements.	D
	Specific recommendations	
	Prostate cancer	
2	Patients presenting with symptoms suggesting prostate cancer should have a digital rectal examination (DRE) and prostate specific antigen (PSA) test after counselling. Symptoms will be related to the lower urinary tract and may be inflammatory or obstructive.	C
3	Prostate cancer is also a possibility in male patients with any of the following unexplained symptoms: <ul style="list-style-type: none">• erectile dysfunction• haematuria• lower back pain• bone pain• weight loss, especially in the elderly. These patients should also be offered a DRE and a PSA test.	C
4	Urinary infection should be excluded before PSA testing, especially in men presenting with lower tract symptoms. The PSA test should be postponed for at least 1 month after treatment of a proven urinary infection.	C

- 5** If a hard, irregular prostate typical of a prostate carcinoma is felt on rectal examination, then the patient should be referred urgently. The PSA should be measured and the result should accompany the referral. Patients do not need urgent referral if the prostate is simply enlarged and the PSA is in the age-specific reference range⁸. **C**
- 6** In a male a patient with or without lower urinary tract symptoms and in whom the prostate is normal on DRE but the age-specific PSA is raised or rising, an urgent referral should be made. In those patients whose clinical state is compromised by other comorbidities, a discussion with the patient or carers and/or a specialist in urological cancer may be more appropriate. **C**
- 7** Symptomatic patients with high PSA levels should be referred urgently. **C**
- 8** If there is doubt about whether to refer an asymptomatic male with a borderline level of PSA, the PSA test should be repeated after an interval of 1 to 3 months. If the second test indicates that the PSA level is rising, the patient should be referred urgently. **D**

Bladder and renal cancers

- 9** Male or female adult patients of any age who present **C**

⁸ The age-specific cut-off PSA measurements recommended by the Prostate Cancer Risk Management Programme are as follows: aged 50–59 years ≥ 3.0 ng/ml; aged 60–69 years ≥ 4.0 ng/ml; aged 70 years and older ≥ 5.0 ng/ml. (Note that there are no age-specific reference ranges for men aged over 80 years. Nearly all men of this age have at least a focus of cancer in the prostate. Prostate cancer only needs to be diagnosed in this age group if it is likely to need palliative treatment.)

with painless macroscopic haematuria should be referred urgently.

- 10** In male or female patients with symptoms suggestive of a urinary infection who also present with macroscopic haematuria, investigations should be undertaken to diagnose and treat the infection before consideration of referral. If infection is not confirmed the patient should be referred urgently. **D**
- 11** In all adult patients aged 40 years and older who present with recurrent or persistent urinary tract infection associated with haematuria, an urgent referral should be made. **C**
- 12** In patients under 50 years of age with microscopic haematuria, the urine should be tested for proteinuria and serum creatinine levels measured. Those with proteinuria or raised serum creatinine should be referred to a renal physician. If there is no proteinuria and serum creatinine is normal, a non-urgent referral to a urologist should be made. **C**
- 13** In patients aged 50 years and older who are found to have unexplained microscopic haematuria, an urgent referral should be made. **C**
- 14** Any patient with an abdominal mass identified clinically or on imaging that is thought to be arising from the urinary tract should be referred urgently. **C**

Testicular cancer

- 15** Any patient with a swelling or mass in the body of the **C**

testis should be referred urgently.

- 16** An urgent ultrasound should be considered in men with a scrotal mass that does not transilluminate and/or when the body of the testis cannot be distinguished. **D**

Penile cancer

- 17** An urgent referral should be made for any patient presenting with symptoms or signs of penile cancer. These include progressive ulceration or a mass in the glans or prepuce particularly, but can involve the skin of the penile shaft. Lumps within the corpora cavernosa not involving penile skin are usually not cancer but indicate Peyronie's disease, which does not require urgent referral. **D**

4.9. Haematological Cancers

Number **grade**

General recommendations

- | | | |
|----------|--|----------|
| 1 | A patient who presents with symptoms suggesting haematological cancer should be referred to a team specialising in the management of haematological cancer, depending on local arrangements. | D |
| 2 | Primary healthcare professionals should be aware that haematological cancers can present with a variety of symptoms that may have a number of different clinical explanations. | D |
| 3 | Combinations of the following symptoms and signs may suggest haematological cancer and warrant full examination, further investigation (including a blood count and film) and possible referral: <ul style="list-style-type: none">• fatigue• drenching night sweats• fever• weight loss• generalised itching• breathlessness• bruising• bleeding• recurrent infections• bone pain• alcohol-induced pain• abdominal pain• lymphadenopathy• splenomegaly. | C |

The urgency of referral depends on the severity of the symptoms and signs, and findings of investigations.

Specific Recommendations

- 4 In patients with a blood count or blood film reported as acute leukaemia, an immediate referral should be made. **D**
- 5 In patients with persistent unexplained splenomegaly, an urgent referral should be made. **C**

Investigations

- 6 Investigation of patients with persistent unexplained fatigue should include a full blood count, blood film and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy), and repeated at least once if the patient's condition remains unexplained and does not improve. **[B(DS)]**
- 7 Investigation of patients with unexplained lymphadenopathy should include a full blood count, blood film and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). **[B(DS)]**
- 8 Any of the following additional features of lymphadenopathy should trigger further investigation and/or referral: **[C(DS)]**
- persistence for 6 weeks or more
 - lymph nodes increasing in size
 - lymph nodes greater than 2 cm in size
 - widespread nature
 - associated splenomegaly, night sweats or weight loss.

- 9 Investigation of a patient with unexplained bruising, bleeding, and purpura or symptoms suggesting anaemia should include a full blood count, blood film, clotting screen and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). **[B(DS)]**
- 10 A patient with bone pain that is persistent and unexplained should be investigated with full blood count and X-ray, urea and electrolytes, liver and bone profile, PSA test (in males) and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). **[C(DS)]**
- 11 In patients with spinal cord compression or renal failure suspected of being caused by myeloma, an immediate referral should be made. **C**

4.10. Skin Cancer

Number		Grade
1	A patient presenting with skin lesions suggestive of skin cancer or in whom a biopsy has been confirmed should be referred to a team specialising in skin cancer.	D
2	All primary healthcare professionals should be aware of the 7-point weighted checklist (see recommendation 1.10.8) for assessment of pigmented skin lesions.	C
3	All primary healthcare professionals who perform minor surgery should have received appropriate accredited training in relevant aspects of skin surgery including cryotherapy, curettage, and incisional and excisional biopsy techniques, and should undertake appropriate continuing professional development.	D
4	Patients with persistent or slowly evolving unresponsive skin conditions in which the diagnosis is uncertain and cancer is a possibility should be referred to a dermatologist.	D
5	All excised skin specimens should be sent for pathological examination.	[C(DS)]
6	On making a referral of a patient in whom an excised lesion has been diagnosed as malignant, a copy of the pathology report should be sent with the referral correspondence, as there may be details (such as tumour thickness, excision margin) that will specifically influence future management.	D

Number	Specific recommendations	Grade
7	<p data-bbox="395 300 561 340">Melanoma</p> <p data-bbox="395 353 1193 667">Change is a key element in diagnosing malignant melanoma. For low-suspicion lesions, careful monitoring for change should be undertaken using the 7-point checklist (see recommendation 1.10.8) for 8 weeks. Measurement should be made with photographs and a marker scale and/or ruler.</p>	D
8	<p data-bbox="395 743 1193 891">All primary healthcare professionals should use the weighted 7-point checklist in the assessment of pigmented lesions to determine referral:</p> <p data-bbox="395 904 813 945">Major features of the lesions:</p> <ul data-bbox="395 958 702 1106" style="list-style-type: none"><li data-bbox="395 958 702 999">▪ change in size<li data-bbox="395 1012 702 1052">▪ irregular shape<li data-bbox="395 1066 702 1106">▪ irregular colour. <p data-bbox="395 1182 813 1223">Minor features of the lesions:</p> <ul data-bbox="395 1236 922 1438" style="list-style-type: none"><li data-bbox="395 1236 922 1276">▪ largest diameter 7 mm or more<li data-bbox="395 1290 667 1330">▪ inflammation<li data-bbox="395 1344 577 1384">▪ oozing<li data-bbox="395 1397 778 1438">▪ change in sensation. <p data-bbox="395 1460 1193 1711">Suspicion is greater for lesions scoring 3 points or more (based on major features scoring 2 points each and minor features scoring 1 point each). However, if there are strong concerns about cancer, any one feature is adequate to prompt urgent referral.</p>	C

Number		Grade
9	In patients with a lesion suspected to be melanoma (see recommendation 1.10.8), an urgent referral to a dermatologist or other suitable specialist with experience of melanoma diagnosis should be made, and excision in primary care should be avoided.	C
Squamous cell carcinomas		
10	Squamous cell carcinomas present as keratinizing or crusted tumours that may ulcerate. Non-healing lesions larger than 1 cm with significant induration on palpation, commonly on face, scalp or back of hand with a documented expansion over 8 weeks, may be squamous cell carcinomas and an urgent referral should be made.	C
11	Squamous cell carcinomas are common in patients on immunosuppressive treatment, but may be atypical and aggressive. In patients who have had an organ transplant who develop new or growing cutaneous lesions, an urgent referral should be made.	C
12	In any patient with histological diagnosis of a squamous cell carcinoma made in primary care, an urgent referral should be made.	C
Basil cell carcinomas		
13	Basal cell carcinomas are slow growing, usually without significant expansion over 2 months, and usually occur on the face. Where there is a suspicion that the patient has a basal cell carcinoma, a non-urgent referral should be made.	C

Number	Investigations	Grade
14	All pigmented lesions that are not viewed as suspicious of melanoma but are excised should have a lateral excision margin of 2 mm of clinically normal skin and cut to include subcutaneous fat in depth.	[B(DS)]

4.11. Head and Neck Cancer

Number		Grade
	General recommendations	
1	A patient who presents with symptoms suggestive of head and neck or thyroid cancer should be referred to an appropriate specialist or the neck lump clinic, depending on local arrangements.	D
2	Any patient with persistent symptoms or signs related to the oral cavity in whom a definitive diagnosis of a benign lesion cannot be made should be referred or followed up until the symptoms and signs disappear. If the symptoms and signs have not disappeared after 6 weeks, an urgent referral should be made.	D
3	Primary healthcare professionals should advise all patients, including those with dentures, to have regular dental checkups.	D
	Specific recommendations	
4	<p>A patient who presents with unexplained red and white patches (including suspected lichen planus) of the oral mucosa that are:</p> <ul style="list-style-type: none">• painful, or• swollen, or• bleeding <p>an urgent referral should be made.</p> <p>A non-urgent referral should be made in the absence of these features. If oral lichen planus is confirmed,</p>	C

the patient should be monitored for oral cancer as part of routine dental examination.⁹

- 5** In patients with unexplained ulceration of the oral mucosa or mass persisting for more than 3 weeks, an urgent referral should be made. **C**
- 6** In adult patients with unexplained tooth mobility persisting for more than 3 weeks, an urgent referral to a dentist should be made. **C**
- 7** In any patient with hoarseness persisting for more than 3 weeks, particularly smokers aged 50 years and older and heavy drinkers, an urgent referral for a chest X-ray should be made. Patients with positive findings should be referred urgently to a team specialising in the management of lung cancer. Patients with a negative finding should be urgently referred to a team specialising in head and neck cancer. **C**
- 8** In patients with an unexplained lump in the neck which has recently appeared or a lump which has not been diagnosed before that has changed over a period of 3 to 6 weeks, an urgent referral should be made. **C**
- 9** In patients with an unexplained persistent swelling in the parotid or submandibular gland, an urgent referral should be made. **D**

⁹ See: National Institute for Clinical Excellence (2004) Dental recall: recall interval between routine dental examinations. *NICE Clinical Guideline* No. 19. National Institute for Clinical Excellence. Available from: www.nice.org.uk/CG019

10 In patients with unexplained persistent sore or painful throat, an urgent referral should be made. **D**

11 In patients with unilateral unexplained pain in the head and neck area for more than 4 weeks, associated with otalgia (ear ache) but with normal otoscopy, an urgent referral should be made. **D**

Investigations

12 With the exception of persistent hoarseness (see recommendation 1.11.7), investigations for head and neck cancer in primary care are not recommended as they can delay referral. **D**

Thyroid cancers

13 In patients presenting with symptoms of tracheal compression including stridor due to thyroid swelling, immediate referral should be made. **D**

14 In patients presenting with a thyroid swelling associated with any of the following, an urgent referral should be made: **D**

- a solitary nodule increasing in size
- a history of neck irradiation
- a family history of an endocrine tumour
- unexplained hoarseness or voice changes
- cervical lymphadenopathy
- very young (pre-pubertal) patients
- patients aged 65 years and older.

- 15** In patients with a thyroid swelling without stridor or any of the features indicated in recommendation 1.11.14, the primary healthcare professional should request thyroid function tests. Patients with hyper- or hypothyroidism and an associated goitre are very unlikely to have thyroid cancer and could be referred, non-urgently, to an endocrinologist. Those with goitre and normal thyroid function tests who do not have any of the features indicated in recommendation 1.11.14 should be referred non-urgently. **D**
- 16** Initiation of other investigations by the primary healthcare professional, such as ultrasonography or isotope scanning, is likely to result in unnecessary delay and is not recommended. **D**

4.12. Brain and CNS Cancer

Number		Grade
	General recommendations	
1	A patient who presents with symptoms suggestive of brain or CNS cancer should be referred to an appropriate specialist, depending on local arrangements.	D
2	If a primary healthcare professional has concerns about the interpretation of a patient's symptoms and/or signs, a discussion with a local specialist should be considered. If rapid access to scanning is available, this investigation should also be considered as an alternative.	D
	Specific Recommendations	
3	In patients with new, unexplained headaches or neurological symptoms, the primary healthcare professional should undertake a neurological examination guided by the symptoms, but including examination for papilloedema. The absence of papilloedema does not exclude the possibility of a brain tumour.	D
4	In any patient with symptoms related to the CNS (including progressive neurological deficit, new onset seizures, headaches, mental changes, cranial nerve palsy, unilateral sensorineural deafness) in whom a brain tumour is suspected, an urgent referral should be made. The development of new signs related to the CNS should be considered as potential indications for referral.	C

Headaches

- 5** In patients with headaches of recent onset **C**
accompanied by either features suggestive of raised
intra-cranial pressure (for example, vomiting,
drowsiness, postural related headache, headache
with pulse synchronous tinnitus) or other focal or
non-focal neurological symptoms (for example,
blackout, change in personality or memory), an
urgent referral should be made.
- 6** In patients with unexplained headaches of recent **D**
onset, present for at least 1 month but not
accompanied by features suggestive of raised intra-
cranial pressure (see recommendation 1.12.5),
discussion with a local specialist or referral (usually
non-urgent) should be considered.
- 7** In patients with a new, qualitatively different **C**
unexplained headache that becomes progressively
severe, an urgent referral should be made.
- 8** Re-assessment and re-examination is required if the **D**
patient does not progress according to expectations.

Seizures

- 9** A detailed history should be taken from the patient **C**
and an eyewitness to the event if possible, to
determine whether or not a seizure is likely to have
occurred.¹⁰

¹⁰ National Institute for Clinical Excellence (2004) The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. *NICE Clinical Guideline* No. 20. National Institute for Clinical Excellence. Available from: www.nice.org.uk/CG020

10 In patients presenting with a seizure, a physical examination (including cardiac, neurological, mental state) and developmental assessment, where appropriate, should be carried out. **C**

11 In any patient with suspected recent onset seizures, an urgent referral to a neurologist should be made. **C**

Other neurological features

12 In patients with rapid progression of: **B / C / D**

- subacute focal neurological deficit **[B]**
- unexplained cognitive impairment, behavioural disturbance, or slowness or a combination of these **[C]**
- personality changes confirmed by a witness (for example, a carer, friend or a family member) and for which there is no reasonable explanation even in the absence of the other symptoms and signs of a brain tumour **[D]**

An urgent referral to an appropriate specialist should be considered.

Risk Factors

13 In patients previously diagnosed with any cancer an urgent referral should be made if the patient develops any of the following symptoms: **C**

- recent onset seizure
- progressive neurological deficit
- persistent headaches
- new mental or cognitive changes
- new neurological signs.

4.13. Bone Cancer and Sarcoma

Number		Grade
General recommendations		
1	A patient who presents with symptoms suggesting bone cancer or sarcoma should be referred to a team specialising in the management of bone cancer and sarcoma, or to a recognised bone cancer centre, depending on local arrangements.	D
2	If a primary healthcare professional has concerns about the interpretation of a patient's symptoms and/or signs, a discussion with the local specialist should be considered.	D
3	Patients with increasing, unexplained or persistent bone pain or tenderness, particularly pain at rest (and especially if not in the joint), or an unexplained limp should be investigated by the primary healthcare professional urgently. The nature of the investigations will vary according to the patient's age and clinical features. <ul style="list-style-type: none">• In older people metastases, myeloma or lymphoma, as well as sarcoma, should be considered.	[C(DS)]
Specific Recommendations		
Bone tumours		
4	A patient with a suspected spontaneous fracture should be referred for an immediate X-ray.	[B(DS)]
5	If an X-ray indicates that bone cancer is a possibility, an urgent referral should be made.	[C(DS)]

- 6** If the X-ray is normal but symptoms persist, the patient should be followed up and/or a repeat X-ray or bone function tests or a referral requested. **[C(DS)]**

Soft tissue sarcomas

- 7** In patients presenting with a palpable lump, an urgent referral for suspicion of soft tissue sarcoma should be made if the lump is: **C**

- greater than about 5 cm in diameter
- deep to fascia, fixed or immobile
- painful
- increasing in size
- a recurrence after previous excision.

If there is any doubt about the need for referral, discussion with a local specialist should be undertaken.

- 8** If a patient has HIV disease, Kaposi's sarcoma should be considered and a referral made if this is suspected. **C**

4.14. Children's Cancer

Number		Grade
General Recommendations		
1	Children and young people who present with symptoms and signs of cancer should be referred to a paediatrician or a specialist children's cancer service, if appropriate.	D
2	Childhood cancer is rare and may present initially with symptoms and signs associated with common conditions. Therefore, in the case of a child or young person presenting several times (for example, three or more times) with the same problem, but with no clear diagnosis, urgent referral should be made.	D
3	The parent is usually the best observer of the child's or young person's symptoms. The primary healthcare professional should take note of parental insight and knowledge when considering urgent referral.	D
4	Persistent parental anxiety should be a sufficient reason for referral of a child or young person, even when the primary healthcare professional considers that the symptoms are most likely to have a benign cause.	D
5	Persistent back pain in a child or young person can be a symptom of cancer and is indication for an examination, investigation with a full blood count and blood film, and consideration of referral.	C

Number		Grade
6	There are associations between Down syndrome and leukaemia, neurofibromatosis and CNS tumours, and between other rare syndromes and some cancers. The primary healthcare professional should be alert to the potential significance of unexplained symptoms in children or young people with such syndromes.	D
7	The primary healthcare professional should convey information to the parents and child/young person about the reason for referral and which service the child/young person is being referred to so that they know what to do and what will happen next.	D
8	The primary healthcare professional should establish good communication with the parents and child/young person in order to develop the supportive relationship that will be required during the further management if the child/young person is found to have cancer.	D

Number	Specific Recommendations	Grade
9	<p data-bbox="389 300 852 344"><i>Leukaemia (children of all ages)</i></p> <p data-bbox="389 353 1219 560">Leukaemia usually presents with a relatively short history of weeks rather than months. The presence of one or more of the following symptoms and signs requires investigation with full blood count and blood film:</p> <ul data-bbox="443 577 1136 1070" style="list-style-type: none"><li data-bbox="443 577 571 622">• pallor<li data-bbox="443 631 587 676">• fatigue<li data-bbox="443 685 801 730">• unexplained irritability<li data-bbox="443 739 746 784">• unexplained fever<li data-bbox="443 792 1136 900">• persistent or recurrent upper respiratory tract infections<li data-bbox="443 909 922 954">• generalised lymphadenopathy<li data-bbox="443 963 1002 1008">• persistent or unexplained bone pain<li data-bbox="443 1016 794 1061">• unexplained bruising.	[C(DS)]
10	<p data-bbox="389 1249 1219 1344">The presence of either of the following signs in a child or young person requires immediate referral:</p> <ul data-bbox="443 1352 817 1458" style="list-style-type: none"><li data-bbox="443 1352 817 1397">• unexplained petechiae<li data-bbox="443 1406 801 1458">• hepatosplenomegaly.	C

Lymphomas

Hodgkin's lymphoma presents typically with non tender cervical and/or supraclavicular lymphadenopathy. Lymphadenopathy can also present at other sites. The natural history is long (months). Only a minority of patients have systemic symptoms (itching, night sweats, fever).

Non Hodgkin's lymphoma typically shows a more rapid progression of symptoms, and may present with lymphadenopathy, breathlessness, SVC obstruction, abdominal distension.

- 11** Lymphadenopathy is more frequently benign in younger children but urgent referral is advised if one or more of the following characteristics are present, particularly if there is no evidence of local infection: **C**
- lymph nodes are non-tender, firm or hard
 - lymph nodes are greater than 2 cm in size
 - lymph nodes are progressively enlarging
 - other features of general ill-health, fever or weight loss
 - the axillary nodes are involved (in the absence of local infection or dermatitis)
 - the supraclavicular nodes are involved.
- 12** The presence of hepatosplenomegaly requires immediate referral. **C**

- 13** Shortness of breath is a symptom that can indicate chest involvement but may be confused with other conditions such as asthma. Shortness of breath in association with the above signs (recommendation 1.14.11), particularly if not responding to bronchodilators, is an indication for urgent referral. **C**
- 14** A child or young person with a mediastinal or hilar mass on chest X-ray should be referred immediately. **C**

Brain & CNS Tumours

Children 2 years and older and young people

- 15** Persistent headache in a child or young person requires a neurological examination by the primary healthcare professional. An urgent referral should be made if the primary healthcare professional is unable to undertake an adequate examination. **D**
- 16** Headache and vomiting that cause early morning waking or occur on waking are classical signs of raised intracranial pressure, and an immediate referral should be made. **C**

- 17** The presence of any of the following neurological **D** symptoms and signs should prompt urgent or immediate referral:
- new onset seizures
 - cranial nerve abnormalities
 - visual disturbances
 - gait abnormalities
 - motor or sensory signs
 - unexplained deteriorating school performance or developmental milestones
 - unexplained behavioural and/or mood changes.
- 18** A child or young person with a reduced level of **C** consciousness requires emergency admission.

Children < 2 years

19 In children aged younger than 2 years, any of the **C** following symptoms may suggest a CNS tumour, and referral (as indicated below) is required.

- Immediate referral:
 - new onset seizures
 - bulging fontanelle
 - extensor attacks
 - persistent vomiting.
- Urgent referral:
 - abnormal increase in head size
 - arrest or regression of motor development
 - altered behaviour
 - abnormal eye movements
 - lack of visual following
 - poor feeding/failure to thrive.
- Urgency contingent on other factors:
 - squint.

Neuroblastoma (all ages)

The majority of children with neuroblastoma have symptoms of metastatic disease which may be general in nature (malaise, pallor, bone pain, irritability, fever or respiratory symptoms), and may resemble those of acute leukaemia.

- 20** The presence of the following symptoms and signs **[C(DS)]** requires investigation with FBC:
- persistent or unexplained bone pain (and X-ray)
 - pallor
 - fatigue
 - unexplained irritability
 - unexplained fever
 - persistent or recurrent upper respiratory tract infections
 - generalised lymphadenopathy
 - unexplained bruising.
- 21** Other symptoms which should raise concern about **C** neuroblastoma and prompt urgent referral include:
- proptosis
 - unexplained back pain
 - leg weakness
 - unexplained urinary retention.
- 22** In children or young people with symptoms that could be **[C(DS)]** explained by neuroblastoma, an abdominal examination (and/or urgent abdominal ultrasound) should be undertaken, and a chest X-ray and full blood count considered. If any mass is identified, an urgent referral should be made.

- 23** Infants aged younger than 1 year may have localised abdominal or thoracic masses, and in infants younger than 6 months of age, there may also be rapidly progressive intra-abdominal disease. Some babies may present with skin nodules. If any such mass is identified, an immediate referral should be made. **C**

Wilms' tumour (all ages)

- 24** Wilms' tumour most commonly presents with a painless abdominal mass. Persistent or progressive abdominal distension should prompt abdominal examination, and if a mass is found an immediate referral be made. If the child or young person is uncooperative and abdominal examination is not possible, referral for an urgent abdominal ultrasound should be considered. **C**
- 25** Haematuria in a child or young person, although a rarer presentation of a Wilms' tumour, merits urgent referral. **C**

Soft tissue sarcoma (all ages)

- 26** A soft tissue sarcoma should be suspected and an urgent referral should be made for a child or young person with an unexplained mass at almost any site that has one or more of the following features. The mass is: **C**
- deep to the fascia
 - non-tender
 - progressively enlarging
 - associated with a regional lymph node that is enlarging
 - >2 cm in diameter in size.
- 27** A soft tissue mass in an unusual location may give rise to misleading local and persistent unexplained symptoms and signs, and the possibility of sarcoma should be considered. These symptoms and signs include: **C**
- head and neck sarcomas:
 - proptosis
 - persistent unexplained unilateral nasal obstruction with or without discharge and/or bleeding
 - aural polyps/discharge
 - genitourinary tract:
 - urinary retention
 - scrotal swelling
 - bloodstained vaginal discharge.

Bone sarcomas (osteosarcoma and Ewing's sarcoma)
(all ages)

- 28** Limbs are the most common site for bone tumours, especially around the knee in the case of osteosarcoma. Persistent localised bone pain and/or swelling requires an X-ray. If a bone tumour is suspected, an urgent referral should be made. **C**
- 29** History of an injury should not be assumed to exclude the possibility of a bone sarcoma. **C**
- 30** Rest pain, back pain and unexplained limp may all point to a bone tumour and require discussion with a paediatrician, referral or X-ray. **C**

Retinoblastoma (mostly children aged under 2 years)

- 31** In a child with a white pupillary reflex (leukocoria) noted by the parents, identified in photographs or found on examination, an urgent referral should be made. The primary healthcare professional should pay careful attention to the report by a parent of noticing an odd appearance in their child's eye. **C**
- 32** A child with a new squint or change in visual acuity should be referred. If cancer is suspected, referral should be urgent, but otherwise referral should be non-urgent. **C**

- 33** A family history of retinoblastoma should alert the primary healthcare professional to the possibility of retinoblastoma in a child who presents with visual problems. Offspring of a parent who has had retinoblastoma, or siblings of an affected child, should undergo screening soon after birth. **C**

Investigations

- 34** When cancer is suspected in children and young people, imaging is often required. This may be best performed by a paediatrician, following urgent or immediate referral by the primary healthcare professional. **D**
- 35** The presence of any of the following symptoms and signs requires investigation with full blood count: **[C(DS)]**
- pallor
 - fatigue
 - irritability
 - unexplained fever
 - persistent or recurrent upper respiratory tract infections
 - generalised lymphadenopathy
 - persistent or unexplained bone pain (and X-ray)
 - unexplained bruising.

5 Algorithms

A series of algorithms now follow summarising the principal recommendations for each cancer site. These give guidance on how to proceed when a patient presents with symptoms suggestive of a cancer. They are intended to be used alongside the text version of the recommendations, which should be consulted for full, detailed guidance.

The definitions of unexplained or persistent presented in the guideline glossary are reproduced here for convenience:

Unexplained

When used in a recommendation, unexplained refers to a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any).

Persistent 'Persistent' as used in the recommendations in this guideline refers to the continuation of specified symptoms and/or signs beyond a period that would normally be associated with self-limiting problems. The precise period will vary depending on the severity of symptoms and associated features, as assessed by the health professional. In many cases, the upper limit the professional will permit symptoms and/or signs to persist before initiating referral will be 4-6 weeks.

Referrals

Referral is to a team specialising in the management of the relevant cancer dependant on local arrangements, unless otherwise specified.

Urgency of referral

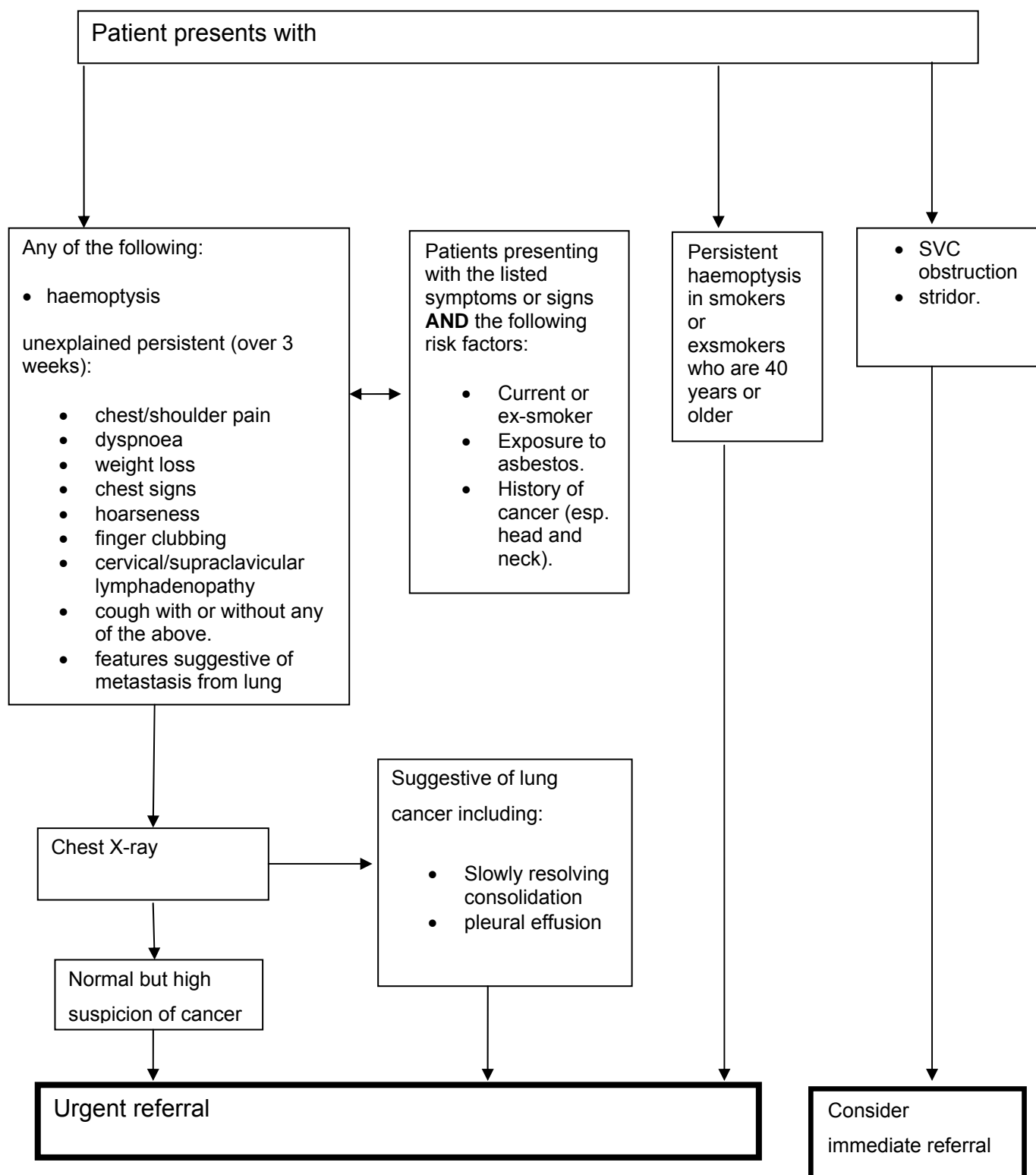
Immediate/emergency.

an acute admission or referral occurring within a few hours, or even more quickly if necessary.

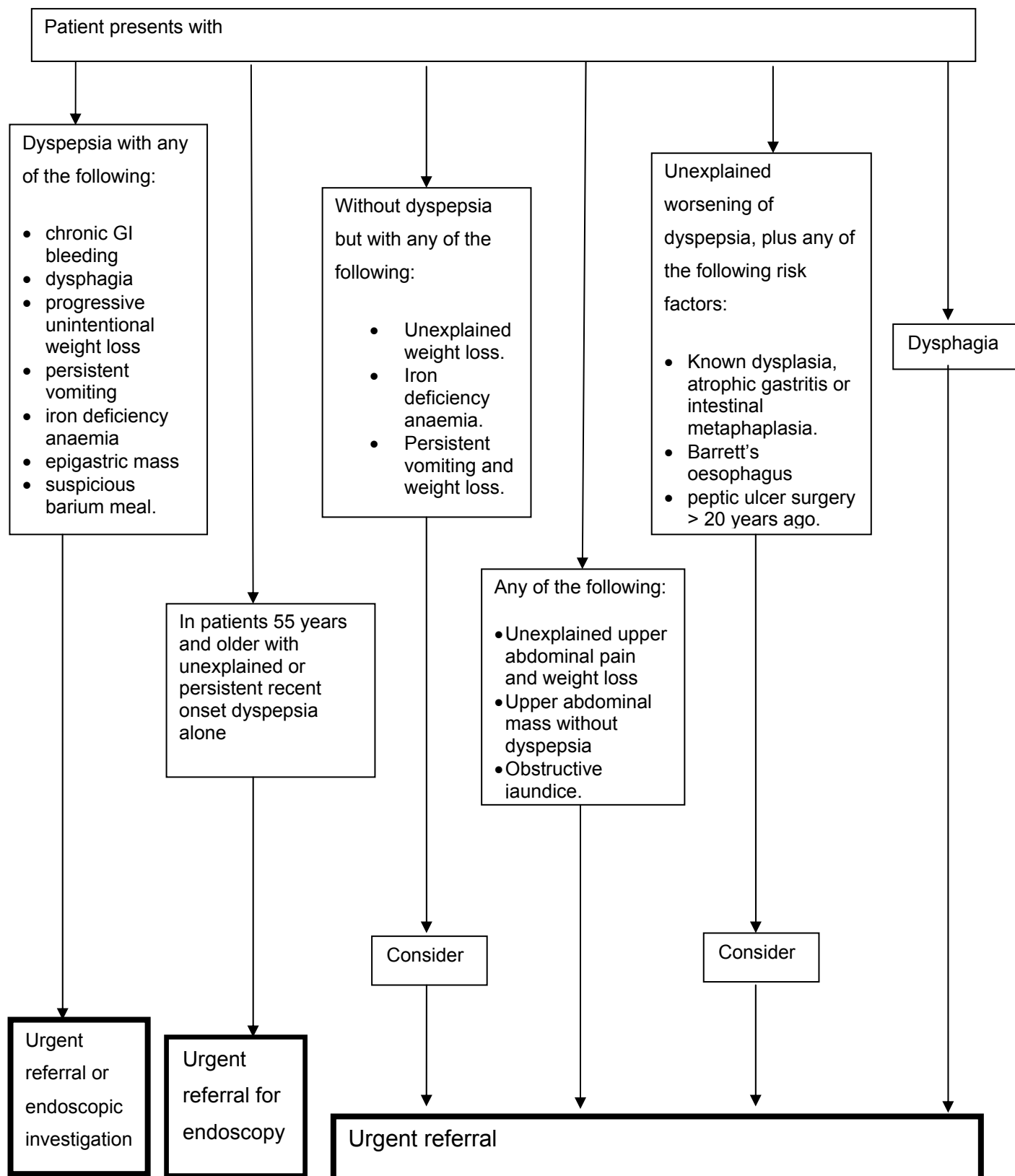
Urgent. the patient is seen within the national target for urgent referrals (currently two weeks).

Non-urgent. all other referrals.

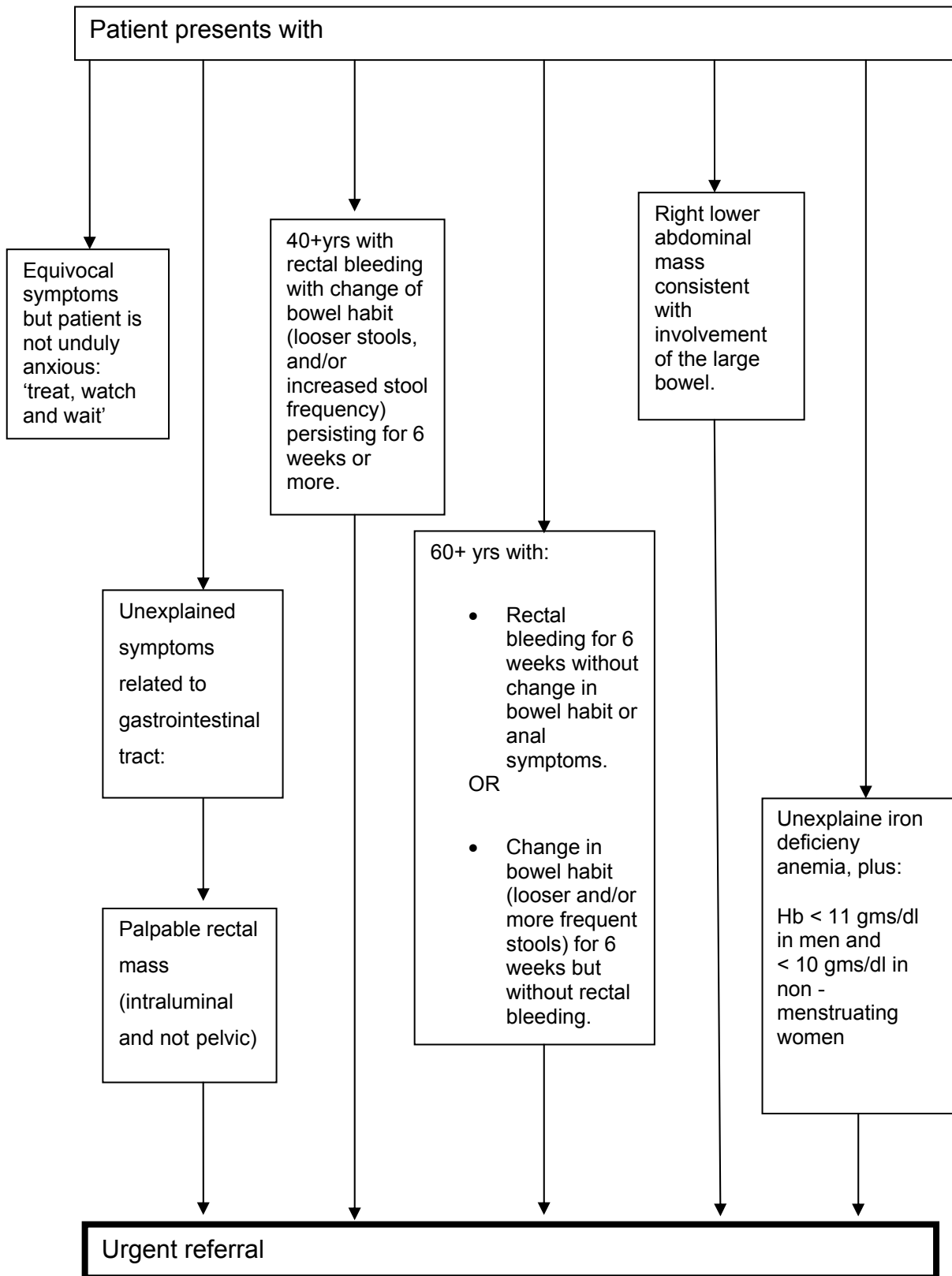
Lung cancer



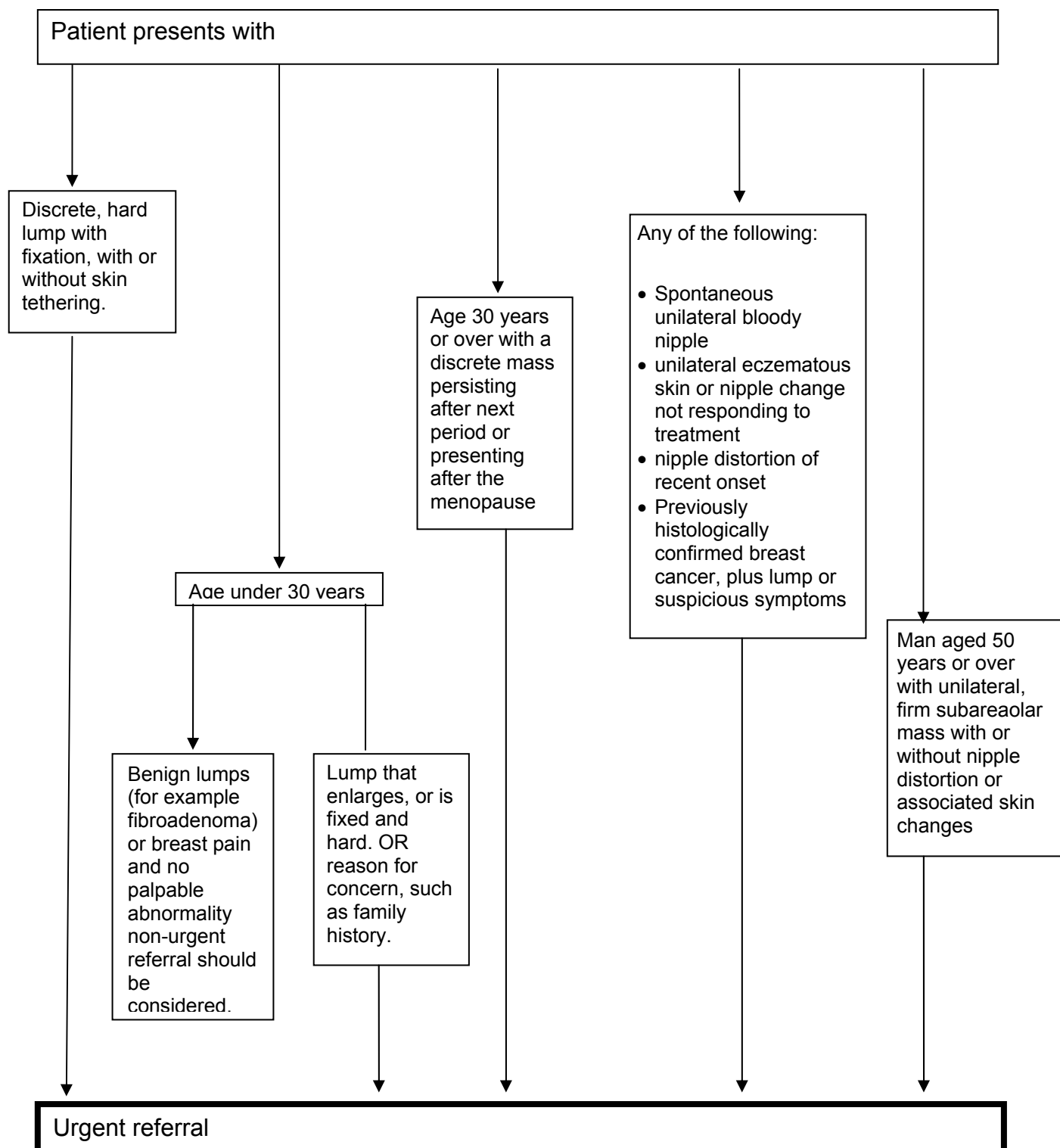
Upper gastrointestinal cancer



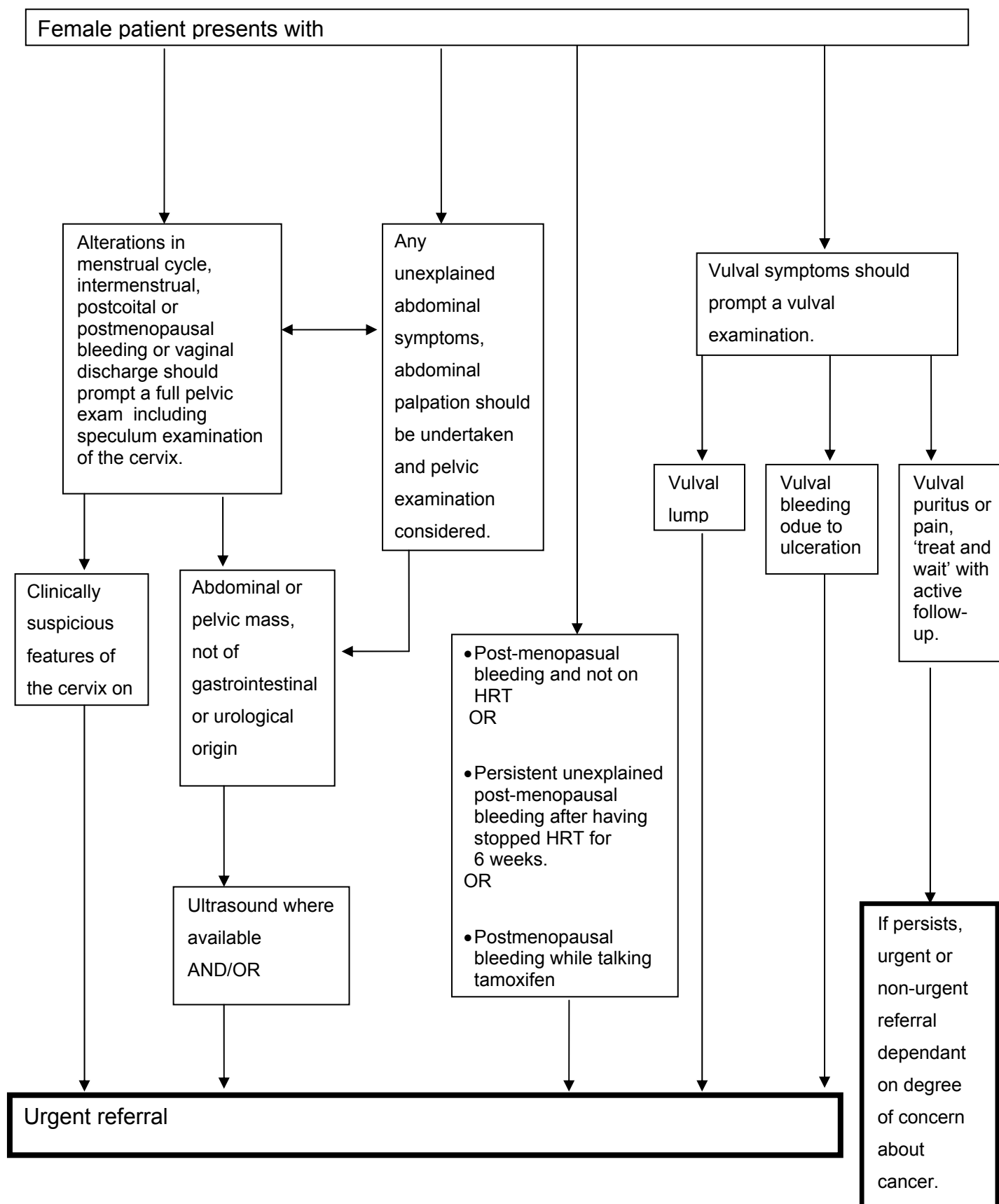
Lower gastrointestinal cancer



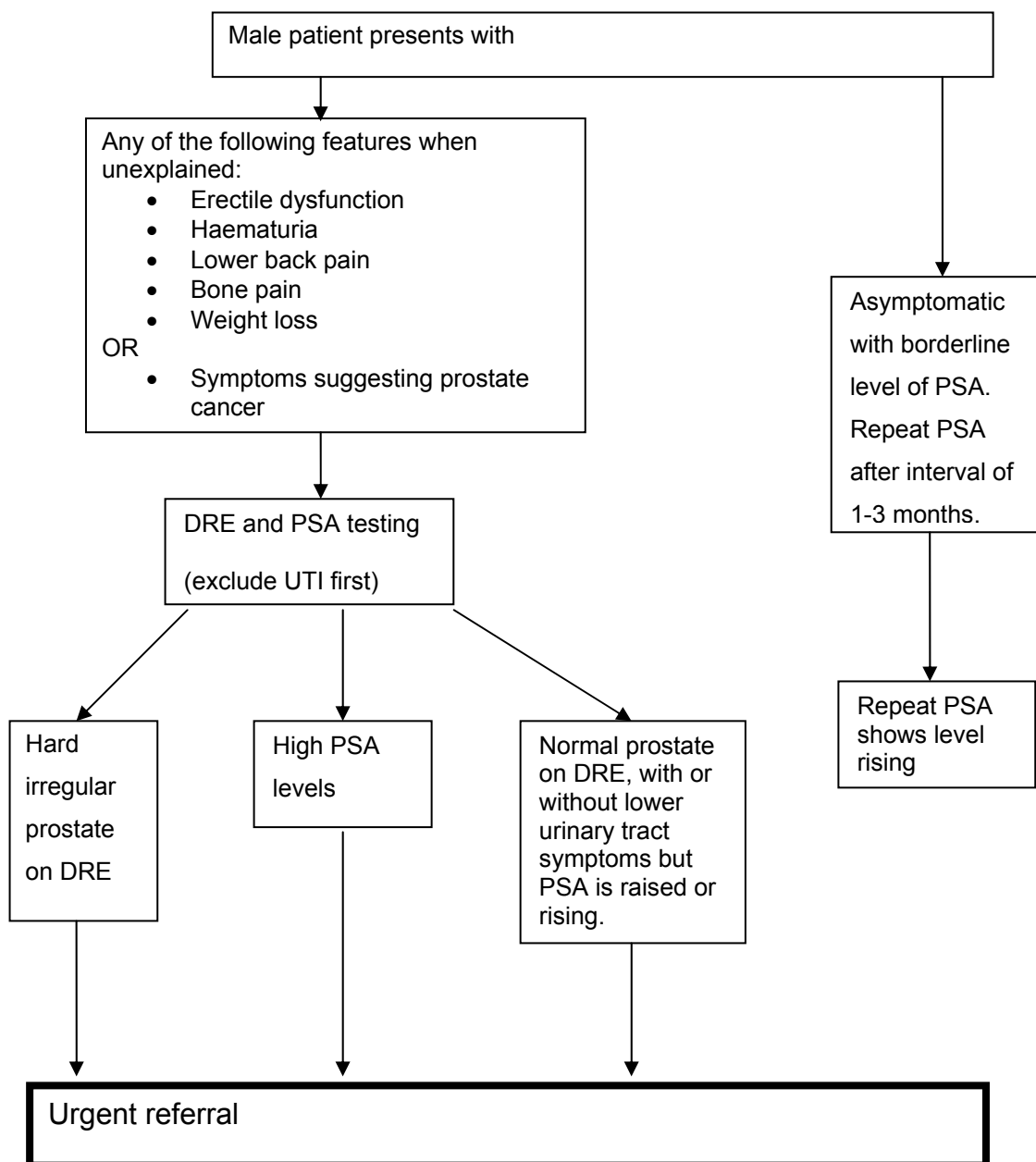
Breast cancer



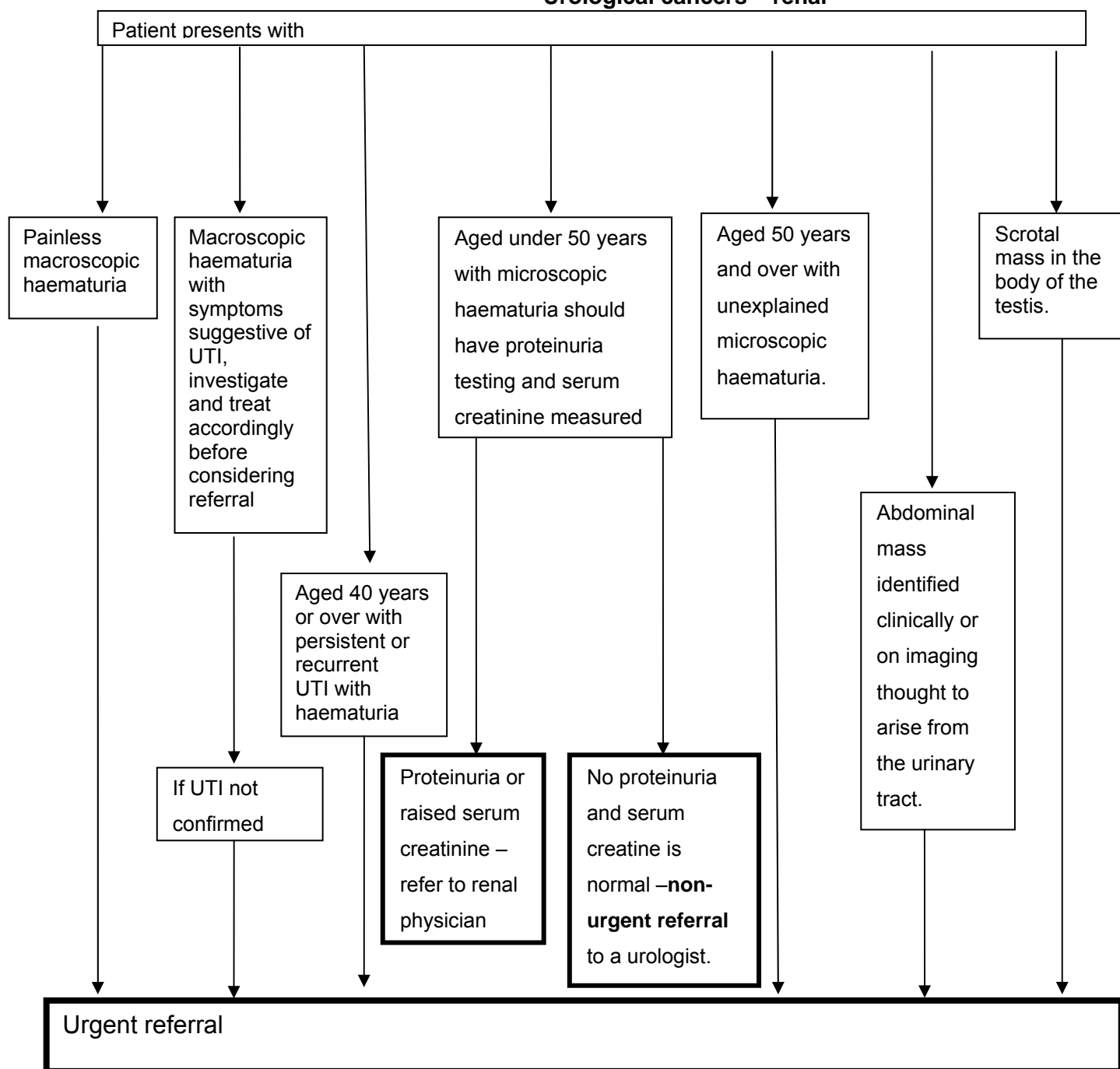
Gynaecological cancers



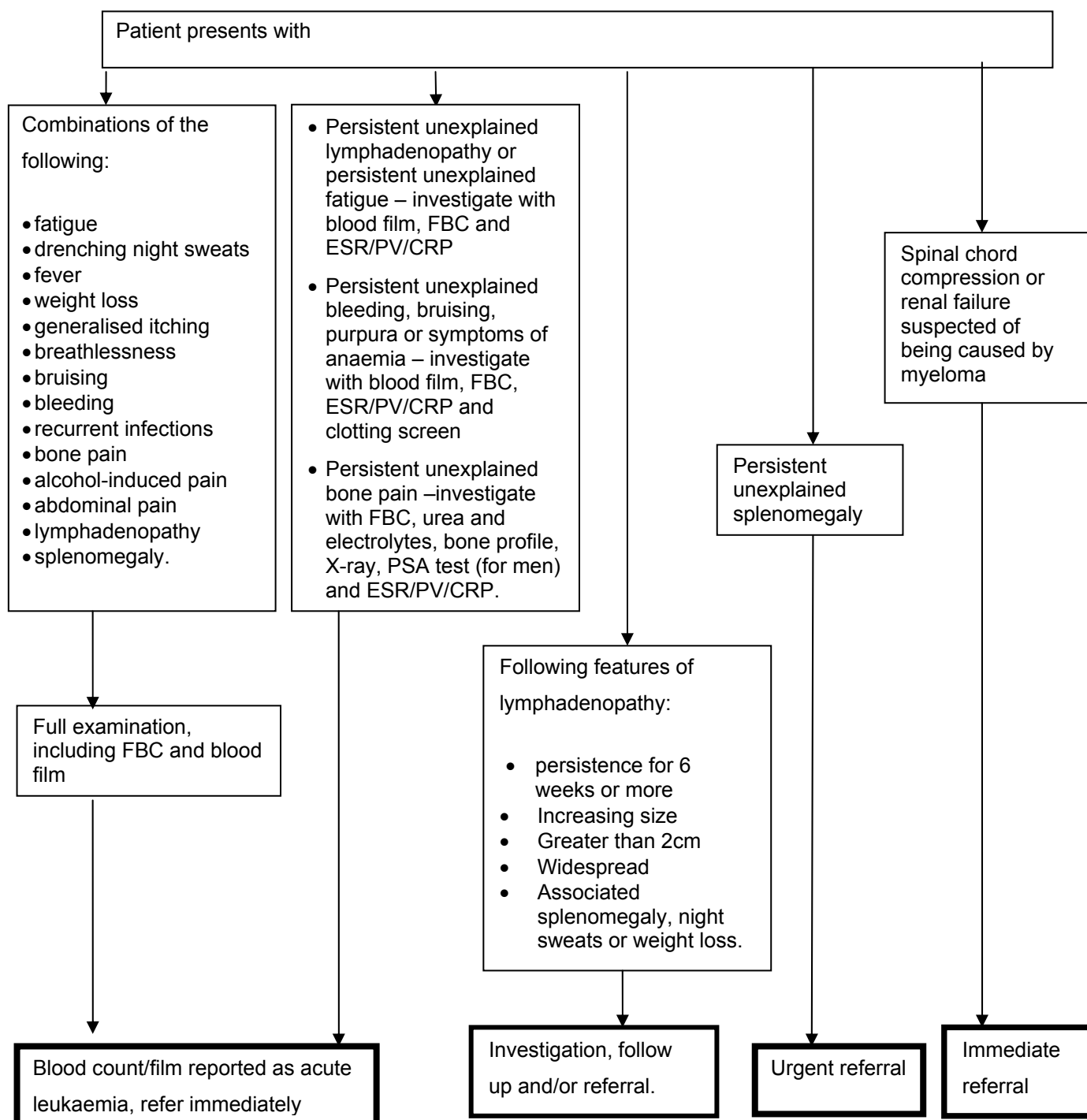
Urological cancers –prostate



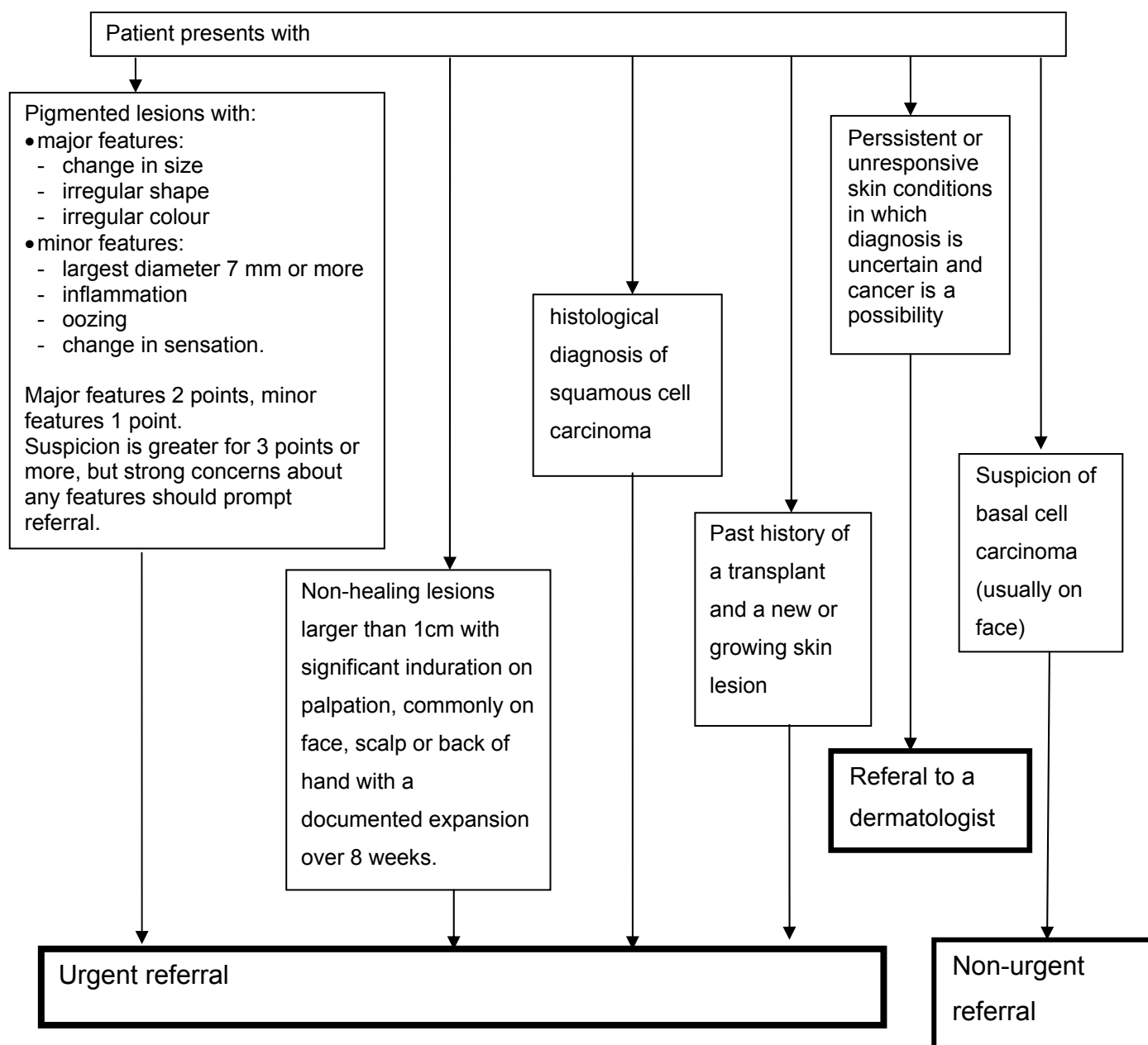
Urological cancers – renal



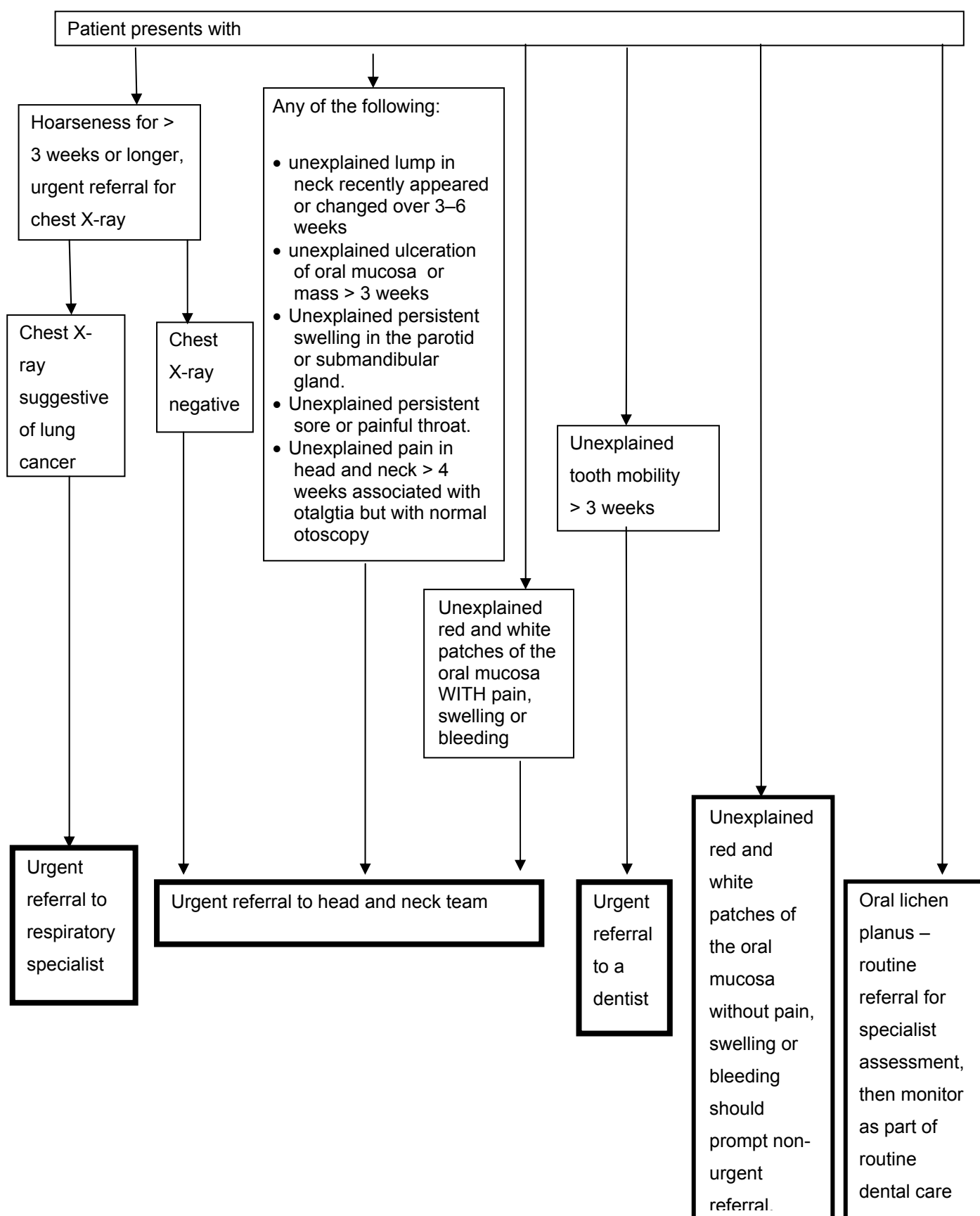
Haematological cancers

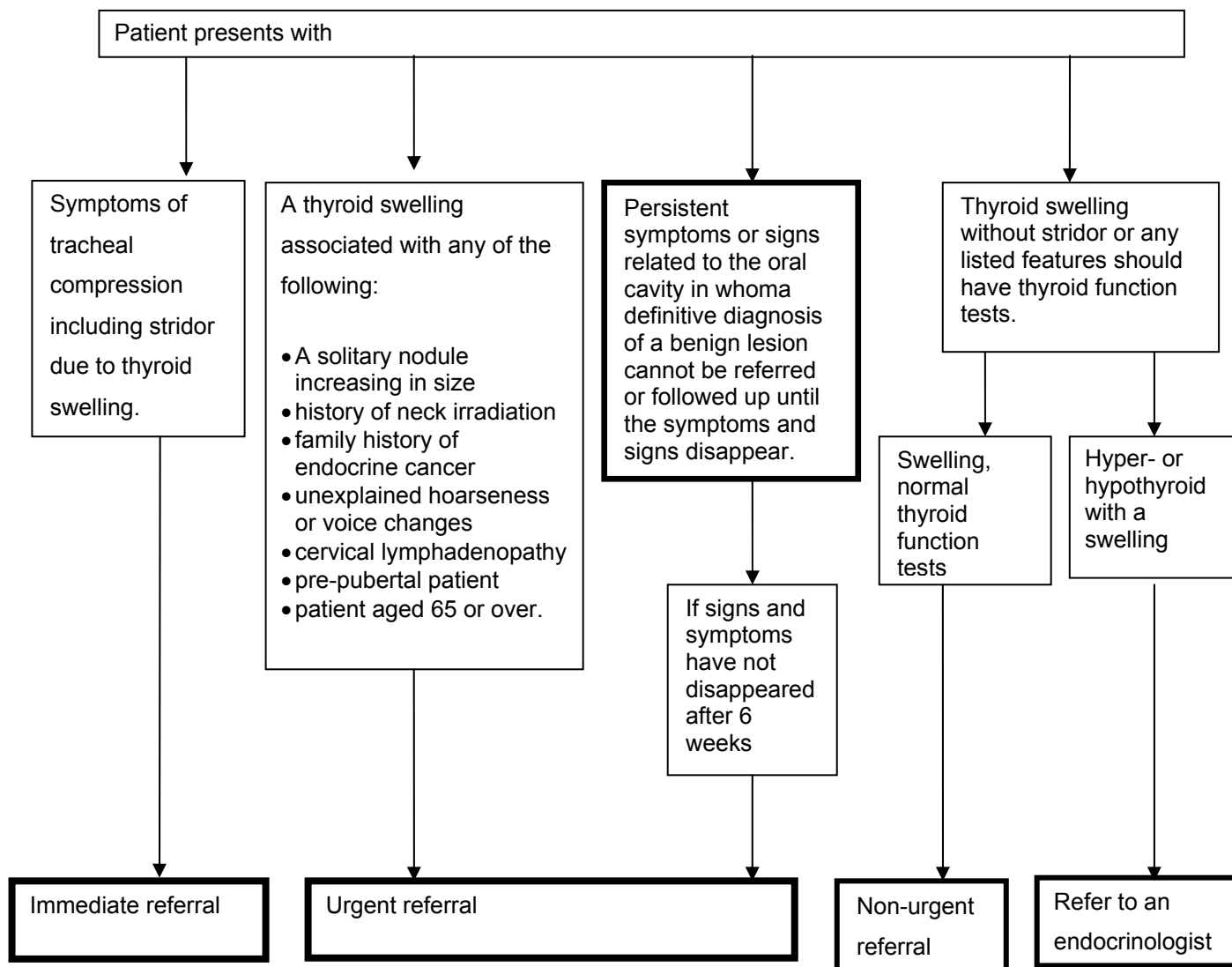


Skin cancers

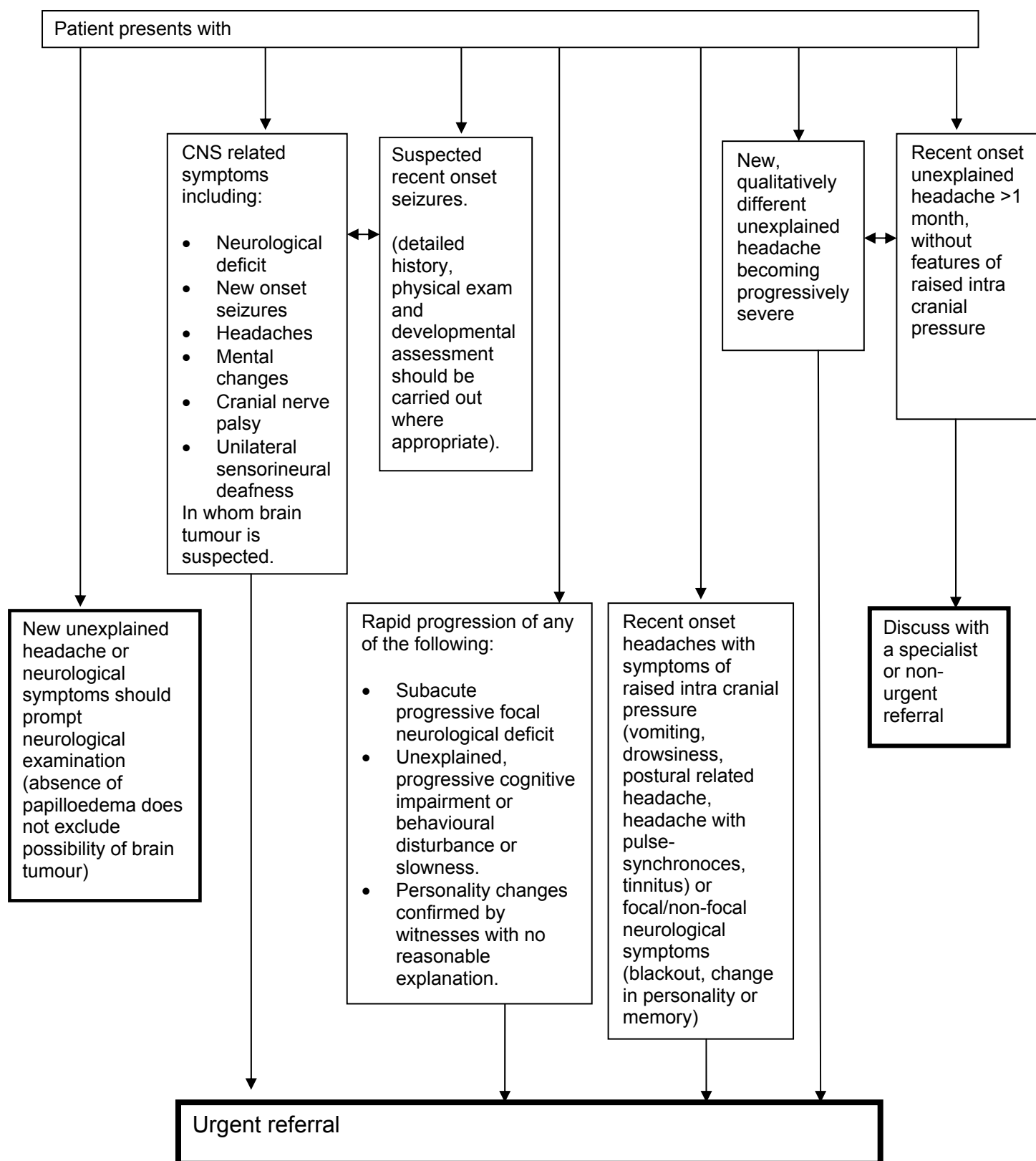


Head and neck cancers

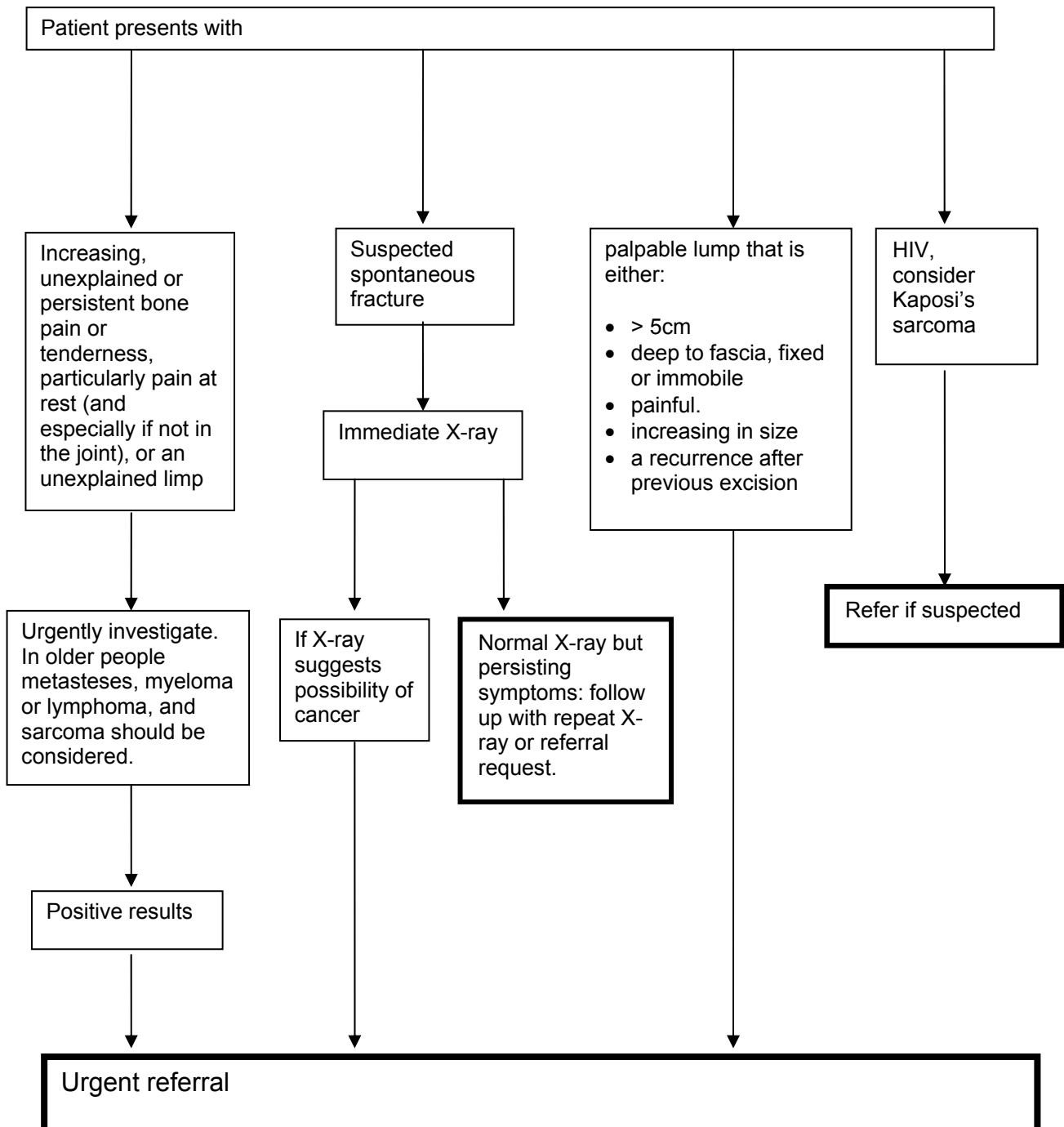




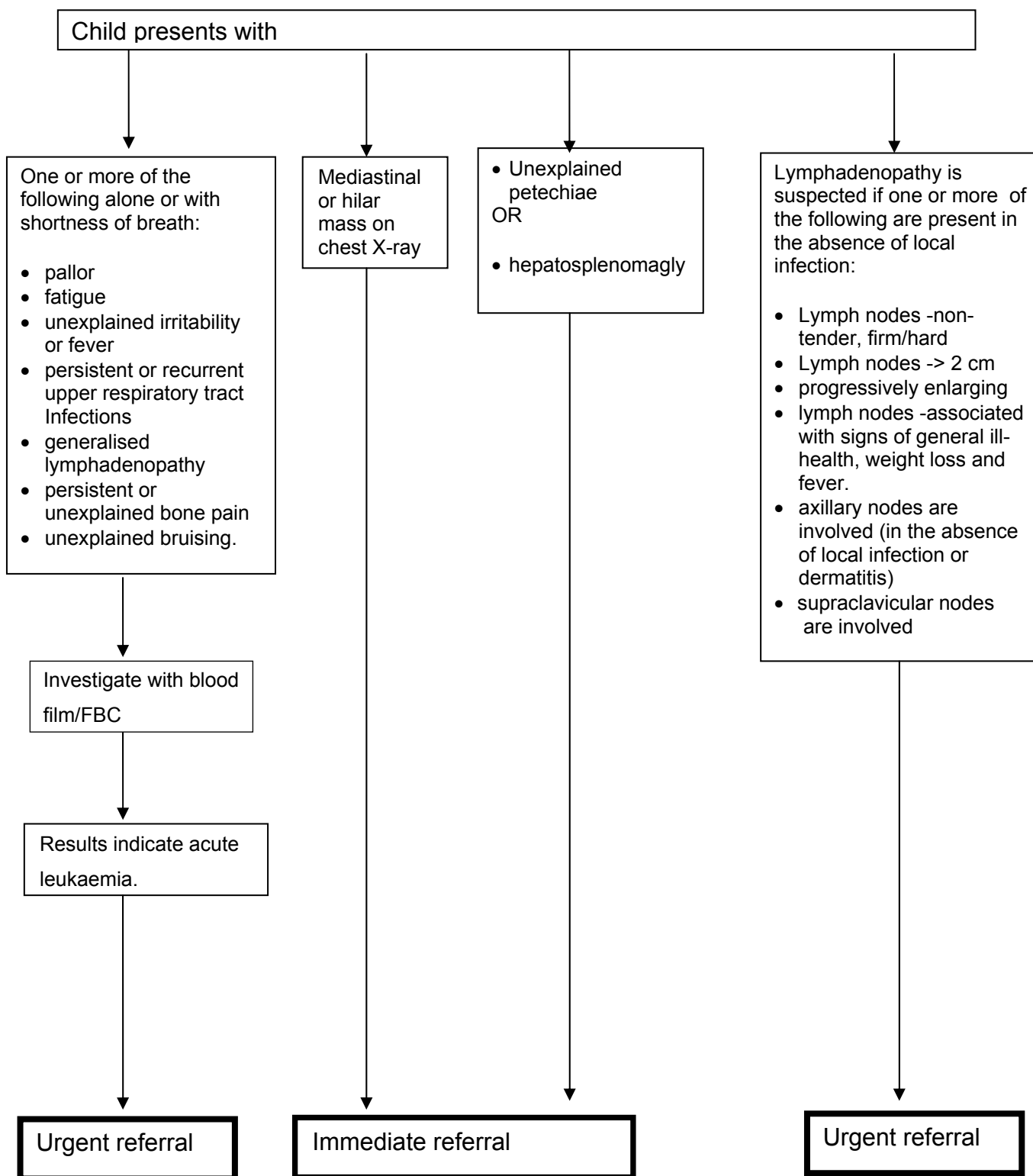
Brain and CNS cancers



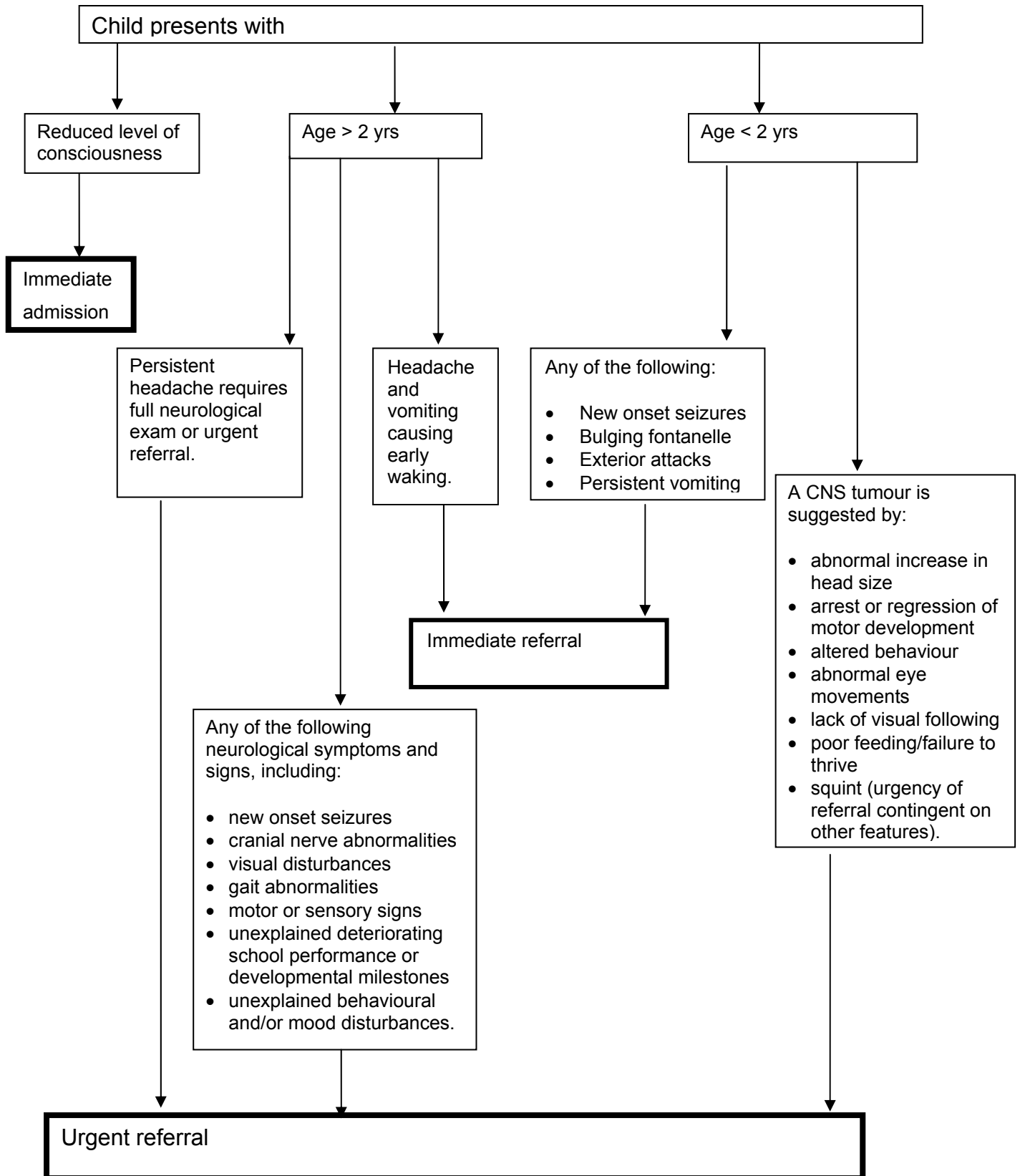
Bone cancers and soft-tissue sarcomas



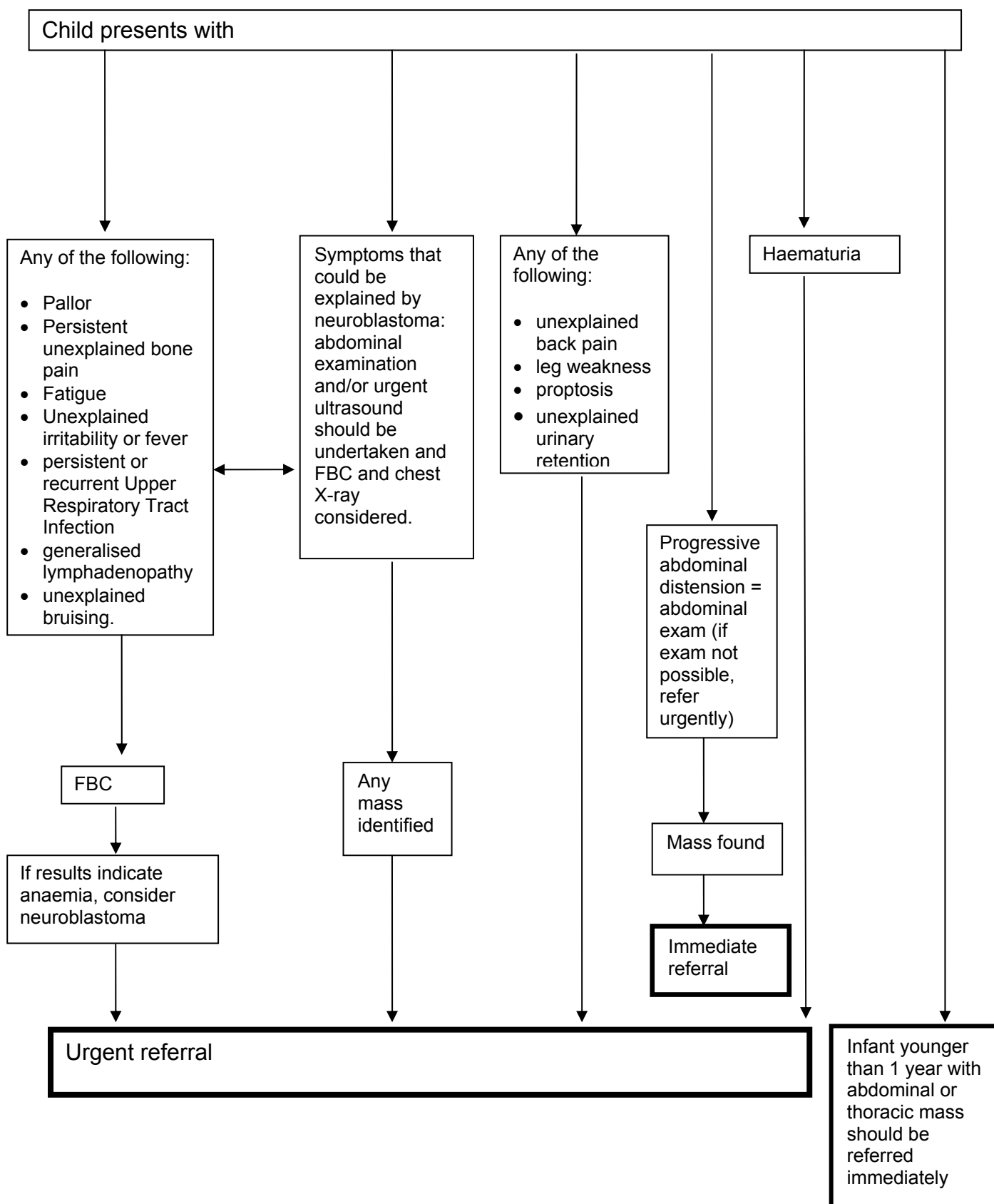
Children's cancers – leukaemia and lymphoma



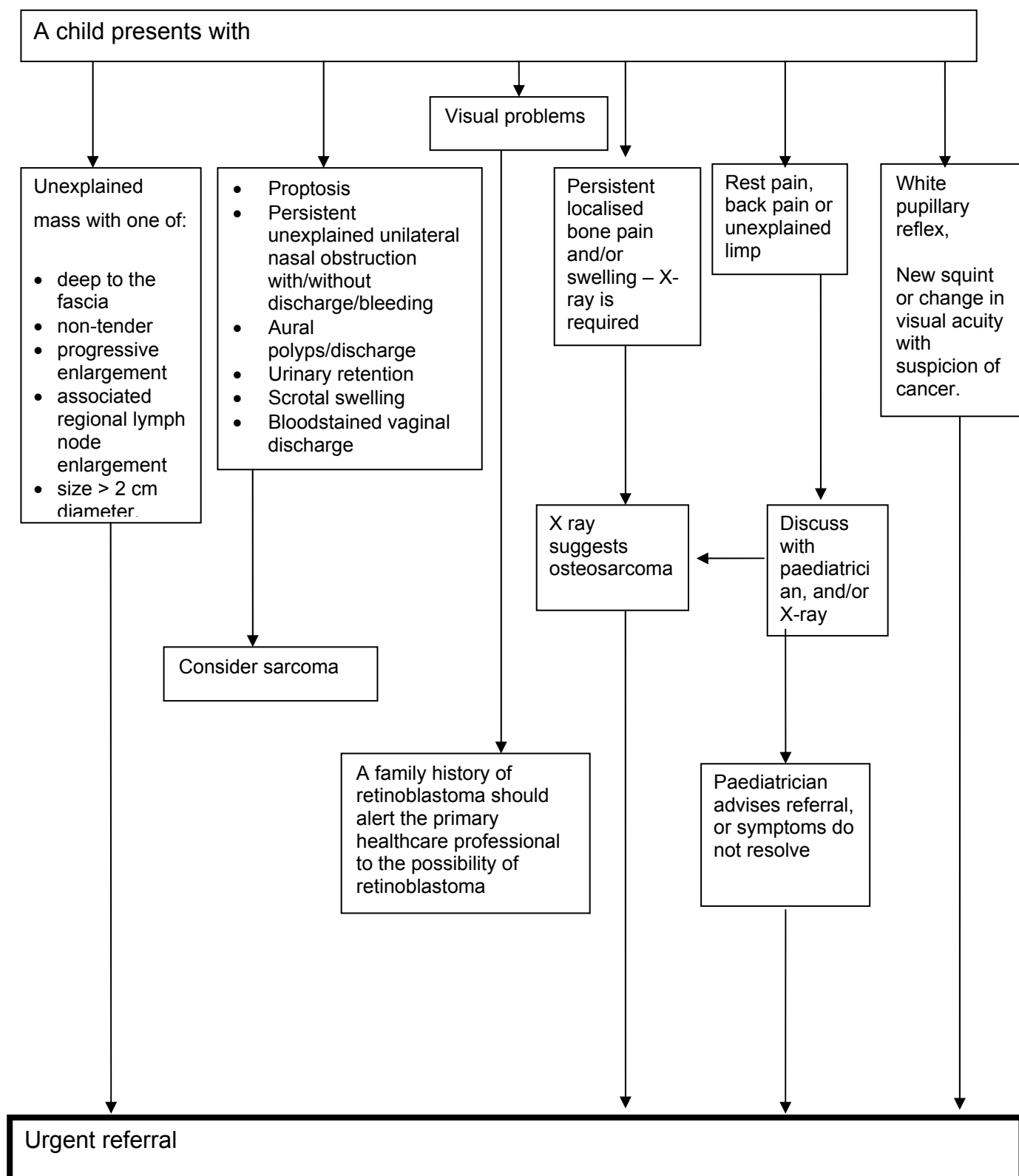
Children's cancers – brain tumours



Children's cancers – neuroblastoma and Wilm's tumour



Children's cancers –bone tumours, sarcoma and retinoblastoma



6 Audit Criteria

6.1 Audit criteria

Criterion: what should happen for a patient?

Standard: the percentage of patients who should receive the care.

Exception(s): clinically acceptable circumstances that would explain why a patient doesn't receive the care described.

Definition of terms: operational definitions of key terms for audit purposes.

Primary health care professionals do not refer many patients with suspected cancer in any one year. The findings of an audit limited to patients referred by one professional in one year will be at risk of misinterpretation because of the small numbers of patients involved. Therefore, the findings of the audit suggested here should be used to generate discussion and learning. The organisation of significant event audit meetings by a primary health care team would be an appropriate way to consider the findings, or delay in diagnosis in individual cases. Significant event audit across the interface with secondary care could be used to investigate the appropriateness of referrals and encourage more efficient referral practice. Many audits of cancer referrals have been undertaken in the past four years, but most have been based in secondary care and have not led to a dialogue between primary and secondary care on improving referral practice. The detection of cancer in a child would be an appropriate topic for significant event audit. In addition, primary care teams should consider the prospective collection of audit information over several years. Consideration should be given to involving patients and carers in audits. Many of the recommendations relate to information given to patients, their support and their involvement in decisions, and it would therefore be appropriate to involve them when possible in audits.

Table 6

Criterion	Standard	Exception	Definition of terms
<p>1. Patients being referred with suspected cancer are offered a) information about the likely diagnosis, b) what to expect from the specialist service, and c) advice about seeking further help whilst awaiting the specialist consultation.</p>	<p>1 a) 100%</p> <p>1 b) 100%</p> <p>1 c) 100%</p>	<p>1 a) Patients who do not want information.</p> <p>1 b) nil</p> <p>1 c) nil</p>	
<p>2. Patients presenting with classical features of the cancers included in the algorithms are a) suspected of having cancer and b) initial investigation or referral is arranged at the first consultation. c) % of patients referred as urgent who are appropriately suspected of having cancer</p> <p>% of patients referred non-urgently who are appropriately assessed as not</p>	<p>2 a) 100%</p> <p>b) 100%</p> <p>c) x% of patients referred urgently have cancer (the % is to be determined from the findings of the review of audits currently being</p>	<p>2 a) nil</p> <p>b) patients who refuse referral or investigation.</p> <p>c) none</p>	

<p>having cancer</p> <p>3. Patients referred for suspected cancer have had preliminary investigations undertaken in primary care as recommended in the guideline.</p>	<p>undertaken)</p> <p>d) y% (% to be determined from the findings of the review of audits currently being undertaken)</p> <p>3. 100%</p>	<p>d) none</p> <p>3. Patients who refuse investigations.</p>	
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Calculation of compliance

Number of patients whose care is consistent with the **criterion**
plus number of patients who meet any **exception** listed

× 100

Number of patients to whom the **measure** applies

7 Support and Information needs of people with suspected cancer at the time of referral

Number		Grade
1	Patients should be able to consult a primary healthcare professional of the same sex if preferred.	D
2	Primary healthcare professionals should discuss with patients (and carers as appropriate, taking account of the need for confidentiality) their preferences for being involved in decision-making about referral options and further investigations (including their potential risks and benefits), and ensure they have the time for this.	D
3	When cancer is suspected in a child, the referral decision and information to be given to the child should be discussed with the parents or carers (and the patient if appropriate).	D
4	Adult patients who are being referred with suspected cancer should normally be told by the primary healthcare professional that they are being referred to a cancer service, but if appropriate they should be reassured that most people referred will not have a diagnosis of cancer, and alternative diagnoses should be discussed.	D
5	Primary healthcare professionals should be willing and able to give the patient information on the possible diagnosis (both benign and malignant) in accordance with the patient's wishes for information. Current advice	D

on communicating with patients and/or their carers and breaking bad news¹¹ should be followed.

6 The information given to patients, family and/or carers as **D** appropriate by the primary healthcare professional should cover, among other issues:

- where patients are being referred to
- how long they will have to wait for the appointment
- how to obtain further information about the type of cancer suspected or help prior to the specialist appointment
- who they will be seen by
- what to expect from the service the patient will be attending
- what type of tests will be carried out, and what will happen during diagnostic procedures
- how long it will take to get a diagnosis or test results
- whether they can take someone with them to the appointment
- other sources of support, including those for minority groups.

7 When referring a patient with suspected cancer to a **D** specialist service, primary healthcare professionals should assess the patient's need for continuing support while waiting for their referral appointment. This should

¹¹ *Improving communication between doctors and patients*. A report of the working party of the Royal College of Physicians (1997)
www.rcplondon.ac.uk/pubs/brochures/pub_print_icbdp

include inviting the patient to contact the primary healthcare professional again if they have more concerns or questions before they see a specialist.

- 8** Consideration should be given by the primary healthcare professional to meeting the information and support needs of parents and carers. Consideration should also be given to meeting these particular needs for the people for whom they care, such as children and young people, and people with special needs (for instance, people with learning disabilities or sensory impairment). **D**
- 9** The primary healthcare professional should be aware that some patients find being referred for suspected cancer particularly difficult because of their personal circumstances, such as age, family or work responsibilities, isolation, or other health or social issues. **D**
- 10** Primary healthcare professionals should provide culturally appropriate care, recognising the potential for different cultural meanings associated with the possibility of cancer, the relative importance of family decision-making and possible unfamiliarity with the concept of support outside the family. **D**
- 11** The primary healthcare professional should be aware that men may have similar support needs to women but may be more reticent about using support services. **D**
- 12** If the patient has additional support needs because of their personal circumstances, the specialist should be informed (with the patient's agreement). **D**

- 13** All members of the primary healthcare team should have available to them information in a variety of formats on both local and national sources of additional support for patients who are being referred with suspected cancer. **D**
- 14** In situations where diagnosis or referral has been delayed, or there is significant compromise of the doctor/patient relationship, the primary healthcare professional should take care to assess the information and support needs of the patient, parents and carers, and make sure these needs are met. The patient should be given the opportunity to consult another primary healthcare professional if they wish. **D**
- 15** Primary healthcare professionals should promote awareness of key presenting features of cancer when appropriate. **D**

7.1 Evidence Statements:

Communication between health care practitioners and patients:

7.1.1 Effective communication between health care practitioner and patient in both the history-taking part of the consultation and during discussion of the management plan positively influences health outcomes for patients. (III)

The evidence base from which these guidelines are drawn has a limited empirical and theoretical base.

Information and support needs at time of referral from primary care:

7.1.2 People want information about their suspected diagnosis and possible treatment. (III)

7.1.3 People have different preferences for information and involvement in decisions about their treatment and care at different stages in the pathway of care. (III)

7.1.4 People prefer information that is available in different formats, is specifically relevant to their condition and for which help in interpreting information is available from health care professionals. (III)

7.1.5 The pre-diagnosis stage is one of great uncertainty for the individual which could involve moving from being a person-without-cancer to a person-with-cancer: for some individuals this process can occur quickly, for others it can take a considerable amount of time. (III)

7.1.6 The pre-diagnosis stage is a time when information and support is not routinely provided (III)

7.1.7 There is a need for support at the time of referral to secondary care. Patients at the primary-secondary care interface would like access to appropriate care, orientation of care to their particular requirements, provision of information and continuity of staff and coordination and communication among professionals. Failure to provide this care can lead to patients feeling left “in limbo”. (III)

7.2 Introduction

A consistent problem during the work on the cancer referral guideline has been the lack of available evidence to answer questions of importance to the guideline development group. This has been particularly true of communication between practitioner and patient and patient support and information needs *at the time of referral from primary care*.

This section deals with communication, patient support and information needs. In view of the lack of specific evidence, this section reviews selected key important papers on communication in health care and “breaking bad news”. Reference is also made to the limited primary research in this area.

The approach has been to use selected review articles, primary papers and consensus statements. Formal systematic literature searching has been undertaken to identify relevant papers on information and support needs in primary care for specific cancer sites, and in general the studies identified have been included in the chapters dealing with each group of cancers.

7.2.1(1) General studies of health care communication between health care practitioners and patients

Guidelines

(Royal College of Physicians, 1997)(21)

The key recommendations for good communication between health care professionals and patients and carers are as follows:

- Listen to patients and respect their views and beliefs
- Give patients the information they ask for or need about their condition, its treatment and process, in a way they can understand
- Provide the most important information first
- Explain how each piece of information will affect patients personally
- Present information in separate categories
- Make advice specific, detailed and concrete
- Use words the patient will understand; confirm understanding by questions; define unfamiliar words; write down key words; draw diagrams as appropriate
- Repeat the information using the same words each time
- Prepare material, written or taped, to back up handwritten notes
- Share information with patients' partners, close relatives or carers if they ask you to do so.
- The content, style and timing of information provision should be tailored to the needs of the individual patient.

(Masera et al, 1997)(22)

The following lists a summary of the essential points of the "Principles for Communicating the Diagnosis" in children & adolescents, as reached by general consensus by the SIOP Psychosocial Committee at their 1995 Montevideo meeting:

- Establish a protocol for communications.

- Communicate immediately at diagnosis and follow up later.
- Communicate in a private and comfortable space.
- Communicate with both parents and other family members if desired.
- Hold a separate session with the child.
- Solicit questions from parents and child.
- Communicate in ways that are sensitive to cultural differences.
- Share information about the diagnosis and the plan for cure.
- Share information on lifestyle and psychosocial issues.
- Encourage the entire family to talk together.

Local interpretation of these general guidelines is required to accommodate prevailing cultural assumptions, medical situations, family dynamics, and resources and abilities of the parents, children and staff members involved.

Secondary studies

There is research evidence that effective communication can improve health outcomes.

(Stewart, 1995)(23)

Stewart has published extensively on patient-centred medicine and the need for effective communication and sharing of decisions between practitioner and patient. Her 1995 systematic review of randomized controlled trials (RCTs) and analytic studies of physician-patient communication in which patient health was an outcome variable is widely cited.

Its key finding is that the quality of communication both in the history-taking segment of the visit and during discussion of the management plan does positively influence patient health outcomes. The outcomes affected, in descending order of frequency, are: emotional health, symptom resolution, function, physiologic measures (i.e., blood pressure and blood sugar level) and pain control.

(Davies and Higginson, 2003)(24)

This study was a systematic review of communication, information and support needs of adults with cerebral glioma. Twelve studies reported in 16 papers were identified for inclusion. The studies included qualitative and quantitative investigations, and many were limited by small sample sizes and to single specialist centres. The studies generally included patients after referral, and any views on needs and experiences at referral were retrospective.

Up to one third of patients and relatives complained that the information they received lacked coherence, and that the traditional outpatient care does not meet patients' needs for support. The proportion of patients who were aware they had a brain tumour within a few weeks of the diagnosis varied from around 50% to 95% between studies. Patients appeared to find 'telling the story of the diagnosis' a helpful step when taking part in a support group.

(Semple and McGowan, 2002)(25)

This study reviewed articles identified from MEDLINE and CINAHL 1990-2001 that reported studies of the information needs of people with head and neck cancers. The review noted two important recent trends. Health service policy changes have placed greater emphasis on patient involvement, and patients increasingly expect more and better information to enable them to understand their health. At the same time, health professionals are adopting a more open style of communication, and accept that most patients want to know their diagnosis.

The review found evidence that effective information can enable the patient to participate in decision making, or decide not to participate. Three levels of participation have been described: passive, where the doctor makes all the decisions; collaborative, where decisions are made jointly; and active, where the patient has the final say in decisions. The available evidence suggests

that around 20% of patients want an active role, 28-40% a collaborative role, and 25-50% a passive role.

When patients are anxious, they do not always retain information effectively; furthermore, anxious patients are less likely to express their concerns. The provision of written information can assist in addressing these difficulties. Badly written information may convey an uncaring and unprofessional attitude.

Therefore, written information should be carefully prepared and clearly presented.

Primary studies

(Krishnasamy et al, 2001)(26)

In this study, a questionnaire was mailed to 466 patients with a diagnosis of lung cancer. The patients were attending 24 randomly selected UK hospitals. The aim of the study was to explore perceptions of healthcare need.

209 (45%) patients returned a completed questionnaire. 26% reported being unwell for a year, and 38% had been unwell for between one and two years. In describing the process of diagnosis, more than 50% reported presenting to their general practitioner within three weeks. 6% presented after two to three months of illness. When asked about their ideas about the diagnosis before consulting the general practitioner, 20% thought they had cancer, 19% a chest infection, 2% asthma, 2% COPD, 2% chronic bronchitis, 2% TB, and 16% did not know. Having seen a general practitioner, 9% waited between one and three months before being seen in a hospital, and 45% were seen within two weeks. The median time to wait for a chest x-ray was two weeks. Of those told the diagnosis by a general practitioner, most felt able to ask questions but 27% felt too upset at the time to ask questions. Patients given information by a hospital doctor were significantly more likely to perceive the information as clear. When asked about key sources of support, 65% identified the general practitioner, and 24% reported this source as being particularly helpful.

7.2.1 (2) Studies of “breaking bad news” in health care professional consultations

One way of considering communication in the consultation with individuals with suspected cancer in primary care is to focus on whether the practitioner considers the individual at ‘high’ or ‘low’ risk of having cancer. If the individual is at ‘low’ risk of having cancer, the consultation can be managed by explanation, reassurance and follow up as appropriate. If the individual is at ‘high’ risk of having cancer, however, then not only is referral indicated but the practitioner must communicate to the individual the concern that the patient may have cancer and as such is “breaking bad news” – although it should be stressed that there will be uncertainty as to whether the “bad news” diagnosis will be confirmed.

There are published recommendations as to how practitioners should break “bad news” (see below). However, a theoretical basis for such recommendations and empirical evidence that they improve health outcomes are lacking.

Guidelines

(National Health and Medical Research Council, 2003)(27)

The Australian National Health and Medical Research Council has produced evidence-based guidelines for the psychosocial care of adults with cancer. Literature reviews were undertaken to identify relevant studies, with particular emphasis on the following cancers: colorectal, breast, prostate, melanoma, lung, gynaecological and non-Hodgkin’s lymphoma. Head and neck cancers and pancreatic cancer were also included.

The guidelines noted that people who perceive they have poor support are more likely to experience greater psychological distress, and that partners and children of patients with cancer are also vulnerable to psychological distress

and in need of support. The experience of the diagnosis of cancer is a stressful event that is followed by symptoms such as anxiety and depression. The experience of cancer is not a single, undifferentiated event, but people with cancer encounter a series of events which may pose different demands and difficulties. The psychosocial care of a person with cancer begins from the time of initial diagnosis i.e. when a decision on referral is made. There is a need for social and cultural sensitivity in assessment of need. Successful strategies for meeting psychosocial support needs may differ with gender.

Effective communication is central to the identification of individuals' specific needs, including for information and psychosocial support.

Potential benefits of effective communication between treatment team members and people with cancer include improvements in the patient's psychosocial adjustment, decision-making, treatment compliance and satisfaction with care (Level I evidence – obtained from a systematic review of all relevant randomised controlled trials). The way clinicians present information significantly affects people's recall of that information (Level III-2 – evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted times series with a control group). Training in communication skills can assist clinicians to improve (Level-III-I – evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)). Continuing training in the clinical setting may be beneficial given evidence that skills need to be reinforced and consolidated over time (Level IV – evidence from case studies, either post-test or pre- and post-test). Patients' psychological adjustment improves when clinicians express empathy and listen actively (Level III-3 – evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel group).

Understanding and recall can be boosted by:

- Giving clear, specific information (Level III-3)
- Explaining medical terms and avoiding medical jargon (Level III-3)
- Presenting information in terms of the specifics for each patient, rather than in a general format (Level III-3)
- Giving the most important information first (Level IV)
- Repeating and summarising important pieces of information (Level III-3)
- Actively encouraging questions (Level II – at least one properly randomised controlled trial)
- Actively checking understanding (Level III-3).

Additional strategies to increase satisfaction, recall and understanding include:

- Providing written information (Level III-3)
- Providing general information tapes (Level II)
- Taping of a consultation (Level II)
- Sending a summary letter as a follow-up to the consultation (Level II)
- Encouraging the presence of a support person (healthcare professional, family or friend) (Level II).

Secondary studies

(Ptacek and Eberhardt, 1996)(28)

This article provides a narrative review of the medical literature on the bad news process, while at the same time highlighting its limitations. It suggests a theoretical framework for considering the bad news process by discussing concepts borrowed from the stress and coping literature, and makes suggestions regarding future empirical work on breaking bad news.

“Bad news” is defined as relating to situations where there is either a feeling of no hope, a threat to a person’s mental or physical well-being, a risk of

upsetting an established life-style, or where a message is given which conveys to an individual fewer choices in his or her life.

The authors reviewed published work to date on “breaking bad news” and summarised recommendations that were repeatedly found in the literature. These are summarised below:

Consensus Recommendations for “Breaking Bad News”

Physical and social setting

Location

- Quiet, comfortable, private

Structure

- Convenient time, no interruptions, enough time available to ensure no rushing
- In person, face-to-face, make eye contact, sit close to patient, avoid physical barriers

People

- Support network: identify and have present at patient’s request

Message

What is said

- Preparation: give a warning shot (“I’m afraid I have bad news”)
- Find out what patient already knows
- Convey some measure of hope
- Acknowledge and explore patient’s reaction and allow for emotions to be expressed
- Allow for questions
- Summarize the discussion: verbally and/or in written form, audiotape
- Consultation

How it is said

- Emotional manner: warmth, caring, empathy, respect
- Language: simple, careful word choice, direct, no euphemisms or technical diagnostic terminology, avoid medical jargon
- Give news at person's pace, allow them to dictate what they are told

7.2.1(3) Studies of health care communication between health care practitioners and individuals with cancer

There is an extensive literature on communication and sharing of decisions with individuals who have been diagnosed as having cancer. Much of this literature has focused on the needs of those working in secondary care, such as oncologists and specialist nurses, who will inform individuals of the definitive diagnosis and provide continuing care and support (Fallowfield & Jenkins, 1999; Maguire, 1999)

It is, however, difficult to apply this literature to individuals seen in primary care before a definitive diagnosis of cancer has been made.

Secondary studies

(The University of York NHS Centre for Reviews and Dissemination, 2000)(29)

This review focused on the communication, information giving and sharing of decisions between health professionals and people with cancer. It does not address issues of communication between patients suspected of having cancer. It draws on evidence from systematic reviews produced by the cochrane consumers and communication group, other systematic reviews and from guidance produced by the national cancer guidance steering group.

The review defines patient-centred care as:

- The use of active listening skills by health care professionals
- Encouraging patients to express their agendas
- Attempting to understand patients' points of view and their expectations
- Working with patients in the management of their illness.

The review summarised the evidence in relation to the following key components of patient-centred care: communicating with patients, informing patients and involving patients in decision-making.

The following recommendations were made:

1. NHS policy initiatives should take into account differences in peoples' preferences for information and involvement in decisions about their treatment and care.
2. Health care professionals need to know how to elicit patients' needs and readiness for information as well as their desire for involvement in decision making. Appropriate communication skills training addressing such issues should be considered and be appropriately evaluated. Key issues include: placing a higher priority on patient information; understanding patients' needs and helping people to access and understand relevant and appropriate information.
3. Personalised or tailored information is an option. Recordings or summaries of key consultations may benefit adults with cancer, without causing additional anxiety. Health professionals could consider giving either written summaries or audio-tapes of consultations to people who have expressed a preference for them.
4. People with cancer should be given the opportunity for involvement in decisions about their treatment and care. However, individual preferences for different levels of involvement need to be respected.

5. Time pressures are likely to be a barrier in implementing initiatives like shared decision-making programmes.

7.2.1(4) Studies of communication and sharing decisions with individuals with suspected cancer in primary care

Some papers specific to certain cancer groups have been summarised in later chapters of the guideline. There is limited primary research on communication and sharing decisions with individuals with suspected cancer in primary care.

7.2.1(5) Studies of the information needs of individuals with cancer

There is an extensive literature on the information needs of individuals who have been diagnosed as having cancer. Much of this literature has focused on the needs of those working in secondary care, such as oncologists and specialist nurses, who will inform individuals of the definitive diagnosis and provide continuing care and support. It is, however, difficult to apply this literature to individuals seen in primary care before a definitive diagnosis of cancer has been made.

Secondary studies

(The University of York NHS Centre for Reviews and Dissemination, 2000)(29)

This review is cited in the previous section.

Patients cannot show informed preferences about their care, or choose to be involved in shared decision-making unless they have access to sufficient and appropriate information. The review highlighted the fact that while a majority of patients with cancer prefer to be given as much information as possible about

their illness, research reporting the experiences of patients with cancer suggests that information is often not available.

The following relevant recommendations were made:

NHS policy initiatives should take into account differences in peoples' preferences for information and involvement in decisions about their treatment and care.

Personalised or tailored information is an option. Recordings or summaries of key consultations may benefit adults with cancer, without causing additional anxiety. Health professionals could consider giving either written summaries or audio-tapes of consultations to people who have expressed a preference for them.

People with cancer should be given the opportunity for involvement in decisions about their treatment and care. However, individual preferences for different levels of involvement need to be respected.

Primary studies

(Jenkins, Fallowfield and Saul, 2001)(30)

As part of a multi-centre study evaluating a communication skills training model for clinicians, the authors collected information preferences using an adaptation of Cassileth's information needs questionnaire from a heterogeneous sample of 2331 patients with cancer.

Results showed that 87% (2027) wanted all possible information, both good and bad news and 98% (2203) preferred to know whether or not their illness was cancer. Cross tabulation of responses revealed no significant differences in information preferences for tumour site or treatment aims but did show an effect of age and sex. The few 58/440 (13.2%) patients who stated that in general they preferred to leave disclosure of details up to the doctor tended to be older (more than 70 years of age) (chi square = 26.01, df = 2, p< 0.0001).

In comparison to men women preferred to know the specific name of the illness (chi square = 4.9, df = 1, p< 0.02) and what were all the possible treatments (chi square = 8.26, df = 1, p< 0.004).

7.2.1(6) Studies of the information needs of individuals with suspected cancer in primary care

There is limited primary research on the information needs of individuals with suspected cancer in primary care. The patient information study on the information preferences of people with cancer (LSHTM 2001) did, however, interview patients about the pre-diagnosis phase and the findings of this research are summarised below.

This research is important as it marks a first step in linking what is known about 'how people become ill' from the social sciences research literature to what happens to cancer patients before their diagnosis is established.

Primary studies

(London School of Hygiene & Tropical Medicine, 2001)(31)

The patient information study was a collaboration between the national cancer charity cancer Bacup and researchers at the London School of Hygiene and Tropical Medicine. It involved in-depth interviews, focus groups and questionnaire surveys of people diagnosed with cancer.

The in-depth interviews sought to explore why patients chose to seek or not to seek information about their condition beyond that shared by their physicians at times during their illness.

This qualitative study was based in outpatient oncology clinics at one London cancer centre. The study participants were 18 people diagnosed with cancer in the previous six months. The main outcome measures were an analysis of patients' narratives to identify key themes and categories.

The key results are as follows:

While all patients wanted basic information on diagnosis and treatment, not all wanted further information at all stages of their illness.

Three arching orientations to their management of cancer limited patients' desire for and subsequent efforts to obtain further information at points on the illness journey: faith, hope & charity.

During the moments when patients did require information, there was a preference for verbal information over written, for specific information over general, and for help in interpreting information from key health professionals. When patients required information, certain barriers were sometimes found to constrain their access to information.

The pre-diagnosis stage (while patients are making first contact with health professionals, before a diagnosis is reached) is a time when information and support is not systematically or routinely provided and this period needs proper consideration.

Two key messages that emerge from the accounts that patients gave of the pre-diagnosis period were:

The incremental nature of "knowing" it is cancer.

The interviews suggested that the pre-diagnosis period is fraught with difficulty with regards to information and support and in terms of individuals' understanding of what is going on. It is a period marked by "uncertainty", which involves moving from a person-without-cancer to a person-with-cancer. Sociologists have termed this process one of "biographical reconstruction", stressing that careful thought should be given to what information and support should be offered at this stage and what should be offered when the individual has a diagnosis of cancer.

Previous research has tended to present a diagnosis of cancer as a single static event, purely in terms of the “bad news” interview and much energy has been expended on describing the best ways of conveying “bad news”. There is a risk that such an approach obscures the incremental nature of communicating and understanding what is going on before and when a diagnosis is made.

Importance of early interactions: pre- and post diagnosis

These early experiences are important because they provide the foundations for later interactions after diagnosis between patients and health professionals. Further research in this area is needed to determine individuals’ information preferences during this early period.

(Adlard and Hume, 2003)(32)

A questionnaire was designed to assess the cancer knowledge of members of the public attending their general practitioner in the UK. The setting for the study was an urban general practice with an inner-city main surgery (predominantly social class IV and V with a high proportion of Asian and Afro-Caribbean patients) and a busy branch surgery in an affluent area (predominantly from the higher socio-economic groups with a substantial Jewish population). Consecutive patients aged 18 and over were asked to complete the questionnaire while waiting to see their general practitioner or practice nurse.

Questions asked patients where they would seek information about cancer, familiarity with cancer terms and organisations. Other questions were designed to assess patients’ abilities to distinguish between common and less common cancers, risk factors for cancer development and symptoms of cancer.

A total of 406 questionnaires were completed and returned (204 and 202 respectively from the two surgeries). The median age of all respondents was

47 (range 17-94); 63% were women and 37% men. Seven percent had a personal history of cancer and 41% had a history of cancer in a family member or close friend in the preceding five years.

Significant deficiencies were identified in the cancer knowledge of respondents. Personal or family history of cancer, younger age and female sex were associated with improved cancer awareness.

Guidelines

(Macmillan Cancer Relief, 2003)(33)

In their resource pack for managing, selecting and producing information materials in a cancer information and support service, Macmillan Cancer Relief identify the following steps in the cancer information pathway as having potential information needs for individuals suspected as having cancer in primary care, see *Table 7*.

Table 7 cancer information pathway (Macmillan Cancer Relief, 2003)(33)

PATHWAY THROUGH SYSTEM	POTENTIAL INFORMATION NEEDS
1. Symptoms discovered	Reassurance and advice to go and seek help Information concerning the symptoms and signs of cancer
2. Goes to: General practitioner or other member of the primary health care team	Information concerning the symptoms and signs of cancer Information about tests required
3. Referred to local centre for further tests	How to get to the hospital and what to expect during investigations When and how the results will be given Psychological support for the patient

	and carers Sign-posting to the relevant information and support network
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7.2.1(7) Studies of the support needs of individuals with cancer

There is an extensive literature on the support needs of individuals who have been diagnosed as having cancer. There is also an extensive literature on the considerable psychological morbidity of individuals with a definitive diagnosis of cancer attending oncology outpatient clinics. For example, it has been reported that 15%-40% of cancer patients develop clinical anxiety and/or depression (Sheard and Maguire, 1999)(34).

It is, however, difficult to apply this literature to individuals seen in primary care before a definitive diagnosis of cancer has been made.

7.2.1(8) Studies of the support needs of individuals being referred from primary care to secondary care

Research has been carried out on the support needs of individuals across the primary-secondary care interface. For example, a patient career diary (Baker et al, 1998)(35) – a generic self-report questionnaire – has been developed to obtain patients' views of services across health-care settings.

Primary studies

(Preston, 1999)(36)

As part of the development work for the patient career diary the researchers conducted a study to discover the views of patients about their experiences across the interface between primary and secondary health care, including referral from general practitioners, outpatient and inpatient care, discharge, and aftercare.

It was a qualitative study involving individual and focus group interviews of patients and interviews of carers. The subjects were 33 patients who had attended at least one outpatient appointment or had been an inpatient between two and four months previously, and eight carers of patients with chronic conditions. The setting was three acute hospitals and one community health service in Leicestershire.

Common themes in the views of patients and carers towards their experiences of care were identified and five themes emerged. The first four themes were: "getting in" (access to appropriate care), "fitting in" (orientation of care to the patient's requirements), "knowing what's going on" (provision of information), and "continuity" (continuity of staff and coordination and communication among professionals).

The fifth theme was "limbo" (difficulty in making progress through the system).

The main features that characterised the feeling of "limbo" were:

An indefinite period of waiting

Uncertainty about what to expect or what would happen next

A feeling of being unimportant and insignificant; and

A feeling of powerlessness and loss of control over what was happening.

The theme of "limbo" was influenced by failures in care in relation to the other four themes.

(Nielsen et al, 2003)(37)

This study was a randomised controlled trial of a shared care programme for patients newly referred with cancer from primary to secondary care. The study was undertaken in a hospital oncology department in Denmark, and the intervention involved (1) knowledge transfer, in which communication from hospital to general practitioner included extensive information about the patients' social and psychological as well as physical problems, plus general information about treatment of common side-effects; (2) names and telephone numbers of doctors and nurses responsible for the patient were provided; (3)

patients were advised to contact their general practitioner when encountering problems, and were told that the general practitioner would receive an information package.

127 patients with cancer were randomised to the control group and 121 to the intervention group. Patients' evaluations (which included use of sections of the patient career diary) of the cooperation between primary and secondary care improved in the intervention group. Men and younger patients (18-49) felt they received more care from the general practitioner and were left less 'in limbo'. Young patients in the intervention group rated the general practitioners' knowledge of disease and treatment significantly higher, although there were no differences in quality of life between the study groups.

This study was restricted to patients with cancer, and commenced after first outpatient consultation, and therefore the findings cannot be applied directly to patients with suspected but not confirmed cancer at the stage of referral.

8 The Diagnostic Process

Number		Grade
1	Diagnosis of any cancer on clinical grounds alone can be difficult. Primary healthcare professionals should be familiar with the typical presenting features of cancers, and be able to readily identify these features when patients consult with them.	D
2	Cancers usually present with symptoms commonly associated with benign conditions. The primary healthcare professional should be ready to review the initial diagnosis in patients in whom common symptoms do not resolve as expected.	D
3	Primary healthcare professionals must be alert to the possibility of cancer when confronted by unusual symptom patterns or when patients thought not to have cancer fail to recover as expected. In such circumstances, the primary healthcare professional should systematically review the patient's history and examination, and refer urgently if cancer is a possibility.	D
4	Cancer is uncommon in children, and its detection can present particular difficulties. Primary healthcare professionals should recognise that parents are usually the best observers of their children, and should listen carefully to their concerns. Primary healthcare professionals should also be willing to reassess the initial diagnosis or to seek a second opinion from a colleague if a child fails to recover as expected.	D

- 5** Primary healthcare professionals should take part in continuing education, peer review and other activities to improve and maintain their clinical consulting, reasoning and diagnostic skills, in order to identify at an early stage, patients who may have cancer, and to communicate the possibility of cancer to the patient. **C**
- 6** Discussion with a specialist should be considered if there is uncertainty about the interpretation of symptoms and signs, and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals when symptoms are not classical (for example, by telephone or email). **D**
- 7** There should be local arrangements in place to ensure that letters about non-urgent referrals are assessed by the specialist, the patient being seen more urgently if necessary. **D**
- 8** There should be local arrangements in place to ensure a maximum waiting period for non-urgent referrals, in accordance with national targets and local arrangements. **D**
- 9** There should be local arrangements in place to identify those patients who miss their appointments so that they can be followed up. **D**
- 10** The primary healthcare professional should include all appropriate information in referral **D**

correspondence, including whether the referral is urgent or non-urgent.

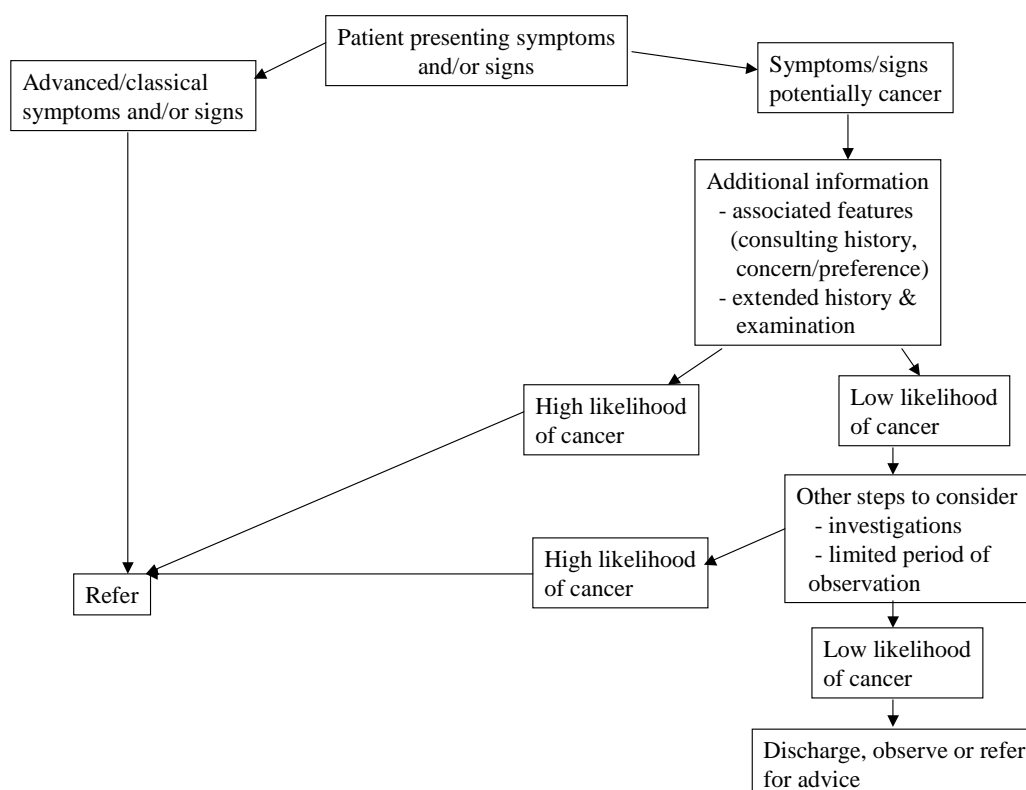
- 11** The primary healthcare professional should use local referral proformas if these are in use. **D**
- 12** Once the decision to refer has been made, the primary healthcare professional should make sure that the referral is made within 1 working day. **D**
- 13** A patient who presents with symptoms suggestive of cancer should be referred by the primary healthcare professional to a team specialising in the management of the particular type of cancer, depending on local arrangements. **D**
- 14** In patients with features typical of cancer, investigations in primary care should not be allowed to delay referral. In patients with less typical symptoms and signs that might, nevertheless, be due to cancer, investigations may be necessary, but should be undertaken urgently to avoid delay. If specific investigations are not readily available locally, an urgent specialist referral should be made. **D**

8.1 Introduction

This chapter considers the process by which primary healthcare professionals come to suspect that a patient has cancer. There is very little evidence about the diagnostic process in primary care directly relevant to cancer. This chapter therefore outlines theoretical models dealing with diagnosis and presents an illustrative example of the assessment of patients presenting with fatigue. It concludes with a review of trials of interventions to improve primary health care professionals' ability to detect cancer.

8.1.1 Models of the diagnostic process

Figure 2: The care pathway



One of the challenges of the NICE referral guideline for suspected cancer is to address the difficulties primary care professionals face when deciding whether or not a particular patient has symptoms and/or signs that support referral. Dealing with cancer symptoms and signs by twelve anatomical sites may best reflect the approach of the secondary care specialist. The primary care professional, however, must consider a wide range of differential diagnoses when faced with a patient who presents with a symptom that is non-specific but which may indicate serious underlying pathology (e.g., weight loss, abdominal pain). In some cases, reaching a suspicion of cancer is relatively straight forward, particularly when the symptoms and/or signs are advanced, or the features are classical (the so-called 'barn door' diagnosis – see *Figure 2*). In these cases, the professional is generally performing pattern recognition.⁽³⁸⁾ In many other cases, however, the symptoms and/or signs are non-specific at the time of presentation to the primary care professional. The diagnostic challenge in these circumstances can be considerable.

Only a small number of patients in primary care present with new cancers. The number of unrestricted general practitioners in England and Wales in 2000 was 29,479.⁽³⁹⁾ This figure excludes general practitioner registrars, assistants and other restricted general practitioners. In 2000, approximately 82% (24,173) of unrestricted general practitioners worked full time and 18% (5306) part time. Assuming that part time work equates on average to 60% time, the total number of full time equivalent unrestricted general practitioners is 27,357. If part time work equates on average to less than 60%, the total number of full time equivalent general practitioners will be a little lower than 27,357.

Based on these figures, *Table 8* shows the average number of numbers of new cases of the more commonly occurring cancers diagnosed each year for the years 1998-2000, and the numbers of cases expected per full time equivalent general practitioner and number of years needed for a general to have one new case in his or her patients. It should be noted that patients with cancer may first present to services other than general practice. For example, some cases of breast cancer will be identified during screening, and other

cancers may be first detected by hospital services. Consequently, the total number of new cases detected by the general practitioner will be less than shown in the table. It is clear, nonetheless, that the detection of a patient with cancer is an uncommon event in primary care populations, with around 7.5 new cases per year per full time equivalent general practitioner. The infallible identification of these few patients from among the 7,000 or so consultations provided by each full time general practitioner per year (i.e. around one new case of cancer per 1,000 consultations) is a considerable challenge.

Table 8 Numbers of cases of new cancers among the patients of a typical full time general practitioner in the year 2000.(40)

	Registrations of newly diagnosed cancers 1998-2000 average England and Wales	Cases per full time GP equivalent per year	Mean number of years needed for a GP to see one case
Breast	35739	1.3	0.8
Lung	33855	1.2	0.8
Colorectal	30636	1.1	0.9
Prostate	22665	0.8	1.3
Bladder	10986	0.4	2.5
Non-Hodgkin's lymphoma	7924	0.3	3.3
Stomach	8622	0.3	3.3
Oesophagus	6309	0.2	5
Leukaemias	5996	0.2	5
Ovary	5924	0.2	5
Pancreas	5798	0.2	5
Melanoma	5549	0.2	5
Uterus	4792	0.2	5
Kidney	4718	0.2	5
Lip, mouth and pharynx	4228	0.2	5
Brain	3806	0.1	10
Multiple myeloma	3236	0.1	10
Cervix	2729	0.1	10
Testis	1704	0.06	17
Larynx	1544	0.06	17
Hodgkin's disease	1271	0.05	20
Total		7.47	

A key feature, therefore, of the diagnostic process for general practitioners is that the incidence of cancer in primary care is low, but that symptoms and signs that may indicate the presence of cancer (e.g., headache, low back pain) are not. One influential approach to this problem is the Bayesian approach to the diagnostic process.⁽⁴¹⁾ A full review of this approach is outside the scope of the guideline but key principles are summarised in *Table 9*. It must be emphasised that the prevalence of disease has a strong effect in the usefulness of a 'test' (specific symptom/sign or investigation). The positive predictive value (probability that disease is present if the patient has symptom, sign or a positive test result) is markedly affected by the prevalence of the disease. If the prevalence is low (as in cancer in primary care), the positive predictive value of the 'test' is low and the negative predictive value (probability that disease is absent if the patient does *not* have symptom, sign or a positive test result) is high.

Table 9 Key points for using diagnostic tests in decision making⁽⁴¹⁾

- The selection and interpretation of diagnostic tests is a sequential process with the goal of reducing uncertainty about a patient's diagnosis.
- A test cannot be interpreted properly without considering what the probability of disease was before the diagnostic test or procedure result was obtained.
- Diagnostic tests help revise the probability of disease, and testing is generally continued until either the threshold for treating or not treating the patient is reached.
- When the pretest probability of disease is high, a positive result tends to confirm the presence of disease, but an unexpectedly negative result is often not sufficiently convincing to rule out disease.
- When the pretest likelihood of disease is low, a normal result tends to adequately exclude the presence of disease, but an unexpectedly positive result is often not sufficiently convincing to confirm the presence of disease.
- The approach of using a single diagnostic test to diagnose a single

disease may be generalised to the use of multiple tests and the diagnosis of multiple diseases in a single patient.

Interest has recently grown in the causes and prevention of medical errors, and delayed diagnosis can be regarded as one category of medical error. Errors have been classified into three groups, knowledge-based (the result of forming the wrong intention or making the wrong plan due to inadequate knowledge or experience); rule-based (failure to apply a rule designed to avoid error or to apply a badly designed rule); and skill-based (an action that was not intended, due to absent-mindedness and failure to monitor actions).(42) The evidence about symptoms and signs presented in the guideline could reduce diagnostic knowledge-based errors (i.e. faulty pattern recognition). However, primary care professionals also need to use skills other than pattern recognition when the presenting features are complex.

One way of dealing with this difficulty is for the guideline to develop algorithms for common symptoms that, in certain situations, may indicate the likelihood of cancer (e.g., headache, dysphagia, weight loss). This would represent the creation of a set of rules for these difficult situations. However, the creation of algorithms for the assessment of common symptoms would be outside the agreed scope of the guideline and would also require extensive additional evidence reviews. Nevertheless, an example dealing with the symptom of tiredness has been included to illustrate the process.

Various approaches to understanding the process by which clinicians reach a diagnosis have been proposed. The literature on the main types of approach (scheme-inductive reasoning, pattern recognition and hypothetico-deductive reasoning)(43) is extensive and a review of these is outside the scope of the guideline. The following comment by Norman & Eva is highly relevant to the current debate as to which of the three strategies is most effective:

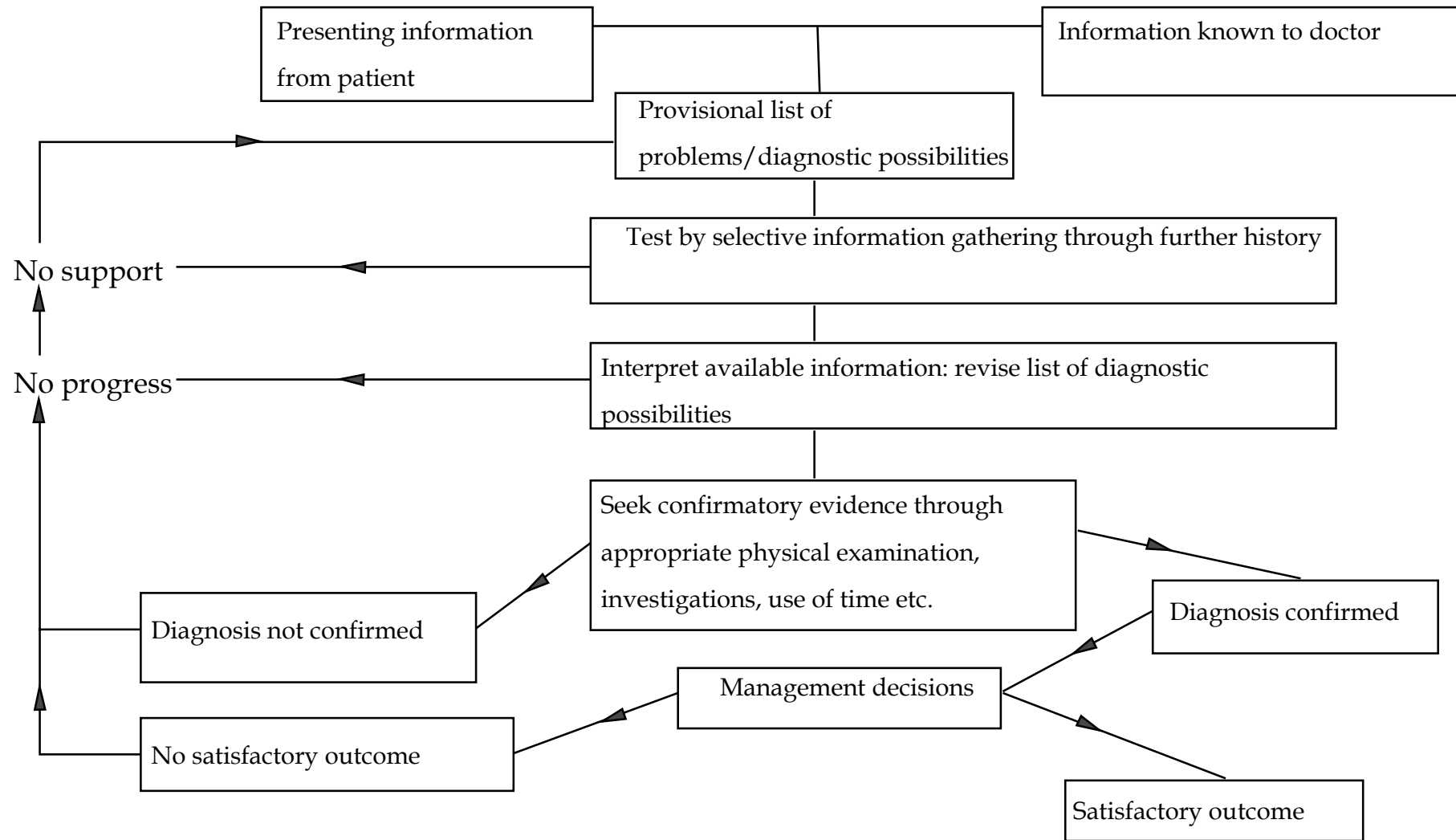
“To assume that any one problem-solving strategy will be shown to be consistently superior to any other amounts to a belief in a massively simplified world. It is far more likely that experts and novices will adopt a combination of

strategies dependent on the problem posed, the stage they are at in finding the solution and their particular knowledge relevant to that problem". (p. 677)

In this chapter the hypothetico-deductive method(44) (educated guessing and testing) is used to illustrate the diagnostic process. This method of multiple hypotheses-guided, problem oriented enquiry has been shown to be used by both general practitioners and hospital doctors.(45). *Figure 3* offers a simplified representation of the stages involved in this process. It is accepted that this is only one of a number of models of problem solving and that it may be used by established practitioners when faced with problems outside their usual area of expertise.

The primary health care professional will draw on accumulated knowledge of the patient, personal experience of patient care, and assessment of the patient's reasons for consulting, in addition to items of clinical information obtained from direct questions or volunteered by the patient, in coming to a view about the significance of the presenting history and examination findings. A process of discussion with the patient then takes place as a prelude to making a decision on what action is required.

Figure 3 The hypothetico-deductive pathway(46)



8.2 An Example: Tiredness/fatigue.

Key clinical question:

How can primary care professionals distinguish tiredness or fatigue due to cancer from tiredness or fatigue caused by other conditions?

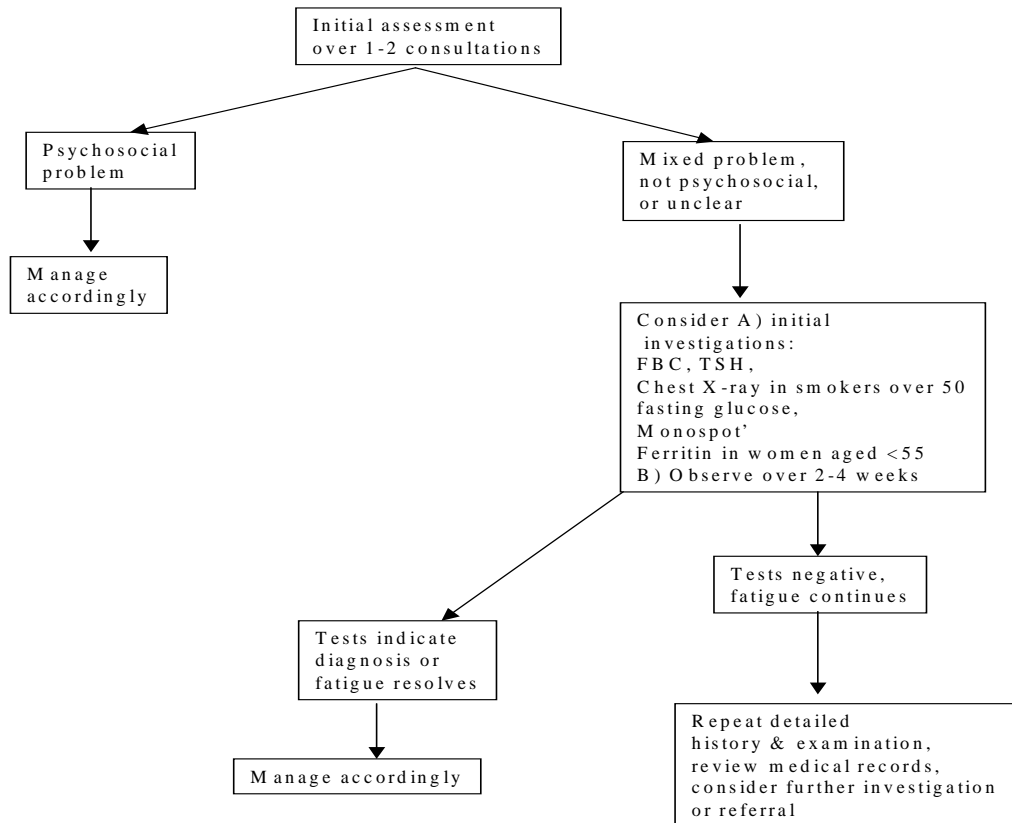
Evidence question:

In patients who present to primary care professionals complaining of tiredness or fatigue, what features are associated with cancer and which are not?

We have excluded studies of chronic fatigue syndrome (including a guideline on cancer-related fatigue(47) and an authoritative review(48) and studies of tiredness or fatigue in people after a diagnosis of cancer.

Fatigue, asthenia, weakness, exhaustion, malaise and tiredness are used more or less interchangeably, but only fatigue and asthenia are defined in the Medical Subject Heading Index.(49) Fatigue is defined as a 'state of weariness following a period of exertion, mental or physical, characterized by a reduced capacity for work and reduced efficiency to respond to stimuli'. Asthenia is defined as a 'clinical sign or symptom manifested as disability or lack of strength and energy'. Despite these definitions, fatigue appears to be the preferred term in the literature. The definitional problems are exacerbated by uncertainty about the definitions and aetiologies of chronic fatigue syndrome and neurasthenia. In the following paper, the focus is on patients newly presenting to primary care complaining of tiredness or fatigue, adopting the definition of asthenia quoted above. *Figure 4* presents an algorithm.

Figure 4 Provisional algorithm for primary care assessment of tiredness/fatigue.



Secondary studies

(Valdini, 1985)(50)

This early review addressed the issue of fatigue of unknown aetiology. After an extensive literature search, five studies were included, representing a total of 940 patients who had been attending a variety of primary care providers, including solo practice, group practice and family practice centres, as well as one outpatient department. The earliest study had been reported in 1944 (the outpatient study), and the most recent in 1983. Age and sex distributions of the

entire patient populations were not reported in the original studies. In addition to the problem of comparing five populations from different settings, the studies had not used a standard definition of fatigue, nor had they employed a standard method of investigation.

In over 50% of the 940 cases, the cause was thought to be psychological. The physical diagnoses are shown in *Table 10*.

Table 10 Physical diagnoses(50)

Cause of fatigue	No. of patients
Infection	117
Cardiovascular	58
Endocrine	57
Medications	25
Haematological	23
Neurological	15
Nutritional	9
Renal	8
Cancer	7
Gastrointestinal	6
Connective tissue disease	1
Allergy	2
Total	345

Of the 117 infections, 42 were influenza-like illnesses, 32 mononucleosis, 16 respiratory infections, and many others in much smaller numbers. The review did not present information about features associated with a diagnosis of cancer in people presenting with fatigue. The review recommended enquiry about nutrition and medications as part of the history, and checking for symptoms and signs of infection. An evaluation for depression, anxiety and stress was also

recommended, as were basic investigations in patients in whom the diagnosis could not be established on the basis of history and examination, although no evidence was provided about the practical value of these tests (blood count, thyroid function tests, fasting blood sugar, urinalysis, stool for occult blood, pregnancy test in women of child bearing age, monospot in younger patients, and a chest x-ray in the elderly).

(Ebell, 2001)(51)

This review was a brief report providing an evidence-based answer to the question: what is a reasonable initial approach to the patient with fatigue? The article was published in the Journal of Family Practice, and the advice was therefore intended for family physicians. The review drew on a review of four primary studies involving patients presenting in primary care, only one of which had been included in the Valdini (1985)(50) review, although all had been undertaken from 1980 or later, and one was unpublished. The proportions of patients reported as having a psychological cause for tiredness were 55%, 50%, 50% and 20% in the four studies; physiological diagnoses were reported in 30%, 50%, 22% and 50% respectively. The second study did not report a category of 'undiagnosed', but in the other three studies, 15%, 28% and 30% were reported as undiagnosed. The review recommended screening patients for depression, and use of directed laboratory evaluation depending on the findings of history and examination, although the approach to investigation should be more aggressive in patients of 65 or older.

(Godwin et al, 1999)(52)

These guidelines were developed to provide physicians with an approach that was, as much as possible, based on evidence so that time and cost were minimized and detection and management of the causes of fatigue was optimised. The guideline group met by email; Medline was searched for relevant

articles 1966 to 1997 using 'fatigue' as a Mesh heading and as a text word. Articles about chronic fatigue syndrome were excluded. The search identified 80 potential articles, but when the inclusion and exclusion criteria were applied, 12 remained. Three further articles were identified from the references lists of the included articles. No randomized trials, cohort studies or case-control studies were identified. Articles reporting studies in primary care were given more weight than articles undertaken in secondary care settings.

The guidelines recommended that adults presenting with fatigue of less than six months duration should be assessed for psychosocial causes and should have a focused history and physical examination to determine whether further investigations should be done. The elderly require special consideration. Table 11 presents the guideline recommendations.

Table 11 Guideline recommendations(52)

Investigation	Always perform?	Perform only in these situations
Appropriate assessment for presence of anxiety or depression	Yes	
Appropriate assessment of current life stresses and past trauma and abuse	Yes	
Focused history and physical examination with special emphasis on medications, existing chronic illnesses, and presence of infection, particularly viral	Yes (to determine whether lab investigations are necessary)	
Haemoglobin test	No	Presence of pallor, tachycardia, dyspnoea, or other symptom suggesting anaemia Dietary or family history suggesting risk of anaemia Patient older than 65*
White blood cell count	No	Fever or other evidence of infection Weight loss, lymphadenopathy Patient older than 65*

Investigation	Always perform?	Perform only in these situations
ESR**	No	Evidence of inflammatory arthritis Concern about occult malignancy Patient older than 65*
Electrolyte assessment	No	Patient taking medication known to affect electrolyte balance (eg. Diuretics, steroids) Indication of a medical condition causing electrolyte imbalance (Cushing's disease, Addison's disease, parathyroidism)
Renal function tests**	No	Patient taking medication known to affect renal function Symptoms or signs possibly associated with renal disease (elevated blood pressure, oedema, generalised pruritis)
Glucose test (urinalysis only for investigating polydypsia and polyurea)	No	History of gestational diabetes Known diagnosis of diabetes mellitus Symptoms of polydypsia and polyurea Unexplained peripheral neuropathy Patient older than 65*
TSH	No	Presence of goitre History of thyroiditis Symptoms and signs suggesting hypothyroidism (dry hair and skin, change in bowel habit, change in menses) Patient older than 65*
Chest X-ray**	No	Smoker with cough or haemoptysis (especially if older than 50) History of exposure to asbestos or other pulmonary occupational hazard Exposure to tuberculosis

Investigation	Always perform?	Perform only in these situations
Other investigations**	No	As indicated by history and physical examination findings Weight loss and changes in bowel habit should prompt gastrointestinal investigation*

*The elderly were not well represented in the literature. The group's consensus, after consultation with experts in care of the elderly, is that they are more likely to have physical causes of fatigue, especially if the symptom is new. The guideline group recommended lowering the threshold for investigation in this group.

**Recommended by group consensus only; no evidence available in literature.

(VHA/DoD guideline: chronic pain and fatigue, 2001)(17)

These guidelines were developed to assist primary care clinicians in all aspects of care of patients with the medically unexplained symptoms of chronic pain and fatigue. Bibliographic databases were searched for publications 1997-2000, and some journals were hand searched. Identified evidence was assessed for quality. The guideline recommendations are summarised in *Table 12*.

Table 12 Guideline recommendations(53)

<ul style="list-style-type: none"> • Establish that the patient has medically unexplained symptoms (MUS)
<ul style="list-style-type: none"> • Obtain a thorough medical history, physical examination, and medical record review • Minimize low yield diagnostic testing • Identify treatable cause (conditions) for the patient's symptoms • Determine if the patient can be classified as chronic multi-symptom illness (CMI) (i.e. has two or more symptom clusters: pain, fatigue, cognitive dysfunction or sleep disturbance) • Negotiate treatment options and establish collaboration with the patient • Provide appropriate patient and family education • Maximize the use of non-pharmacologic therapies: graded aerobic exercise with close monitoring; cognitive behavioural therapy. • Empower patients to take an active role in their recovery.

Primary studies

The studies reported here exclude those that were included in the Ebell (2001)(51) and Valdini (1985)(50) reviews.

(Pawlikowska et al, 1994)(54)

A fatigue questionnaire plus the GHQ-12 was completed by 15,283 adults aged 18-45 registered with six general practices in the UK. The questionnaire had been mailed to a total of 31,651 people, giving a response rate of 48.3%. Non-responders were more likely to be men (53%) and slightly younger than responders (30.8 years vs. 32.4 years for responders, $P < 0.001$).

5799 (38%) of responders had a fatigue score above the cut off for substantial fatigue, and 5621 (36.7%) scored above the cut off for psychological disorder in the GHQ-12. Scores for the GHQ-12 and the fatigue questionnaire were moderately correlated (0.62). Age was only weakly correlated with fatigue and general health scores. The mean fatigue score in men was 24.1, and in women 25.2 ($P < 0.0001$). Stratifying by psychological distress did not remove the excess of fatigue in women. 40.1% attributed fatigue to psychosocial issues (work, family, lifestyle), and 16.7% to psychological factors (anxiety, depression); 14.7% gave physical reasons (e.g. surgery, anaemia).

(Ridsdale et al, 1993)(55)

The findings of this study were not summarised in the Ebell (2001)(51) review. It was undertaken in four UK general practices, and included patients aged 26 and over complaining of fatigue or being 'tired all the time'. Patients completed a questionnaire at enrolment and another after six months, the questionnaires also

being administered to an age and sex matched control identified from the practice register. All patients also underwent a follow up examination two weeks after the first consultation.

220 patients were included, 56 (25%) males and 164 (75%) women. 34 (16%) had been tired/fatigued for between two weeks and one month, 66 (32%) one to three months, 34 (16%) for four to six months, and 74 (36%) longer than six months. 69 (33%) had one or more abnormal result on laboratory tests, and the doctors judged the result as clinically important in 19 of 210 (9%) patients. The clinical diagnoses were anaemia (eight), hypothyroidism (three), infection (three), glandular fever (three), diabetes (one), and carcinomatosis (one). A history of psychological disturbance was positively associated with the duration of fatigue.

(Kroenke et al, 1988)(56)

This study was also not included in the Ebell (2001)(51) review. It was undertaken in an army primary care centre in the USA. Attending patients were asked to complete a screening questionnaire to identify those who reported fatigue as a major problem (excluding those with fatigue of less than 30 days duration, those under the care of a psychiatrist, and those with diagnosed major illnesses, including cancer). A detailed assessment was undertaken of each of patient reporting fatigue, including examination, laboratory tests and psychometric and functional status questionnaires, plus one year follow up.

Of the 102 patients identified, 66% were women, and the mean age was 57 years. Fatigued patients had a higher ESR than the controls, but otherwise there were no differences in laboratory test results. A new diagnosis of diabetes was made in four patients, and anaemia in one. Four patients had faecal occult blood, but none had cancer. Fatigued patients were much more likely than controls to have psychometric test scores indicative of depression or anxiety. During follow

up for one year, no patients died, cancer developed in 2 (2%) of the fatigued patients and one (4%) of the 26 controls.

(Fuhrer and Wessely, 1995)(57)

This study involved 367 French general practitioners identifying 3784 patients aged 18-64 who had fatigue, either as a presenting symptom, a diagnosis, or a persistent problem during the week 12-19 November 1984. 2324 (61%) were women. Data were collected about the general practitioners' diagnoses and management, and patient information through a questionnaire. Although women were more likely to report fatigue than men, they were only slightly more likely to initiate a consultation for this problem.

Those aged 55-64 were less likely to present with fatigue than younger patients. The study presented information about the association between selected diagnoses and fatigue, but the diagnosis of cancer was not included. Depression and psychological problems were diagnosed in 50% of patients.

(Skapinakis et al, 2003a)(58)

In this WHO collaborative study, 25,916 patients attending primary care providers in 14 countries completed the GHQ-12, and those scoring above a certain threshold completed a more detailed instrument. The sample included 5438 people (62% women), 58% older than 35 years. One practice from the UK took part, and in this practice two (0.2%) of 428 attendees gave fatigue as the presenting complaint, although 115 (15.1%) had 'substantial unexplained fatigue' (i.e. they reported fatigue in response to direct questioning, for example 'In the past month, have you felt tired all the time?'). In the entire sample, 6.3% gave fatigue as the presenting complaint, and 8.0% had 'substantial unexplained fatigue'. Fatigue as a presenting complaint was more common in low income countries, but substantial unexplained fatigue was more common in high income

countries. Unexplained fatigue persisted in one-fifth to one-third at 12 months follow up, depending on the definition of fatigue.

(Skapinakis et al 2003b)(59)

This research group also reported on differences in the definition of fatigue between countries and the impact this has on the numbers of cases identified.(60) Widening the definition resulted in more prevalence but less overlap with psychiatric disorders.

(Verdon et al. 2003)(61)

This study was a randomised controlled trial of iron supplementation in non-anaemic women presenting with fatigue in primary care. In 366 women, fatigue was the main reason for consulting. 222 were excluded because of psychiatric disorders, physical disorders, refusals or other reasons. 144 were enrolled in the study, and 136 (94%) completed. 75 were randomised to receive iron, and 69 placebo. The level of fatigue after one month decreased in the iron group by 29%, compared with 13% in the placebo group (P=0.004). Subgroup analysis showed that only women with ferritin concentrations < or = 50 micrograms/litre improved with oral iron supplementation.

(Cathebras et al, 1992)(62)

In this study, 686 patients attending two Canadian family medicine centres completed a symptom report questionnaire. 93 (13.6%) reported fatigue, and was a major reason for the consultation in 46 (6.7%). 17.2% of patients with fatigue had major depression in the past month (8.8% among non-fatigued), and 45.2% had had a diagnosis of major depression at some time in the past (28.2% among non-fatigued). Between one third and one half of patients were no longer fatigued at 12 month follow up.

(De Rijk et al, 2000)(63)

Patients attending a women's general health care practice aged over 16 years were invited to complete questionnaires about fatigue. 152 women completed at least one questionnaire (mean age 34.8 years). 74% of respondents had suffered some fatigue in the past two weeks, but only 19 (12.3%) intended to consult because of this. 24 of 107 (22%) actually discussed fatigue during their consultation, although only 11.2% had intended to do so. Caring for young children and having a job were associated with increased likelihood of discussing fatigue.

(Hall et al, 1994)(64)

197 patients were identified in a US practice through a computer register of encounters and among people consulting. Cluster analysis was used to identify features associated with an 'organic' diagnosis and anxiety, depression, and mixed anxiety/depression groups. The assignment to groups was undertaken by the study authors based on review of the primary cause of fatigue, according to the diagnoses of the primary care physician.

The features classified as marital problems, decreased libido, nausea/vomiting, taking care of a sick relative, dizziness, bereavement, dissatisfaction at work/school, dieting, hectic life style, boredom, change in bowel habit, arthralgia, palpitations, memory loss, confusion, night sweats, irritability and increased appetite, did not occur more often among the organic group than in the other three clusters. The proportion of males, married patients and white patients in the organic group was higher than in the other clusters.

(Shahar and Lederer, 1990)(65)

A retrospective chart review was undertaken of the records of 508 patients aged 18 or over at one rural family practice in Israel, to extract information in the previous ten years of symptoms of asthenia (fatigue, lassitude, weakness). Asthenic complaints were recorded in the charts of 164 patients (32%); peak prevalence occurred in the third decade and in the summer months (June to September). The female:male ratio was 1.7:1. In nearly 50% of encounters, the physician did not reach a diagnosis. 64% had only one or two episodes, 27% had recurrent episodes, and 9% had persistent asthenic complaints but no evidence of the chronic fatigue syndrome. In the episodic group, 29% were diagnosed as intercurrent infection. 9% as psychiatric disorders, 5% anaemia, 2% pregnancy, 7% others, and 48% undetermined. In the recurrent group, the diagnoses were intercurrent infection 18%, psychiatric disorders 16%, pregnancy 7%, anaemia 2%, undetermined 57%.

8.3 Interventions to improve the ability of primary healthcare professionals to suspect cancer

Key Clinical Question:

How can the primary healthcare professionals be helped to refer patients with suspected cancer at an early stage?

Evidence Question:

What interventions can help primary healthcare professionals reduce delay in identifying patients with suspected cancer without leading to the referral of many patients who do not have cancer?

Evidence statements:

There are few studies of the effectiveness of interventions to improve healthcare professionals' identification and referral of suspected cancers. The majority of relevant studies involve educational interventions to improve identification of skin cancers. The findings of these studies are inconsistent, but tend to indicate that educational interventions can improve the identification of skin cancers (II).

In undertaking this review we sought systematic reviews of relevant interventions to improve primary care professional's identification or referral of patients who may have cancer. For inclusion, studies had to involve health professionals in their work settings. Studies employing simulations, for example use of dummies to develop examination skills, were excluded. Studies of interventions to improve adherence to cancer screening guidance or of use of investigations not directly related to identification of suspected cancer were also excluded.

For inclusion, the studies had to be randomised trials involving primary health care professionals and testing interventions designed to improve identification or referral of patients with suspected cancer.

No systematic review dealing specifically with the identification or referral of suspected cancer was identified. Consequently, we have included findings from an overview of reviews of interventions to promote the implementation of research findings. Five randomised trials were identified for inclusion.

Secondary studies

(Bero et al, 1998)(66)

Systematic reviews of interventions to improve professional practice published between 1966 and 1995 were sought through bibliographic searches of several databases. Eighteen reviews met the inclusion criteria.

In general, the passive dissemination of information was found to be ineffective. The use of computerised decision support has led to improvements in clinical management but not diagnosis. Patient mediated interventions appeared to improve preventive health care, and educational outreach improved prescribing behaviour. The use of several interventions in combination was more effective than the use of single interventions alone. The findings are summarised in *Table 13*.

Table 13 Interventions to promote behavioural change among health professionals(66)

Consistently effective interventions

- Educational outreach visits (for prescribing in North America)
- Reminders (manual or computerised)
- Multifaceted interventions (a combination that includes two or more of the following: audit and feedback, reminders, local consensus processes, or marketing)
- Interactive educational meetings (participation of healthcare providers in workshops that include discussion or practice)

Interventions of variable effectiveness

- Audit and feedback (or any summary of clinical performance)
- The use of local opinion leaders (practitioners identified by their colleagues as influential)
- Local consensus processes (inclusion of participating practitioners in discussions to ensure that they agree that the chosen clinical problem is important and the approach to managing the problem is appropriate)
- Patient mediated interventions (any intervention aimed at changing the performance of healthcare providers for which specific information was sought from or given to patients)

Interventions that have little or no effect

- Educational materials (distribution of recommendations for clinical care, including clinical practice guidelines, audiovisual materials and electronic publications)
 - Didactic educational meetings (such as lectures)
-

(Grimshaw et al, 2001)(67)

This was another overview of systematic reviews of interventions to change provider behaviour. Forty-one reviews were identified for inclusion, and in general the findings of Bero et al (1998)(66) was substantiated. However, only one review of interventions targeted at referral was identified, and only one review of interventions targeted at investigations. Neither of these reviews were judged to have included adequate numbers of studies of sufficient quality to enable firm conclusions to be drawn about the effect of interventions to change these aspects of provider behaviour.

(Grimshaw et al, 2004)(68)

This study is the most recent systematic review of the effectiveness of methods of disseminating and implementing guidelines. It involved searches of various databases (Medline, Healthstar, Embase, Sigle) and the

specialised register of the Cochrane Effective Practice and Organisation of Care (EPOC) group. The review included randomised controlled trials, controlled clinical trials, controlled before and after studies, and interrupted time series. Participants were medically qualified healthcare professionals, and the outcomes of guideline dissemination and implementation strategies of interest were objective measures of provider behaviour and/or patient outcome.

A total of 235 studies were identified for inclusion. The key findings of the review were that:

- Reminders were the most frequently evaluated and are potentially effective;
- Educational outreach was the next most commonly evaluated intervention, and it may result in modest improvements in the process of care, although it can require significant resources;
- Evidence about the effectiveness of audit and feedback and patient directed interventions was less robust. Audit and feedback appears to result in modest effects, and patient mediated interventions in moderate effects.

The review identified very few studies of interventions to improve the identification and referral of patients with suspected cancer in primary care, although there were several studies of interventions to improve adherence to preventive measures such as cervical screening and mammography. In view of the small number of relevant studies and the narrow range of cancers addressed, conclusions about the effectiveness of interventions to improve identification and referral of suspected cancer cannot be drawn.

(Grimshaw, 1998)(69)

This was a review of randomised controlled trials of interventions to improve general practitioner out-patient referrals. It was included in a PhD dissertation. Only four studies met the inclusion criteria. The included RCTs addressed referral in the following contexts: 1) Referrals for investigation of upper gastrointestinal symptoms; 2) referrals to psychiatrists or community psychiatric nurses of patients with long term mental illness; 3) referral of patients with orthopaedic problems to orthopaedic surgeons; and 4) the total number of all referrals from participating general practices. No study was specifically concerned with referral of patients with suspected cancer. Only one of the studies (number 3) was considered unequivocally positive, the intervention consisting of a joint consultation involving the specialist and general practitioner with the patient in place of referral. The other studies had negative or ambiguous findings.

(Solomon et al, 1998)(70)

This was a systematic review of RCTs of interventions to change physician investigation behaviour. The investigations were not restricted to those used in suspected cancer, and the physicians in the included studies were from both primary and secondary care. Forty-nine studies were identified for inclusion.

The review reported that methods to develop consensus among physicians had relatively limited impact. Audit with feedback was variably successful, but more successful when combined with an educational intervention. Continuous quality improvement programmes appeared to be relatively effective, and administrative interventions (restricting investigation privileges, for example) could be, but were not always highly effective.

Primary studies

Randomised trials of interventions to improve diagnostic ability of primary care professionals to manage familial breast and ovarian cancers

(Watson et al, 2002)(71)

This cluster randomised controlled trial of educational interventions on general practitioner management of familial breast and ovarian cancer involved 688 general practitioners in 170 UK practices. Group A were provided with an information pack and in-practice educational session, group B were mailed an information pack, and group C received no intervention at all. All general practitioner referral letters between March 1999 and December 2000 were audited and referrals classified as appropriate or inappropriate.

The appropriateness of referrals improved among general practitioners who either received the guidelines alone (68.7% of referrals appropriate), or with an educational session (75.0% appropriate). In the group that did not receive the guideline or any other intervention, only 52.6% of referrals were judged appropriate.

Randomised trials of interventions to improve diagnostic ability of primary care professionals to identify skin cancers

(Del Mar et al, 1995)(72)

Australian general 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. Over 50 doctors, mostly in general practice, were selected in each of two Australian cities. The cities were chosen on the basis of their similarity; both being in relatively isolated tropical areas and near the coast, and with populations of around 55 000 and 65 000

people working in industries with substantial agricultural and tourist components.

The cities were sufficiently far apart so that intervention in one was unlikely to affect clinical behaviour in the other. The city that received the active intervention was chosen at random. The control group city included 45 general practitioners, seven surgeons and one dermatologist. The intervention group comprised 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.

A copy of the histology report of every melanocytic skin lesion that practitioners excised over the next two years was reviewed. 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.

There was no significant 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.

(English, 2003)(73)

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)(72) in which participants were randomised by town rather than practice.

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. 488 practices were invited to take part and 223 participated. Computer generated randomisation was undertaken which stratified by practice size. Doctors randomised to the intervention group were trained to use an algorithm and instant camera. After randomisation, participants and research assistants who visited practices were not blinded to assignment. All coding of outcome data was done blind to assignment.

1221 general practitioners were identified of whom 468 participated in the trial. Similar numbers of general practitioners in the two groups left their practices during the trial. Only 302 (65%) general practitioners completed a questionnaire at the end of the study on how they had managed their last three patients with pigmented lesions. All pathology reports on excisions of pigmented skin lesions from November 1998 to August 2000 were obtained.

From the results of the earlier trial by Del Mar et al (1995)(72), it was calculated that nine months of follow up were needed to achieve 80% power. 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.

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 (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.

(Raasch et al, 2000)(74)

This randomised control trial was undertaken to assess the value of an educational intervention based on audit and feedback to family physicians in Australia. Clinical performance of family physicians was judged by the ability to make a correct clinical diagnosis (i.e. the diagnosis was compatible with the histology of the excised lesion) and to provide adequate surgical treatment. There were 46 family physicians allocated to either an intervention (23) or control group (23) from a total of 91 who were initially approached but either declined to participate or failed to respond.

To ensure similarity of most characteristics, randomisation of doctors who agreed to participate was carried out using a random number table.

Practitioner characteristics for doctors in the intervention and control groups were noted such as age, sex, years in practice and number of partners, full/part time and qualifications. The intervention and control group practitioners differed only on the mean number of doctors per practice. Non-participants were likely to be older and have been in practice longer. The doctors were made aware only of the fact that a skin cancer study was taking place and were not informed whether they were in an intervention or control group.

One control group doctor recorded no data from the start, leaving 22 in this category. Two doctors from the intervention group and two from the control group dropped out during the study and were not replaced. All doctors who dropped out had moved from the city or practice. 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.

It was estimated that 356 patient consultations for clinically suspicious or dysplastic skin lesions would be required by the intervention and control group before and after the intervention to detect a 10% difference in the proportion of correct diagnoses with 80% power ($\alpha = 0.05$).

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.

Improvements in performance occurred in both study groups; the only significant benefit of the intervention was improved recording of the clinical diagnosis on pathology request forms. Two factors were identified by the authors as potentially explaining the lack of effectiveness of the intervention. The patient populations consulting the doctors in the two study groups were significantly different, and the study took place in a small community in which elimination of risk of contamination between study groups could not be achieved.

(Gerbert et al,1998)(75)

This US 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. There were 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.

Of the 62 primary care residents who completed the pre-test, ten were unable to attend the post-test (five from the control group and five from the intervention group). There were no statistically significant differences in age, gender, dermatology experience, or pre-test scores between those primary care residents who completed the post-test and those who did not. Control and intervention groups of primary care residents and dermatologists were

assessed for their ability to diagnose and make evaluation plans for six categories of skin lesions including three types of skin cancer – malignant melanoma, squamous and basal cell carcinoma and three of their noncancerous differential diagnoses, actinic keratosis, seborrheic keratosis and nevus.

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 the control group 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 control group across all six diagnostic categories (a gain of 13 percentage points vs. 5, $P < 0.05$) 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.

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.

(Gerbert et al, 2002)(76)

In this US study, primary care doctors were randomly allocated to two groups – control (N=32 doctors) or intervention (N=39 doctors) in which subjects took part in a skin cancer triage tutorial, developed from the intervention used in Gerbert et al (1998)(75). The tutorial modules were registration, pretest, pretest scores with individualised feedback, skin cancer instruction, posttest I, posttest II (eight weeks after completing the course), and exit survey. The tutorial was internet based. The change between pre- and posttest scores constituted the study outcome, the tests including the presentation of digital images of skin lesions.

Only 27 of the 39 doctors in the intervention group completed the tutorial intervention. In the control group, the scores declined from pretest to posttest. In the intervention group, scores significantly improved for overall diagnosis and evaluation planning, diagnosis of malignant melanoma and seborrheic keratosis, diagnosis and evaluation planning of basal cell carcinoma and squamous cell carcinoma, and evaluation planning for actinic keratosis. Improvement was maintained for five of the eight outcomes at posttest II (not maintained for overall diagnosis, diagnosis of basal cell carcinoma, diagnosis of seborrheic karatosis and evaluation planning for actinic keratosis).

9 Lung cancer

Number **Grade**

General recommendations

- 1** A patient who presents with symptoms suggestive of lung cancer should be referred to a team specialising in the management of lung cancer, depending on local arrangements. **D**

Specific recommendations

- 2** **An urgent referral for a chest X-ray should be made when a patient presents with:** **D**

- haemoptysis, or
- any of the following unexplained persistent (that is, lasting more than 3 weeks) symptoms and signs:
 - chest and/or shoulder pain
 - dyspnoea
 - weight loss
 - chest signs
 - hoarseness
 - finger clubbing
 - cervical and/or supraclavicular lymphadenopathy
 - cough with or without any of the above
 - features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin).

A report should be made back to the referring primary healthcare professional within 5 days of referral.

Number		Grade
3	An urgent referral should be made for any of the following: <ul style="list-style-type: none">• persistent haemoptysis in smokers or ex-smokers who are aged 40 years and older• a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation).•	D
4	Immediate referral should be considered for the following: <ul style="list-style-type: none">• signs of superior vena caval obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)• stridor.• Risk Factors	C
5	Patients in the following categories have a higher risk of developing lung cancer: <ul style="list-style-type: none">• are current or ex-smokers• have smoking-related chronic obstructive pulmonary disease (COPD)• have been exposed to asbestos• have had a previous history of cancer (especially head and neck). An urgent referral for a chest X-ray or to a team specialising in the management of lung cancer should be made as for other patients (see 1.3.1 above) but may be considered sooner, for example if symptoms or signs have lasted for less than 3 weeks.	C

Number		Grade
	Investigations	
6	Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems should prompt an urgent referral for chest X-ray.	D
7	If the chest X-ray is normal, but there is a high suspicion of lung cancer, patients should be offered an urgent referral.	D
8	In individuals with a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms, lung cancer should be considered and a chest X-ray arranged. If this indicates a pleural effusion, pleural mass or any suspicious lung pathology, an urgent referral should be made.	C

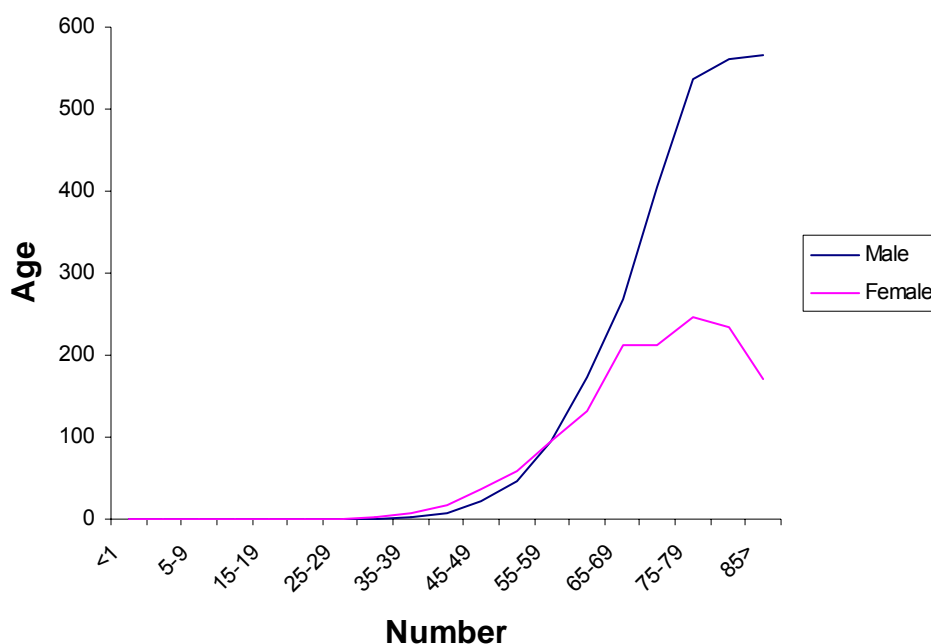
Introduction

Incidence

Lung cancer is the most common cancer in England and Wales.(77) Only 1% of cases occur before 40 years of age and 85% of cases occur in those 60 years or over. About 90% of patients are smokers or ex-smokers(2). Global incidence is generally four to six times higher in males than in females.

There were 30,485 recorded new cases of lung cancer in 2001 in England and Wales, 11,940 in females and 18,545 in males.

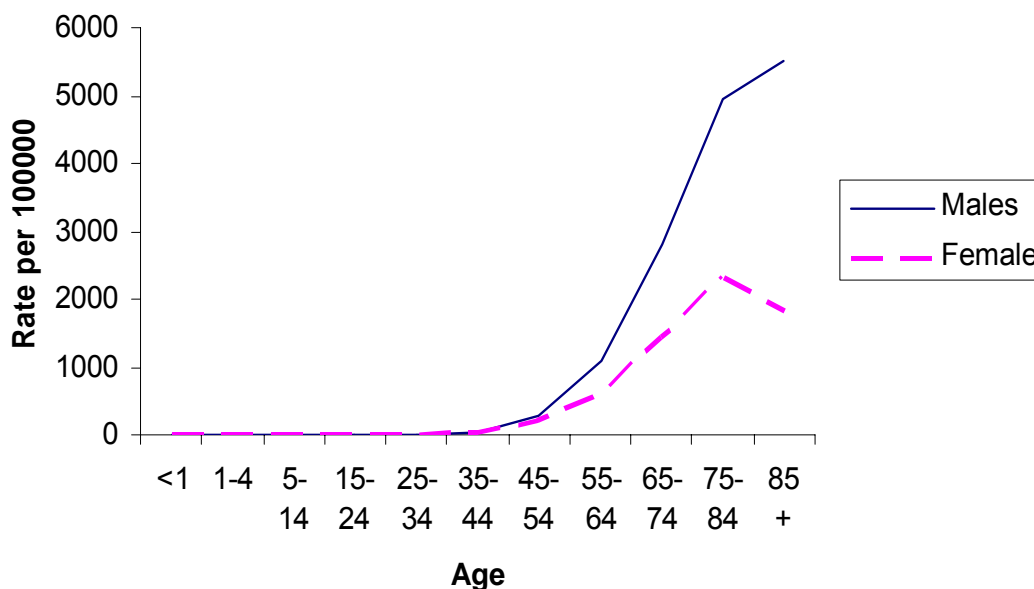
Figure 5: Newly diagnosed cases of lung cancer in 2001 in England and Wales. (77)



Mortality

Mortality figures for 2002 showed that mortality from lung cancer was low for both sexes in those aged under 40 years, but then increases sharply with registration rates decreasing in women over 75 years. The total deaths in 2002 were 17,426 in males and 11,342 in females, shown graphically in Figure 6.

Figure 6: 2002 Mortality rate for Lung, trachea and bronchial cancer in England and Wales. (78)



Audits of referral for suspected lung cancer

The systematic review of cancer waiting time audits (CRD, 2004) identified 43 audits. Fifteen audits evaluated GP conformity to the referral guidelines, the percentage of referrals being considered appropriate ranging from 78% to 100%. The proportion of patients who had been referred under the two week wait referral system who were found to have cancer ranged from 5% to 60% (14 audits). The proportion of patients with cancer who had been referred via the two week wait referral system ranged from 0% to 43% (three audits).

9.1 Symptoms and Signs

9.1.1 Key Clinical Question:

Which symptoms, signs and other features raise a suspicion of lung cancer, and which make cancer less likely as a diagnosis?

9.1.2 Evidence Question:

In people attending primary care services with lung problems, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of cancer, and which are not?

9.1.3 Evidence Statements:

The incidence is low in those aged under 50, but peaks in both males and females around 80. (III)

The incidence of lung cancer is decreasing in men but increasing in women. (III)

Common presenting symptoms include persistent or unexplained cough, haemoptysis, unexplained weight loss, dyspnoea and chest/shoulder pain. (III)

Lung cancer may present with metastases or enlarged lymph nodes. (III)

Other less common presenting features include pneumonia, clubbing and hoarseness. (III)

90% of cases of lung cancer are caused by smoking. (III)

Asbestos exposure can cause mesothelioma. (III)

Guidelines

The DoH Referral Guidelines for Suspected Cancer(2) listed the following as predominant symptoms at presentation: cough, dyspnoea, haemoptysis, weight loss, chest/shoulder pain and/or hoarseness.

The guidelines also noted that more than 90% of patients were symptomatic at the time of diagnosis and that chest x-ray findings were abnormal in the vast majority of symptomatic patients. However, a normal chest x-ray did not exclude a diagnosis of lung cancer.

The guidelines recommended that in most cases it was appropriate for a general practitioner to request a chest x-ray as an initial investigation, with referral to a chest physician if the chest x-ray was suggestive/suspicious of lung cancer. In a limited number of circumstances, urgent referral to a chest physician was appropriate without requesting a chest x-ray.

Sputum cytology was rarely indicated prior to referral for a specialist opinion. In most cases where lung cancer was suspected it was appropriate to arrange an urgent chest x-ray before urgent referral to a chest physician.

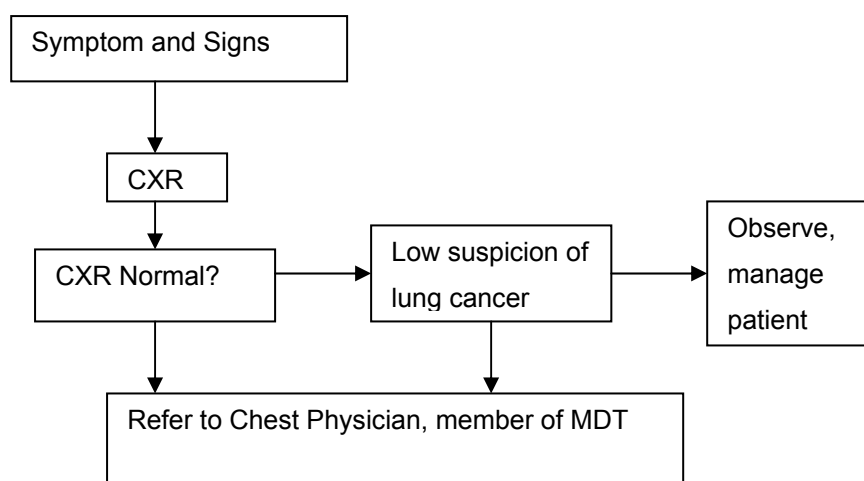
Urgent referral for a chest x-ray was recommended for:

- haemoptysis
- unexplained or persistent (more than three weeks)
- cough
- chest/shoulder pain
- dyspnoea
- weight loss
- chest signs
- hoarseness
- finger clubbing
- features suggestive of metastasis from a lung cancer (eg brain, bone, liver or skin)
- persistent cervical/supraclavicular lymphadenopathy.

Urgent referral to a chest physician was recommended for any of the following:

- chest x-ray suggestive/suspicious of lung cancer (including pleural effusion and slowly resolving consolidation).
- persistent haemoptysis in smokers/ex-smokers over 40 years of age.
- signs of superior vena caval obstruction (swelling of face/neck with fixed elevation of jugular venous pressure).
- stridor (consider emergency referral).

Other relevant guidelines include those developed for NICE; the diagnosis and treatment of lung cancer(79). It included a diagnosis of lung cancer algorithm, the section relating to primary care can be seen below:



The NICE guideline(79) recognised that the symptoms and signs of lung cancer can be difficult for the general practitioner to distinguish from those of other diseases. The main symptoms and signs at presentation identified in the guideline are displayed in the table below:

Table 14 Range of frequency of initial symptoms and signs of lung cancer(79)

Symptoms and signs	Range of frequency (%)
Cough	8-75
Weight loss	0-68
Dyspnoea	3-60
Chest pain	20-49
Haemoptysis	6-35
Bone pain	6-25
Clubbing	0-20
Fever	0-20
Weakness	0-10
SVCO	0-4
Dysphagia	0-2
Wheezing and stridor	0-2

The SIGN guideline(80) was based on a revision of its guideline published in 1998(81). It covered presentation, diagnosis, investigations and all aspects of treatment. It did not address other thoracic malignant disease such as mesothelioma (malignant pleural tumour) or secondary lung cancers.

The SIGN guidelines reported that high quality evidence on presentation and referral for lung cancer was scarce. Most of the data used were drawn from observational studies and existing recommendations on good practice. The symptoms with which lung cancer presents include cough, sputum, breathlessness and wheeze, which are also commonly experienced by cigarette smokers with chronic obstructive pulmonary disease (COPD). Non specific symptoms such as tiredness and weight loss are also common in lung cancer. Information about the common symptoms of lung cancer were available from case series. No evidence was identified regarding the possible predictive value of combinations of symptoms.

The stated aim of the Scottish Executive Health Department's Referral Guidelines for Suspected Cancer was to facilitate appropriate referral between primary and secondary care for patients in whom a general

practitioner suspected cancer. The guidelines were designed to identify patients most likely to have cancer and requiring urgent assessment by a specialist, and to assist general practitioners identify patients unlikely to have cancer. The guidelines were based on published literature and unpublished audits of symptoms in patients presenting with cancer.

Secondary studies

Liedekerken et al, 1997(82)

A literature search for papers reporting the relationship between prolonged cough (defined as being of six weeks duration or more) and lung cancer was undertaken. A MEDLINE search (1966-1995) was performed and papers were retrieved after scanning references. Sensitivity, specificity and positive and negative predictive values were recorded and studies were excluded if there were insufficient data for the calculations to be made or if patients were chosen selectively, other than by setting.

No study originating from primary care could be identified. One paper reported on the relationship between prolonged cough and lung cancer, and was based on 6027 patients in a specialised setting. It revealed a high negative (0.99) and a low positive (0.03) predictive value, a sensitivity of 0.48 and a specificity of 0.71. Little information was given as to the method by which studies were assessed other than stating that those relating to primary and secondary care were processed separately. A thorough attempt was made to identify evidence that evaluated the significance of prolonged cough in patients with lung cancer but few studies came to light.

Primary studies

Sridhar et al, 1998(83)

This prospective study sought to determine the relative frequency of clubbing in small cell lung carcinoma (SCLC) versus non-small cell lung carcinoma

(NSCLC) in patients diagnosed with lung cancer. The primary data were derived from the treating cancer centre at a tertiary teaching hospital in the US. A consecutive series of 111 patients with a pathological diagnosis of lung cancer were examined for the presence or absence of digital clubbing. It was not always possible to examine patients prior to confirming the pathological diagnosis. Comparisons were made between patients with and without clubbing on the following: age, sex, substance use, tobacco, smoking history, family history of lung cancer and subtype of cancer.

Clubbing was present in 32 (29%) of the 111 patients with lung cancer. Clubbing was more common in women (40%) than in men (19%; χ^2 test $P=0.011$) and occurred more commonly in patients with non-small cell lung carcinoma (35%) than those with small cell lung carcinoma (4%; χ^2 test $P=0.0036$).

Table 15 Small cell versus non-small cell lung carcinoma.(83)

	Small Cell Carcinoma	Non-small Cell Carcinoma
Total	23	88
Men	14	45
Women	9	43
Clubbing		
Yes	1	31
No	22	57

Nine women had small cell lung carcinoma, of whom one had clubbing. None of the 14 men with small cell lung carcinoma had clubbing. No other factors such as the subtype of non-small cell lung carcinoma, age of the patient, family history of lung or other cancers and tobacco smoking were related to clubbing.

Sarlani et al, 2003(84)

Facial pain as a presenting symptom of non-metastatic lung cancer was evaluated in thirty-two patients (one case report and 31 cases identified from

the dental literature since 1983). This series comprised 12 males (37.5%) and 20 females (62.5%). The mean age at presentation was 54 years (range 34 to 78). The vast majority of the patients were smokers or former smokers. The facial pain preceded the diagnosis of lung cancer by a mean of nine months (range 1-48). Facial pain related to non-metastatic lung cancer was almost invariably unilateral, always ipsilateral to the tumour. Eighteen of the 32 cases (56.3%) involved right-sided pain and 12 (37.5%) left-sided pain. The pain most commonly affected the ear, the jaws and the temporal region. Pain in or around the ear was present in 20 of the 32 cases (62.5%) and jaw pain in 14 cases (43.8%).

Pain was commonly misdiagnosed as atypical facial pain, dental pain or pain associated with temporomandibular disorders (TMD) or trigeminal neuralgia.

Herth et al, 2001(85)

This UK study was a case series of lung cancer in patients with haemoptysis. A retrospective review of the records of 722 patients was undertaken at a tertiary referral centre for pulmonary diseases between January 1990 and December 1993. A source and aetiology for the bleeding was identified in 587 patients (81%) at the initial evaluation. In the remaining 135 patients (19%) no aetiology for the bleeding could be determined and this group was targeted for further follow-up. However, for 20 patients, follow-up data could not be obtained. Eighty-one patients (60%) were smokers, 16 (12%) had a history of chronic obstructive pulmonary disease (COPD) and ten (7%) had a history of tuberculosis.

Of the 115 patients followed-up, lung cancer developed in seven (6%). All seven patients developed lung cancer within the first three years after the initial workup. Their mean age was 49.7 years (range 43 to 61 years). Lung cancer developed in these seven patients despite negative bronchoscopy and normal chest radiographic findings at initial presentation. Endobronchial and transbronchial biopsies were performed when indicated and all specimens were routinely examined for cytology and microbiology. Using the cohort study

analysis for unpaired differences, a 10% probability was found for lung cancer developing after haemoptysis of unknown origin if the patient was a current smoker and > 40 years old.

(Koyi et al, 2002)(86)

All patients referred to a specialised centre between January 1997 and December 1999 were investigated in this prospective Swedish study. General practitioners were encouraged to refer all suspected cases of lung carcinoma including those with a very poor prognosis as early as possible. It was intended to reach a definite diagnosis with a biopsy and/or cytology investigation, although this was not possible in 50 of the 364 patients (13.7%). Diagnosis for these patients was instead based on x-ray findings, clinical data and symptoms. Compared to other Swedish studies, the more comprehensive approach to data collection resulted in a sample of older age groups. This affected the distribution of cancer types with more squamous cell carcinomas and fewer adenocarcinomas.

Table 16 First symptoms of lung cancer and the symptoms that prompted a visit to the doctor.(86)

Symptom	First symptom N (%)	Reason to visit doctor, N (%)
Cough	86 (24.9)	81 (23.5)
Dyspnea	52 (15.1)	59 (17.1)
Fatigue	49 (14.2)	29 (8.4)
Pain in thorax	17 (4.9)	18 (5.2)
Back pain	13 (3.8)	11 (3.2)
Haemoptysis	11 (3.2)	17 (5.1)
Cough and fever	9 (2.6)	9 (2.6)
Abdominal pain	8 (2.3)	11 (3.2)
Fever	7 (2.0)	7 (2.0)
Neurological symptoms	8 (2.3)	12 (3.5)
Hoarseness	7 (2.0)	8 (2.3)
Others	39 (11.4)	55 (15.7)
Total	306 (88.7)	317 (91.8)

(Melling et al 2002)(87)

The proportion of patients referred according to lung cancer guidelines was analysed in a case series of 400 patients randomly selected from the former Yorkshire Cancer Registry database in 1993 to assess how different pathways resulted in varying management. The sample was stratified by three age groups (<65, 65-75, >75). Those with missing case notes or receiving private treatment or extra-regional care were excluded. General practitioner and hospital case notes were traced for 362 out of 400 patients (90.5%). The 'with chest x-ray diagnosis' group consisted of patients who presented to their general practitioner with a respiratory related complaint. Less than half of lung cancer patients (173, 47.8%) presented to hospital with a chest x-ray diagnosis of lung cancer. A total of 148 patients in the 'without chest x-ray diagnosis group' were referred to hospital because of their symptoms but with no prior chest x-ray. Forty-one (11.3%) presented as self referrals to A&E and

the remainder were referred without a diagnosis of lung cancer by other routes, mainly via general practitioners.

Table 17 shows that 80% of the 'with diagnosis group' presented to their general practitioner with mainly lung related symptoms (cough, chest pain or infection, haemoptysis or dyspnoea) compared to 69 (46.6%, CI: 38.4%, 55.0%) of those without a diagnosis. Patients who did not present initially with a lung cancer diagnosis were less likely to receive specialist care (62%: 96%) or have histological confirmation (57.1%: 80.3%) or receive surgery or radical radiotherapy (6.9%: 13.9%). Surgery, chemotherapy and palliative radiotherapy were all used most frequently in the 'with chest x-ray diagnosis group', but the difference was only significant for surgery (P=0.035). It was concluded that patients presenting to hospital without a suspicious chest x-ray were less likely to have specialist care, histological confirmation of their cancer and had lower rates of active treatment.

Table 17 Presenting symptoms with and without diagnosis.(87)

	Principal presenting symptom [†]					
	With diagnosis		Without diagnosis		Acute	
Symptoms	n	%	n	%	n	%
Cough	57	32.9	16	10.8	1	2.4
Chest pain	26	15.0	16	10.8	3	7.3
Chest infection	26	15.0	14	9.5	1	2.4
Shortness of breath	22	12.7	24	16.2	8	19.5
Haemoptysis	18	10.4	7	4.7	3	7.3
Weight loss	12	6.9	14	9.5	0	0
Other pain	7	4.0	23	15.5	6	14.6
Other (non respiratory)	17	9.8	44	29.7	19	46.3

[†]Some patients had more than one principal presenting symptom

(Mansson et al, 2001)(88)

In this case series, information on diagnostic activities was collected from the records of patients whose differential diagnoses included colorectal, breast,

lung or prostate cancer. Data collection took place in four primary healthcare centres in Sweden from different periods between 1992 and 1997 and involved a sample of 6812 patients ≥ 30 years of age.

Pulmonary diagnostic codes comprised the greatest part of the study (9422 codes corresponding to 65%). Most of these codes were assumed to be accounted for by infectious diseases in the upper airways. C-reactive protein tests were taken 865 times and nasopharyngeal cultures 580 times. Blood haemoglobin and ESR were tested 822 and 579 times respectively. Chest x-rays were performed 643 times. The yield of malignancy following chest x-ray was low, 0.4%.

Table 18 Number of selected diagnostic codes according to classification of diseases in the primary health care from the Swedish Board of Social Welfare 1987 with a possible association with pulmonary cancer.(88)

Diagnostic codes with pulmonary cancer as a differential diagnosis (n=9422)			
Shortness of breath (786A)	415	Upper airway disease (460)	3340
			Epiglottis, larynx, lung and bronchus (162)
Cough (786C)	420	Inflammation in the epiglottis, larynx and trachea (464)	114
Haemoptysis (786D)	9	Bronchitis (acute and chronic) (466, 491)	2426
		Pneumonia (486)	619
		Emphysema (492)	94
		Asthma (493)	1714
		Pleuritis (511)	82
		Other diseases in the respiratory organ (519R)	168

(Interdisciplinary Group for Cancer Care Evaluation G.I.V.I.O, 1989)(89)

The quality of diagnostic and therapeutic care was examined in a case series of 380 patients with lung cancer seen in 20 Italian general hospitals between January and June 1987. A maximum of 30 patients was accepted from each of the participating hospitals. A total of 380 cases with median age 63 years (range 37-86) entered the study. Histologic and cytologic findings were available for 363 cases. Eighty-seven percent were males. Symptoms most frequently reported at presentation were cough in 175 (46%), shortness of breath in 86 (23%), chest pain in 87 (23%), haemoptysis in 75 (20%) and fever in 52 (14%). Lung cancer appeared to be a chance diagnosis in 48 (13%) patients who did not have any specific symptom and whose disease was found on routine chest x-ray. Finally, 26 (9%) patients had symptoms due to distant metastases at diagnosis, whilst no information was available in six cases.

(Mansson et al, 1994)(90)

The records of a sample of 40 (26 men and 13 women) subjects with lung cancer reported to the Swedish Cancer Registry 1980-1984 were examined using hospital records in this case series, with special reference to the general practitioners' role. The mean and median ages at the time of the diagnosis was 69 and the range was 43-85 years. The initial symptoms were cough followed by dyspnoea, chest pain, fever, weight loss and tiredness. Other presenting symptoms were oedema, haemoptysis, facial pain, pricking sensations in the throat, stuffed nose, dizziness, frequent colds and tumour outside the throat. Symptoms included palpable lymph nodes (two patients), dyspnoea, liver enlargement, cachexia, tendency to fall and an episode of unconsciousness. No abnormal signs were found on physical examination in ten patients (26%).

Table 19 Initial symptoms in patients with pulmonary cancer.(90)

Symptom	Number	%
Cough	13	33
Dyspnoea	7	18
Chest pain	6	15
Fever	4	10
Weight loss	4	10
Tiredness	4	10
Other symptoms	12	31
Health control	4	10

(Sridhar et al, 1990)(83)

The hospital charts of a case series of 127 patients with adenosquamous lung carcinoma identified between 1975 and 1988 were reviewed. Men constituted 72% and 90% were smokers. Nearly two-thirds of the patients were between 50 and 70 years of age. The symptoms in order of decreasing frequency were cough, weight loss, expectoration, anorexia, chest pain, dyspnoea, weakness, haemoptysis, pneumonia, fever, nausea, vomiting, dizziness and chills. Most patients had multiple symptoms. Haemoptysis was a more common presenting symptom in men than in women ($P=0.05$). Weight loss was more frequent in men than in women but this difference was not significant.

Table 20 Symptoms in the 127 patients with adenosquamous lung carcinoma(83)

Symptoms	Present		Absent		Not documented	
	n	%	n	%	n	%
Cough	68	54	18	14	42	32
Weight loss	54	43	25	20	48	38
Expectoration	49	39	17	13	61	48
Anorexia	45	35	10	8	72	57
Chest pain	41	32	29	23	57	45
Dyspnea	38	30	17	13	72	57
Weakness	38	30	3	2	86	68
Haemoptysis	30	24	37	29	60	47
Pneumonia	16	13	4	3	107	84
Fever	16	13	46	36	65	51
Nausea	13	10	18	14	96	76
Vomiting	9	7	11	9	107	84
Dizziness	8	6	6	5	113	89
Chills	6	5	42	33	79	62

Risk Factors

Secondary studies

Ruano-Ravina et al, 2003(91)

In this systematic review, studies were identified through a search of MEDLINE and EMBASE for relevant studies published from 1985 onwards. Editorials, commentaries and studies involving less than 50 cases were excluded. The risk of developing smoking-related lung cancer was found to depend on several factors including duration of habit (number of cigarettes per day), age at initiation and type of tobacco. Passive smoking was considered a risk factor for lung cancer (RR reported to be approximately 1.5) although exposure was very difficult to measure. Many occupational groups including construction labourers, carpenters, and wood or timber workers were identified as at risk. Individuals in contact with dust or microscopic particles (asbestos, wood dust, silica) were at higher risk of developing lung cancer despite the effects of environmental pollution being difficult to assess. Ecological studies lacked information on certain confounders such as tobacco use.

Survival was rated as being better in women than men, and slight ethnic differences were observed, with higher mortality rates among African-Americans. Certain diseases increased the risk of developing lung cancer, in particular tuberculosis, chronic obstructive pulmonary disease and silicosis. Family history of lung cancer was associated with increased risk. In one study, women reporting a family history of lung cancer had a 1.9 fold risk (95% CI 0.7-5.6) of developing lung cancer and those reporting a family history of cancer had a 1.8 fold risk of developing lung cancer (95% CI 1.0-3.2). Lung cancer was more common in families with a record of breast and ovarian cancer.

(Alberg and Samet, 2003)(92)

This article reviewed the epidemiology of lung cancer. The authors concluded that a single etiologic agent, cigarette smoking, was by far the leading cause of lung cancer accounting for approximately 90% of cases in the United States. They also stated that the risk of lung cancer among cigarette smokers increased with the duration of smoking and the number of cigarettes smoked per day and that this observation had been made repeatedly in cohort and case-control studies.

The likelihood of developing lung cancer was reported to decrease among those who quit smoking compared to those who continue to smoke. As the period of abstinence from smoking cigarettes increased, the risk of lung cancer decreased. However, even for periods of abstinence of >40 years, the risk of lung cancer among former smokers was found to be elevated compared to never smokers. Studies showed comparable reductions in risk following smoking cessation, regardless of sex, type of tobacco smoked and histologic type of lung cancer.

Almost one quarter of lung cancer cases among never-smokers were estimated to be attributed to exposure to passive smoking. Estimates derived from case-control studies of the proportion of lung cancer that is contributed to by occupational exposures ranged widely, but most point estimates or ranges included values from 9 to 15%. The authors reported that asbestos exposure may pose a risk to building occupants and that radon was associated with lung cancer.

(Tyczynski et al, 2000)(93)

This review addressed the epidemiology of lung cancer in Europe. Tobacco smoking featured as the most prominent risk in developing lung cancer. A clear dose-response relation was reported between lung-cancer risk and the number of cigarettes smoked per day, degree of inhalation and age at

initiation of smoking. A person who has smoked all their life has a lung cancer risk 20-30 times greater than a non-smoker. Lung cancer risk decreases with time since smoking cessation.

The observation that the risk of lung cancer is greater in women than in men exposed to equivalent amounts of tobacco smoke is not supported by studies which concluded that the risk is similar between the two sexes. Passive exposure to tobacco smoke also increases the risk of lung cancer and it is estimated that environmental exposure to tobacco smoke increases risk by 15-25%.

Additional risk factors include exposure to asbestos, with risk being almost two-fold among those with the longest periods of exposure. A synergistic (multiplicative) effect between asbestos and tobacco smoking has been documented in three comprehensive reviews. Occupational exposure to carcinogens and residential exposure to radon may increase the risk of lung cancer in men who have never smoked. The combined effect of smoking and radon exposure however, is unknown.

(Macbeth et al, 1996)(94)

The risk factors associated with lung cancer have been identified as including tobacco, asbestos and radon. The influence of genetic factors and the effects of chromosomal abnormalities has also been assessed. At least thirty retrospective and eight prospective studies have established a link between cigarette smoking and lung cancer. It has been estimated that 85-90% of all lung cancers can be linked to active smoking. The use of cigarettes carries a significantly greater risk of developing lung cancer than either pipe or cigar smoking.

The age of starting cigarette smoking, the duration of smoking and the nicotine content of the cigarettes are all important factors. The risk of lung cancer at the age of 60 years is reported to be three times greater for those who started smoking between the ages of 14 and 16 years compared to those

who began ten years later. It has been calculated that someone aged 35 years who smokes 25 or more cigarettes per day has a 13% chance of dying from lung cancer before the age of 75 years. Exposure to known carcinogens including asbestos, radon, chromium, nickel and inorganic arsenic compounds increases the risk of lung cancer. Even a short exposure may be sufficient to cause lung cancer, if the concentration of asbestos is high enough. Miners who are exposed to high concentrations of radon have an increased risk of lung cancer, but its role in domestic housing as a factor causing lung cancer is uncertain. Several studies have shown an increased risk in the siblings of patients who develop lung cancer.

9.2 Investigations

9.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care before referral?

9.2.2 Evidence Question:

In patients attending primary care services with symptoms that may be caused by cancer, which investigations when compared with the “gold standard” are predictive of a diagnosis of cancer, and which are not?

9.2.3 Evidence Statements:

A chest x-ray is the principal diagnostic investigation in primary care. (III)

False negative chest x-ray results do occur in lung cancer. (III)

Sputum cytology is not a discriminatory investigation in symptomatic patients. (III)

Secondary Papers

Schreiber, 2003(95)

A systematic review and meta analysis was undertaken in the USA to determine the test performance characteristics of various investigations for the diagnosis of suspected lung cancer. The investigations included sputum cytology, bronchoscopy, transthoracic needle aspirate (TTNA) or biopsy. The search covered MEDLINE, Healthstar and Cochrane Library databases from 1966 to July 2001 among other sources. Studies included in the review had to involve samples of at least 50 patients. The pooled specificity for sputum cytology from 16 studies was 0.99 and the pooled sensitivity was 0.66, but sensitivity was higher for central than for peripheral lesions (0.71 vs. 0.49 respectively).

Most of the studies on sputum cytology involved the identification of patients from cytology laboratory samples without regard to the indication for sputum cytology testing. Studies of the accuracy of sputum cytology for the diagnosis of lung cancer were difficult to summarise due to methodological problems. The studies showed highly variable estimates of sensitivity and no clear reasons for this. Sensitivity calculations may have been affected by the different thresholds for considering cytology 'positive' with regard to the category of 'suspicious' and whether insufficient specimens were excluded or classified as negative also may have influenced the results.

Primary studies

Simpson et al, 1988(96)

The indications and diagnostic yield of general practitioner referrals for static miniature chest radiography were investigated in this study. A total of 1205 consecutive general practitioner referrals for chest radiography to the Leeds Chest Clinic were included. All films were read by chest physicians and were classed as normal, abnormal but not requiring further investigation, or abnormal requiring recall to the clinic. Patient notes were reviewed one year later to assess outcome.

Of the 1205 films, 878 (73%) were classified as normal. In 132 (11%) cases the patient was recalled. Of those patients with significant pathology 15 had pneumonia, 14 a cardiac lesion, five had active tuberculosis, three had malignant effusions, four had pulmonary metastases and one had a pneumothorax. There was a low recall rate (5%) and prevalence of significant pathology (1%) in those patients under 40 years of age. In the over 60 age group there was much higher recall rate (23%) with 13% having significant pathology.

Of the 15 patients with lung carcinoma, nine had died by one year and only three had received active treatment (two radiotherapy and one surgery). The

symptoms most likely to be associated with significant pathology were cough, haemoptysis, wheeze, dyspnoea and weight loss. Non-specific symptoms of malaise, tiredness or general ill health, chest pain and hypertension were rarely associated with abnormal radiographs. The study did not identify symptoms solely predictive of carcinoma because cases of cancer were placed in a category of 'significant pathology', which also included pneumonia, cardiac lesions, active tuberculosis and pneumothorax. No pathological or histological verification of the diagnosis of cancer was reported.

(Pederson, 2003)(97)

This study prospectively assessed the diagnostic value of an elevated platelet count and other routine laboratory tests for predicting malignancy in 126 patients with radiologically suspected lung cancer. Patients were divided by pathologic diagnosis into those with benign disorders (N=65) or malignancies (N=61). Cytological examination of sputum and pleural fluid and percutaneous transthoracic needle biopsy were among the investigations performed.

All 126 consecutive subjects were admitted to the outpatient clinic with an abnormal chest x-ray. Thrombocytosis (platelet count $>400 \times 10^9/l$) was present in 8% (5/65) of patients with benign disease and in 57% (35/61) of patients with malignant disease ($P < 0.00001$).

Table 21: Diagnostic value of laboratory tests in the prediction of malignancy.(97)

	Sensitivity	Specificity	Negative predictive value	Positive predictive value
Platelet count	0.57	0.92	0.70	0.88
Leukocyte count	0.52	0.63	0.59	0.57
Serum LDH	0.48	0.80	0.62	0.69
ESR	0.59	0.81	0.68	0.75
Haemoglobin	0.41	0.85	0.60	0.71
Platelet count combined with:				
Leukocyte count	0.59	0.98	0.73	0.95
LDH	0.54	0.94	0.75	0.87
ESR	0.67	0.98	0.83	0.95
Haemoglobin	0.48	0.98	0.76	0.94
Leukocyte count + LDH	0.62	1.00	0.79	1.00
Leukocyte count + ESR	0.65	1.00	0.83	1.00
Leukocytes + haemoglobin	0.53	1.00	0.79	1.00
LDH + ESR	0.71	1.00	0.89	1.00
LDH + haemoglobin	0.52	0.98	0.82	0.92
ESR + haemoglobin	0.59	0.98	0.84	0.93
All tests together	0.67	1.00	0.88	1.00

The prevalence of thrombocytosis in patients with primary lung cancer was 53% (27/51). Elevated platelet count was more common in advanced disease (stage III and IV). The sensitivity of thrombocytosis for predicting malignancy was 0.57 and the specificity 0.92. When elevated platelet count, serum lactate dehydrogenase and erythrocyte sedimentation rate were combined, a sensitivity of 0.71 and a specificity of 1.00 was achieved.

(Holmberg, 1993)(98)

The value of routine convalescent chest radiography was assessed retrospectively using medical records from patients with pneumonia admitted to a Swedish hospital during 1981 and 1985. All patients had pneumonia. The

study included 1011 patients (544 males and 467 females, mean age 66 years, range 15-97), of whom 678 underwent chest radiography and clinical examination one to two months after the acute onset of illness. Excluded cases comprised those with incorrect diagnoses (N=59), those who had no x-ray performed (N=15), patients with severe chronic debilitating disease resulting in multiple episodes of pneumonia (N=30), age < 15 years (N=19) and various other reasons.

Thirteen of the 1011 patients with pneumonia had previously undiagnosed pulmonary carcinoma. Many of these carcinomas (8/13) were identified by an acute chest x-ray. Pulmonary carcinoma was found by the convalescent chest x-ray in 2/88 patients not feeling well and in 2/524 patients feeling well at follow-up. ESR was of no value in detecting underlying pulmonary carcinoma at follow-up in patients with pneumonia. Of the 232 inpatients (181 men and 51 females, mean age 68 years, range 38-89) with pulmonary carcinoma, 29 (12.5%) presented with an acute respiratory tract infection; most of these patients did not recover as expected and their correct diagnosis was made following a chest x-ray requested because of the persistent symptoms.

Table 22 Initial symptoms in 232 patients with pulmonary carcinoma (many patients had more than one symptom).(98)

	No of patients	Frequency (%)
Cough	92	39.7
Dyspnoea	65	28
Haemoptysis	38	16.4
General malaise	35	15.1
Acute respiratory infection	29	12.5
Routine check-up	28	12.1
Thoracic pain	25	10.8
Hoarseness	8	3.5
Neurological symptoms	5	2.2
Enlarged lymph nodes	3	1.3
Others	6	2.6

9.3 Delay and diagnostic difficulties

9.1.1 Key clinical questions:

What diagnostic difficulties do primary care practitioners themselves report in determining whether a woman/man who presents with symptoms/signs suggestive of lung cancer may or may not need urgent referral with suspected lung cancer?

In people attending primary care services, which psychosocial and socio-demographic factors are associated with delayed presentation of lung cancer? Which factors influence delay by patient and which delay by provider?

9.1.2 Evidence questions:

What diagnostic difficulties do primary care practitioners themselves report in determining whether a patient may or may not need urgent referral with suspected lung cancer?

In people attending primary care services, which psychosocial and socio-demographic factors are associated with delayed presentation of lung cancer? Which factors influence delay by patient and which delay by provider?

9.1.3 Evidence Statements:

Delay can occur when patients fail to recognise the significance of a symptom such as prolonged cough (III)

Presentation with non-respiratory symptoms such as shoulder pain may be associated with difficulty in diagnosis (III)

Papers covering delay or diagnostic difficulties are scarce but those with relevant findings are summarised below.

Primary studies

(Gorman et al, 2002)(99)

General practitioners in the UK were surveyed about the use of investigations prior to referral of patients with suspected lung, large bowel, non-melanoma skin and breast cancer. The study was confined to one health board in Lothian. The questionnaire was distributed in May 1997 to 134 general practices, following a pilot study in eight practices. Information was sought about referral choices, communication, quality of care, liaison between community and hospital, health promotion, treatment outcomes and palliative care. The main outcome measures were determinants of primary care referral behaviour and clinical investigation strategies, and perceptions of quality in secondary care and health promotion services.

Seventy-nine general practices (59%) returned completed questionnaires. Most cases of suspected lung cancer, approximately half of suspected colorectal cancer cases and very few cases of suspected breast cancer were investigated in primary care before referral to hospital. It was unlikely that a practice would investigate further in primary care a woman with symptoms suggestive of breast cancer, but with lung cancer investigations prior to referral would be done in three quarters of cases and in 45% of those with colorectal cancer symptoms. Practices highlighted their wish for fast track facilities and an increase in the availability of open access investigation and diagnostic services.

(Varney et al, 1996)(100)

A three-year case series study using UK hospital data sought to identify the early symptoms of lung cancer in order to decrease delay in identification of lung cancer. Cough was the initial complaint in 117 patients. In 80% the cough was a new symptom, usually reported as dry, in 20% a previous cough had clearly changed, and 30% of all patients had quit smoking because of the

cough. Most consulted their general practitioner promptly but 26 patients delayed consulting by an average of 12 months. In those who consulted promptly, there was a mean delay of seven months between reported symptoms and the first chest x-ray. Asthma treatment, antibiotics and steroids were commonly prescribed during this time.

A total of 104 patients reported shoulder or chest pain as the first complaint: the tumours were always located in the upper lobes, with pain referred to the shoulder, anterior chest wall or scapula on the affected side. Most were initially treated with nonsteroidal anti-inflammatory drugs and shoulder injections. Only 12 delayed consulting their general practitioner by an average of 3.5 months. Patients who consulted promptly had their first chest x-ray five months later on average. Sixty of these were current smokers. Additional presenting symptoms were: breathlessness (35 patients); weight loss with malaise (17 patients); haemoptysis (ten patients); and hoarseness (nine patients).

10 Upper gastrointestinal cancer

Number		Grade
	General recommendations	
1	A patient who presents with symptoms suggestive of upper gastrointestinal cancer should be referred to a team specialising in the management of upper gastrointestinal cancer, depending on local arrangements.	D
	Specific recommendations	
2	An urgent referral for endoscopy or to a specialist with expertise in upper gastrointestinal cancer should be made for patients of any age with dyspepsia ¹² who present with any of the following: <ul style="list-style-type: none">• chronic gastrointestinal bleeding• dysphagia• progressive unintentional weight loss• persistent vomiting• iron deficiency anaemia• epigastric mass• suspicious barium meal.	C
3	In patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, an urgent referral for endoscopy should be made.	D

¹² The definition of dyspepsia is taken from the NICE guideline on *Dyspepsia: management of dyspepsia in adults in primary care* (www.nice.org.uk/CG017). Dyspepsia in unselected patients in primary care is defined broadly to include patients with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting.

Number		Grade
4	In patients aged less than 55 years, endoscopic investigation of dyspepsia is not necessary in the absence of alarm symptoms.	D
5	In patients presenting with dysphagia (interference with the swallowing mechanism that occurs within 5 seconds of having commenced the swallowing process), an urgent referral should be made.	C
6	<i>Helicobacter pylori</i> status should not affect the decision to refer for suspected cancer.	C
7	In patients without dyspepsia, but with unexplained weight loss or iron deficiency anaemia, the possibility of upper gastrointestinal cancer should be recognised and an urgent referral for further investigation considered.	C
8	In patients with persistent vomiting and weight loss in the absence of dyspepsia, upper gastro-oesophageal cancer should be considered and, if appropriate, an urgent referral should be made.	C
9	An urgent referral should be made for patients presenting with either: <ul style="list-style-type: none">• unexplained upper abdominal pain and weight loss, with or without back pain, or• an upper abdominal mass without dyspepsia.	C

Number		Grade
10	In patients with obstructive jaundice an urgent referral should be made, depending on the patient's clinical state. An urgent ultrasound investigation may be considered if available.	C
11	In patients with unexplained worsening of their dyspepsia, an urgent referral should be considered if they have any of the following known risk factors: <ul style="list-style-type: none">• Barrett's oesophagus• known dysplasia, atrophic gastritis or intestinal metaplasia• peptic ulcer surgery more than 20 years ago.•	C
	Investigations	
12	Patients being referred urgently for endoscopy should ideally be free from acid suppression medication, including proton pump inhibitors or H ₂ receptor antagonists, for a minimum of 2 weeks.	C
13	In patients where the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be carried out in accordance with local arrangements.	D
14	All patients with new onset dyspepsia should be considered for a full blood count in order to detect iron deficiency anaemia.	D

Number		Grade
11	<p>In patients with unexplained worsening of their dyspepsia, an urgent referral should be considered if they have any of the following known risk factors:</p> <ul style="list-style-type: none">• Barrett's oesophagus• known dysplasia, atrophic gastritis or intestinal metaplasia• peptic ulcer surgery more than 20 years ago.•	C
	Investigations	
12	<p>Patients being referred urgently for endoscopy should ideally be free from acid suppression medication, including proton pump inhibitors or H₂ receptor antagonists, for a minimum of 2 weeks.</p>	C
13	<p>In patients where the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be carried out in accordance with local arrangements.</p>	D
14	<p>All patients with new onset dyspepsia should be considered for a full blood count in order to detect iron deficiency anaemia.</p>	D

Introduction

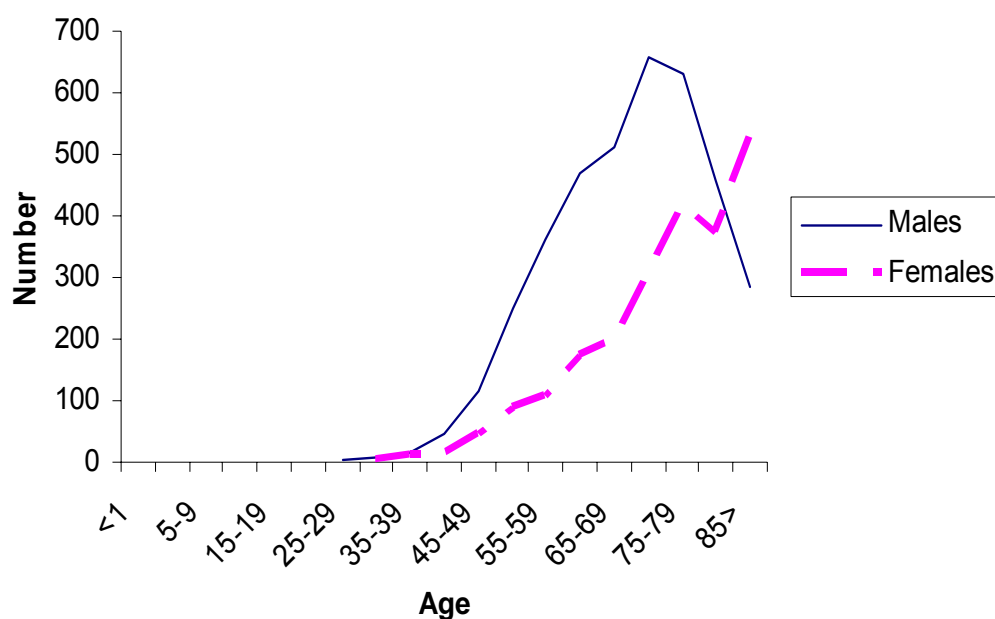
Incidence

Cancer of the oesophagus

The Office for National Statistics recorded 6,080 newly diagnosed cases of oesophageal cancer in 2001 in England and Wales, of which 3,806 were in males and 2,274 in females.

Numbers of registrations of oesophageal cancer have continued to increase over the last 20 years and the figures for 2001 are shown below.

Figure 7 2001 Newly diagnosed cases of malignant neoplasm of the oesophagus in 2001 in England and Wales. (77)

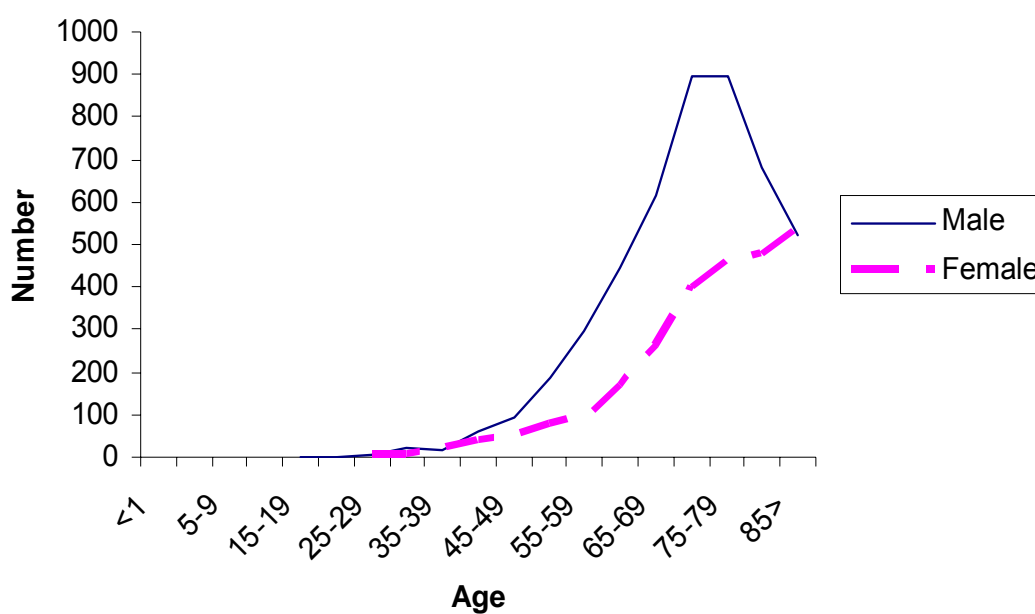


Cancer of the stomach

In 2001 there were 4,741 newly diagnosed cases of stomach cancer in males and 2,626 in females in England and Wales. Incidence recorded by the Office for National Statistics was low in both men and women in those under 50 years and increases rapidly with age peaking in those aged 85 years and over

The 2001 registrations of stomach cancer demonstrate a continuing trend of increased incidence and are shown below.

Figure 8 Newly diagnosed cases of malignant neoplasm of the stomach in 2001 in England and Wales. (77)

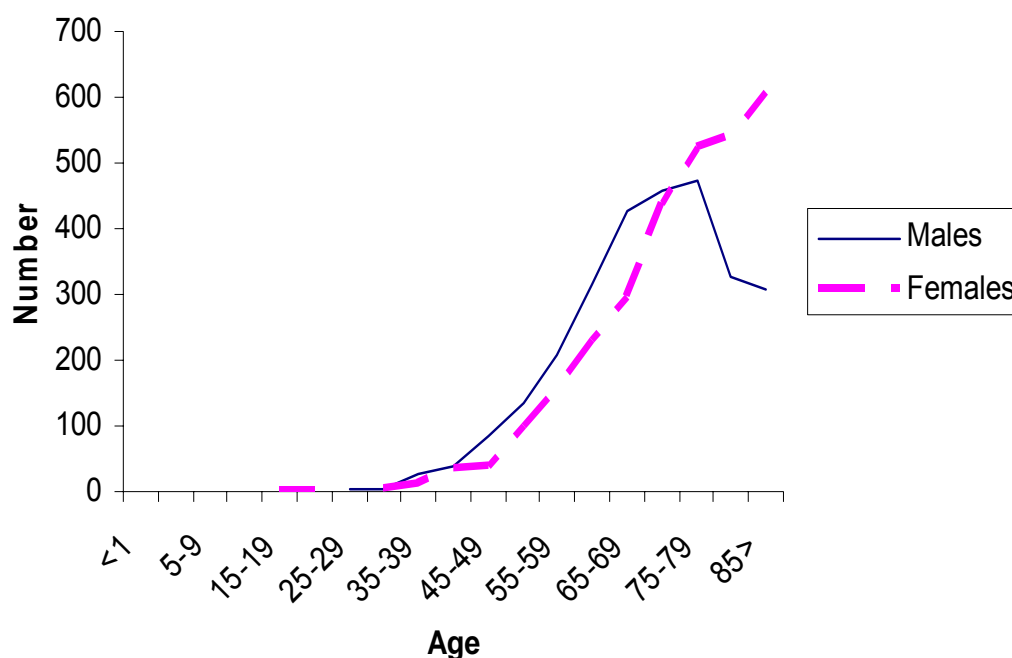


Pancreatic cancer

There were 2,807 cases of pancreatic cancer in males and 2,986 in females in 2001. Incidence indicates that it is rare in those aged under 50 years in both sexes.

2001 statistics show a similar trend but with the incidence in males over 80 years beginning to decline (Figure 9).

Figure 9 Newly diagnosed cases of pancreatic cancer in 2001 in England and Wales. (77)

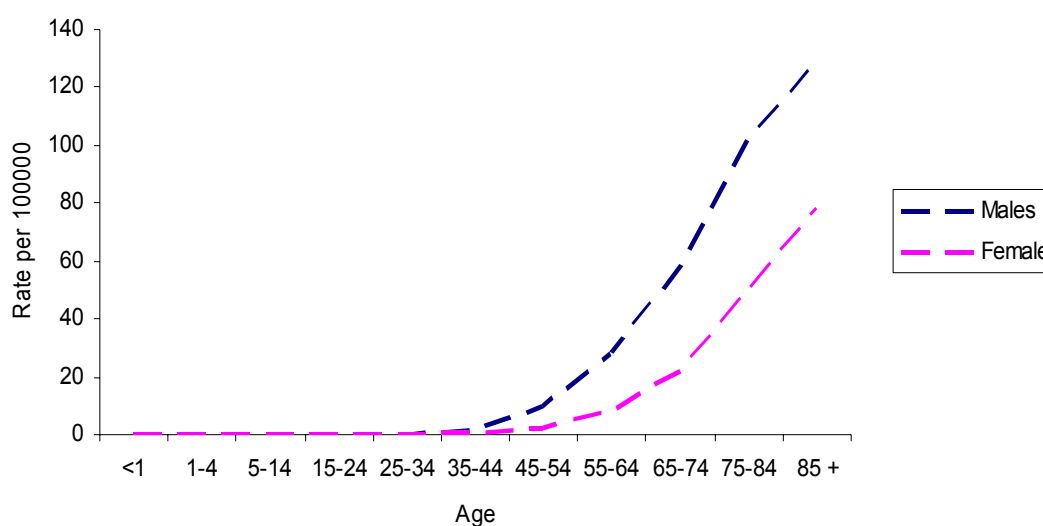


Mortality

Cancer of the oesophagus

Mortality rates from cancer of the oesophagus have been increasing over the last 20 years. In 2002 the number of deaths from cancer of the oesophagus was 4,001 in males and 2,329 in females.

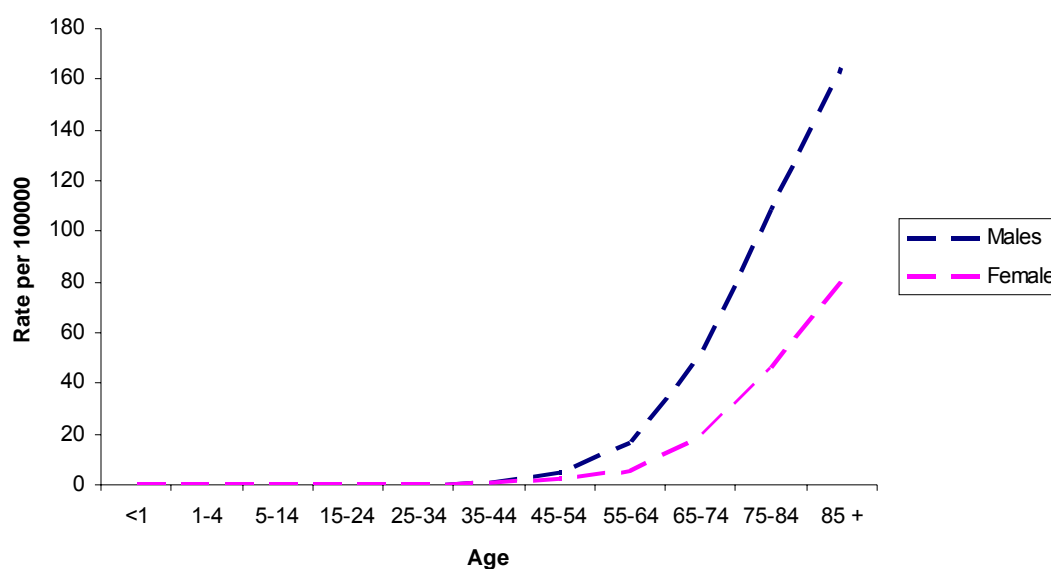
Figure 10 Mortality figures from cancer of the oesophagus for 2002 in England and Wales. (78)



Cancer of the stomach

The 2002 mortality data for cancer of the stomach demonstrates a higher rate of mortality in males than in females, with numbers totalling 3,211 in males and 2,105 in females. Mortality is low in those aged under 35 years and increases with age (shown in Figure 11).

Figure 11 Mortality figures from stomach cancer for 2002 in England and Wales. (78)

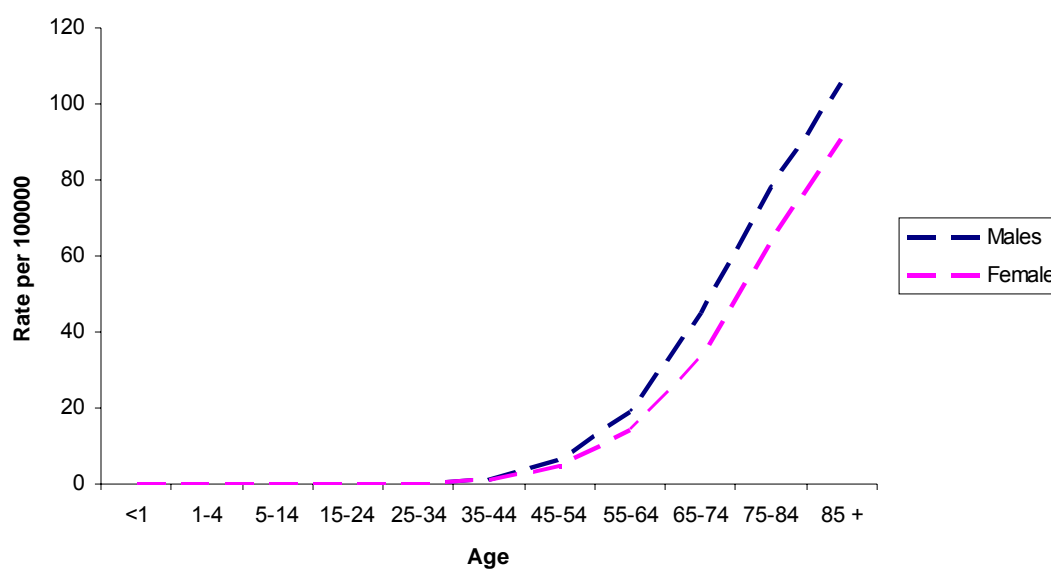


Pancreatic cancer

Trends in mortality from pancreatic cancer are similar to the incidence rates as the disease has a poor survival rate.

In 2002 the number of deaths due to cancer of the pancreas was 3,169 females and 2,952 males in England and Wales. (Shown in Figure 12)

Figure 12 Mortality figures from pancreatic cancer for 2002 in England and Wales. (78)



10.1 Symptoms and Signs

10.1.1 Key Clinical Question:

In people attending primary care services with upper gastrointestinal problems, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of cancer, and which are not?

10.1.2 Evidence Question:

In people attending primary care services with symptoms and signs that might be associated with upper gastrointestinal cancers, which symptoms and signs and other features including family history, when compared with the 'gold standard', are predictive of a diagnosis of cancer, and which symptoms and signs are not? Are any non-clinical features associated with a diagnosis of cancer?

10.1.3 Evidence Statements:

Upper gastrointestinal cancers are relatively uncommon in primary care. The typical general practitioner will encounter a case of oesophageal cancer once every five years, a case of stomach cancer once every three years, and a case of pancreatic cancer once every five years. (III)

The incidence of oesophageal, stomach and pancreatic cancers rises from around aged 50 years. (III)

Oesophageal and gastric cancer

The risk of gastric cancer is increased among smokers by a ratio of between 1.5 and 2.5. (III)

Barretts' oesophagus increases the risk of oesophageal cancer by 40-125 fold. (III)

Dyspepsia is very common, and a poor predictor of cancer. (III)

In a patient presenting with dyspepsia, weight loss (2kg or over) and dysphagia are features associated with cancer, . (III)

Other features associated with 20-30% of cases of gastric cancer include haematemesis, persistent vomiting, and anaemia, although these features may be less discriminatory than dysphagia and weight loss. (III)

Pancreatic cancer

Smoking is a risk factor for pancreatic cancer (risk ratio 1.6-3.1). (III)

The most common presenting symptom of pancreatic cancer is abdominal pain, occurring in approximately 70% of cases. (III)

Jaundice is the next most common feature, occurring in approximately 50% of cases. (III)

Non-specific symptoms and signs are common in pancreatic cancer, and include nausea and vomiting, weight loss, change in bowel habit and onset of diabetes. (III)

Guidelines

Oesophageal and gastric cancers

(NICE, 2004)(101)

Guidelines on the management of adults with dyspepsia in primary care have been published by NICE in 2004. Dyspepsia was defined as: '*any symptom of the upper gastrointestinal tract, present for four weeks or more, including upper abdominal pain or discomfort, heartburn, acid reflux, nausea, or vomiting.*'

When referred to broadly in this way, the guideline indicated that dyspepsia occurs in 40%, leads to general practitioner consultation in 5% and referral for endoscopy in 1% of the population annually. In patients with signs or symptoms sufficiently severe to merit endoscopy, 40% have functional or non-ulcer dyspepsia, 40% have gastro-oesophageal reflux disease and 13% have some form of ulcer. Gastric and oesophageal cancers were reported as very rare, occurring in 3% of endoscopies although many cases arise from on-going hospital investigation rather than primary care referral.

The guideline found that dyspeptic symptoms were a poor predictor of significant disease, and in primary care described symptoms were a poor predictor of underlying pathology.

(SIGN, 2003)(102)

The SIGN guidelines recommend referral for endoscopy for patients with alarm symptoms and also those aged 55 or over with persistent or recurrent dyspepsia. The guideline found no evidence to support the mandatory use of early upper GI endoscopy to investigate patients over 55 years old who present with new onset uncomplicated dyspepsia. A non-invasive *H. pylori* test and treat policy may be as appropriate as early endoscopy for the initial investigation and management of patients over the age of 55 years presenting with uncomplicated dyspepsia (level A recommendation). However, referral for assessment should be considered for patients over 55 years old with uncomplicated dyspepsia whose symptoms persist after initial management with the *H.pylori* test and treat strategy.

Secondary studies

(Heading et al, 1999)(103)

This was a systematic review of studies of the population prevalence of upper gastrointestinal symptoms in the UK. Studies were included if they had been published up to December 1997, if sample size and response rate were reported, if vague terms such as dyspepsia or indigestion were defined, abdominal pain or discomfort enquired about, and patients with a history or evidence of organic disease had not been excluded. Follow-up studies on groups of patients previously studied were excluded.

A total of 25 studies were identified, but 15 did not meet the defined inclusion criteria. In the ten included studies, the reported prevalence of upper abdominal symptoms (mostly upper abdominal pain or discomfort) ranged from approximately 8% to 54%, while the prevalence of heartburn ranged from 10% to 48%, and regurgitation from 9% to 45%, and 21% to 59% for both or either.

The most likely explanation for the broad range of prevalence reported in the case of upper abdominal symptoms is variation in the definition of symptoms. In the case of heartburn and regurgitation, different use of these terms by various investigators and subjects were viewed as contributing to the range of results.

Primary studies

Oesophageal and gastric cancers

(Numans et al, 2001)(104)

This was a multicentre case series study of the diagnostic features of gastro-oesophageal malignancy undertaken in the Netherlands. The subjects were 861 consecutive patients who were investigated with first time gastroscopy between 1986 and 1988. The diagnostic features were then validated in a

second population (N=1153 from the same region during the next six years). These patients were referred by 150 of the original 196 general practitioners asked to participate in the first study, and the gastroscopies were performed in the same hospitals between 1988 and 1994. Univariate and multivariate analyses identified four symptoms predictive of malignancy that were then compared with the classic 'alarm symptoms'.

During the first study period, malignancy was found in 21 patients (2.4%). The presence of weight loss, presence of dysphagia, absence of pain during the night and the absence of heartburn were predictors of malignancy. Classic symptoms were statistically significant as indicated in Table 23. The authors used the findings to assess a scoring system for symptoms that should trigger endoscopy (*Table 24*).

Table 23 Presence and absence of characteristics in patients with a diagnosis of gastro-oesophageal malignancy. Crude odds ratio (OR), 95% confidence intervals (95% CI) and P-values for a diagnosis of malignancy by patient characteristics in the study population.(104)

Characteristic	Present	Absent	N	OR	95% CI	P
Age > 45	18	3	861	4.7	1.4- 24.9	0.01
Sex (male)	13	8	861	1.3	0.5-3.6	0.76
History of dyspepsia	7	13	789	0.3	0.1-0.9	0.02
History of peptic ulcer	3	18	771	0.5	0.1-1.6	0.30
History of any UGI episode*	10	11	861	0.4	0.2-1.1	0.08
Prior barium meal	14	7	360	2.9	1.1-8.4	0.04
Use of H ₂ RA	7	14	861	0.8	0.3-2.2	0.87
Smoking >5/days	13	8	813	2.4	0.9-6.8	0.08
Alcohol >4/days	2	16	782	2.0	0.2-9.1	0.57
Dysphagia	13	8	835	6.2	2.3- 17.6	<0.01
Vomiting	8	13	834	1.9	0.7-5.1	0.23
Weight loss	14	7	861	6.6	2.4- 19.5	<0.01
Fatigue	14	6	804	4.3	1.5- 13.7	<0.01
Melaena	3	16	815	2.2	0.5-8.1	0.38
Regurgitation	12	9	786	1.9	0.7-5.1	0.23
Retrosternal pain	13	6	754	1.9	0.7-6.1	0.29
Heartburn during the night	2	18	809	0.2	0.0-0.9	0.02
Heartburn during the day	4	16	807	0.2	0.1-0.7	<0.01
Complaints while bending over	1	18	758	0.1	0.0-0.6	<0.01
Pain during the night	3	17	820	0.2	0.0-0.6	<0.01
Epigastric pain	12	6	824	0.4	0.1-1.3	0.13
Empty stomach pain	5	16	800	0.5	0.1-1.4	0.20
Bloating	14	5	823	1.2	0.4-4.4	0.92

Characteristic	Present	Absent	N	OR	95% CI	P
Nausea	11	9	817	1.2	0.4-3.3	0.88
Pain after a meal	7	11	761	0.7	0.2-2.0	0.62
Haematemesis	1	19	834	0.9	0.0-5.9	1.00
Duration > 3 months	8	12	758	0.6	0.2-1.7	0.45
Abnormal physical examination	7	12	835	0.6	0.2-1.6	0.34
Hb <7 female / <7.5 male	0	1	164	0	0.0-29.5	1.00
Hemoccult +	1	1	60	3.4	0.0-277.6	0.83

History of any upper gastrointestinal episode' means that the patient has consulted the current or any other physician with any complaint or non-malignant disease that has been diagnosed as originating from the upper gastrointestinal tract. This includes the whole range from functional dyspepsia and NUD to GORD and peptic ulcer, but it excludes malignancy in the upper abdomen. Bold case indicates classical alarm 'symptoms'. Underlined italics indicate additional features included in full statistical model (see *Table 24*).

Table 24 'Full' and 'classical' alarm symptoms models. Adjusted odds ratios (OR), 95% confidence intervals and scoring list values of patient characteristics associated with a diagnosis of malignancy in the study population (N=861).(104)

Patient characteristics	OR	95% CI	Full scoring list	OR	95% CI	Alarm scoring list
Age (yrs)	1.0	1.0-1.1	/10	1.1	1.0-1.1	/10
Sex	1.4	0.5-4.3	Male +1	2.1	0.7-6.5	Male +1
History of any UGI episode (year/n)	0.4	0.1-1.1	Yes -2	0.3	0.1-1.0	-2
Smoking (>5/day versus <5 or 0/day)	2.6	0.9-8.0	Yes +2	2.8	0.9-9.0	+2
H ₂ -receptor antagonist (year/n)	1.4	0.4-4.3	Yes +1	0.8	0.2-2.7	-1
Weight loss (>2kg / <2kg)	4.4	1.6-12.5	Yes +4	2.8	0.9-8.6	2
Dysphagia (years/n)	6.1	2.1-17.6	Yes+4	5.2	1.8-15.5	3
Pain during the night (year/n)	0.3	0.1-1.1	Yes -3			
Heartburn during the day (year/n)	0.2	0.1-0.8	Yes -4			
Fatigue				2.1	0.7-6.9	1
Vomiting				1.4	0.4-4.5	1
Meleana				3.0	0.7-13.4	2

(Irving et al, 2002)(105)

This UK case series sought to determine the impact of the two week target for referrals for suspected cancer. A total of 90 patients with oesophago-gastric

cancer treated at Cumberland Infirmary between 1999 and 2001 were included.

65 patients were diagnosed with oesophageal cancer and 25 with gastric cancer. Dysphagia was the most common presenting symptom and was experienced by 58 patients in the study (64%), being more common in patients with oesophageal rather than gastric malignancies (77% versus 32%).

(Crean et al, 1982)(106)

In this UK study, a formal decision system was developed for assessment of patients with dyspepsia. The value of symptoms in duodenal and gastric ulcer, gastric carcinoma and alcohol related dyspepsia was investigated. 1000 patients attending a dyspepsia clinic were recruited and relevant clinical information was collected in a standardised manner.

Symptom scores indicated that a brief history of dyspepsia occurring in a patient over 55 should raise the possibility of gastric cancer; when the symptoms 'daily pain or discomfort', 'early repletion' and haematemesis or 'coffee ground vomit' were combined, the probability of gastric cancer was increased.

(Adachi et al, 1993)(107)

This retrospective study carried out in Japan sought to identify the most effective approaches for detecting superficial oesophageal carcinoma. Clinical histories were investigated by review of hospital charts. The method of recruiting patients was not explicitly described, and it is not clear whether the sample comprised a consecutive series. The case series provided data on the symptoms associated with early stage and more advanced oesophageal cancer.

Symptoms were more frequent and the size of lesions larger with increasing depth of invasion. A piercing sensation was present mostly in superficial

oesophageal carcinoma, while pain or dysphagia were present both in advanced oesophageal cancer and submucosal carcinoma. No calculations were performed to assess the predictive values of the symptoms described.

(Ojala et al, 1982)(108)

This retrospective case series was an investigation of the presenting signs and symptoms of patients with carcinoma of the oesophagus and gastric cardia attending a university hospital in Finland over the period 1964 to 1977. The study included 225 patients, 139 males, and 86 females (see *Table 25*).

Table 25 Incidence of symptoms in 225 patients with carcinoma of oesophagus or gastric cancer.(108)

Results	Upper third (N=9) N and %	Middle third (N=68) N and %	Lower third (N=61) N and %	Gastric cardia (N=81) N and %	Total N and %
Dysphagia	8 (89%)	66 97%	58 95%	77 89%	209 93%
Weight loss	5 (56%)	20 29%	32 52%	47 54%	104 46%
Vomiting	0 -	7 10%	28 46%	39 45%	74 33%
Gastric pain	0 -	7 10%	20 33%	29 33%	56 25%
Thoracic pain	1 11%	11 16%	14 23%	21 24%	47 21%
Anorexia	0 -	4 6%	4 7%	8 9%	16 7%
Haematemesis or melaena	0 -	2 3%	4 7%	7 8%	13 6%
Belching, hiccups, dyspepsia	0 -	1 1%	5 8%	4 5%	10 4%
Pharyngeal pain	2 22%	4 6%	3 5%	0 -	9 4%
Sensation of a lump	3 33%	3 4%	0 -	0 -	6 3%
Anaemia	0 -	0 -	0 -	6 7%	6 3%
Cough, hoarseness	2 22%	2 3%	1 2%	0 -	5 2%
Others	2 22%	8 12%	3 5%	7 8%	20 9%

Age at the time of diagnosis varied from 37-84 (mean 62.5) years. The most common symptoms were dysphagia (obstruction or pain upon swallowing and/or regurgitation) (93%), weight loss (46%), vomiting (33%), gastric cancer (25%), thoracic pain (21%), anorexia (7%) and symptoms of gastrointestinal bleeding (9%). Respiratory symptoms (cough and hoarseness) occurred principally with tumours of the upper oesophagus. Gastrointestinal bleeding and anaemia were found in tumours of the lower oesophagus and gastric cardia. Other symptoms including poor general condition, infections, backache or pain in the lower abdomen occurred in 9% of patients. Dysphagia was the chief symptom in a large percentage of patients regardless of the location of the initial symptom. All diagnoses were verified histologically either on the basis of biopsies taken at endoscopy or from specimens obtained at surgery.

The mean duration of symptoms before the establishment of the diagnosis was 4.1 months in carcinoma of the oesophagus and 4.3 months for gastric cancer (cardia).

(Fielding et al, 1980)(109)

This study reviewed patients with histologically proven adenocarcinoma of the stomach and reported the natural history and associated signs and symptoms of early gastric cancer. The study reviewed all patients notified to the Birmingham Cancer Registry during the period 1960 to 1969.

A total of 13,288 cases of gastric cancer were recorded. Ninety (0.7%) were identified as having 'early' gastric cancer. Most of the 90 patients experienced symptoms related to the gastrointestinal tract but in contrast to patients with advanced gastric cancer only 9% had lost weight on admission. The mean age at presentation of the 90 patients was 62.3 years and the condition was most common in the fifth and sixth decades. Fifty-nine patients were men and 31 women. Forty-six patients had presented with a solitary symptom and 44 with a combination of symptoms. The most common symptom was epigastric pain (26 cases), and weight loss occurred in only 17 cases. Twenty-one

patients had presenting symptoms listed as 'other' which included malaise, stomach troubles and general weakness. Type II and type III lesions had been manifested predominantly by epigastric pain and type I lesions by haematemesis. No patient had physical signs of a gastric primary neoplasm. The length of history varied and in 14 cases it was a year or more.

(Scottish Audit of Gastric and Oesophageal Cancer, 2002)(110)

The audit was based on data from 3,293 patients with upper gastrointestinal tumours (1490 oesophageal, 539 oesophago-gastric junction, and 1264 gastric) diagnosed 1997-1999, and included 98% of all such tumours diagnosed in Scotland during the study period. Information was collected from hospital records and investigation reports. The median age of patients was 72 years. Patients delayed presenting to their doctors by more than 4 months in 30% of cases.

Among patients with oesophageal adenocarcinomas, 14% were previously known to have Barrett's oesophagus. Approximately one third has a history of gastro-oesophageal reflux. Risk factors associated with gastric cancer included H pylori infection, previous gastric surgery, previous peptic ulcer disease and pernicious anaemia. A previous history of an ulcer was present in 1 in 5 patients who developed gastric cancer. Endoscopy and biopsy was the primary method of diagnosis (94% of patients); 0.9% of patients had a ruptured oesophagus following endoscopy, with 27% dying from this complication.

(Crean et al, 1994)(111)

The aim of this UK study was to develop a diagnostic decision system for dyspepsia, by recording the symptoms and clinical features of the common causes of dyspepsia as well as their distribution between diseases. The study included patients (N=1540) referred to hospital, data being recorded from 1974 to 1987. The authors included 107 inpatients with 'organic disease', although the majority of subjects were outpatients seen on referral by general

practitioners (N=1433). The period of follow-up was not given. Biopsy specimens were taken depending on findings but it is not clear how many samples were analysed. The study had not been included in the Talley (1998)(112) review.

For the purposes of this study dyspepsia was defined as 'any form of episodic recurrent or persistent abdominal pain or discomfort, or any other symptoms referable to the upper alimentary tract, excluding bleeding or jaundice, of duration four weeks or longer'. Of the 1540 patients at diagnosis, 3% (50) were diagnosed with gastric carcinoma.

(Gillen et al, 1999)(113)

The main aim of this study was to assess whether concern over occult malignancy was valid in UK patients aged <55 years presenting with uncomplicated dyspepsia. Patients were identified between 1989 and 1993 from the West of Scotland Cancer Registry.

A total of 169 patients aged <55 years were diagnosed with gastroesophageal malignancy over the five year period, an incidence of about one per 28,000 total population/year. Only five patients were found to have upper gastro intestinal malignancy when undergoing investigation in the absence of 'sinister' symptoms (see *Table 26*).

Table 26 Sinister symptom prevalence in gastric and oesophageal cancer patients.(113)

	Prevalence of sinister symptoms in gastric cancer patients	Prevalence of sinister symptoms in oesophageal cancer patients
Weight loss	61.8%	63.0%
Persistent vomiting	35.6%	35.6%
Dysphagia	23.7%	84.9%
Anaemia	22.4%	5.5%
Haematemesis/melaena	18.4%	2.7%
Palpable mass	9.2%	0

A total of 84 patients had gastric cancer. Their median age was 50 years (range 31-54 yr) and 65 were men. Case sheets could be retrieved for 76. Of these, 71 (93.4%) had at least one sinister symptom at the time of initial referral for investigation. The most common presenting symptoms identified for gastric and oesophageal cancer patients were weight loss, persistent vomiting, dysphagia, anaemia, haematemesis, melaena and palpable mass.

(Voutilainen et al, 2003)(114)

Voutilainen and colleagues investigated the impact of clinical symptoms and referral volume of patients with dyspepsia on the detection of gastric and duodenal lesions. Data were collected prospectively on all patients referred for upper gastrointestinal endoscopy by general practitioners in 1996. The included study population was 3378 patients; male to female ratio 1:1.3 and mean age 58 years.

Alarm symptoms were defined as anaemia, dysphagia, weight loss and/or vomiting. Of the 1104 patients referred with alarm symptoms, 12 (1%) were diagnosed with gastric cancer, compared with 0.1% for those referred with dyspepsia, 0.5% referred for failure of empirical treatment, 0% referred for reflux, and 0.3% referred for other symptoms. The authors calculated that

alarm symptoms were associated with an increased risk factor of 3.6 (95% CI 2 to 10.7) for gastric cancer.

Pancreatic cancer

(Wilson et al, 2000)(115)

The objectives were to identify the symptoms experienced by patients with pancreatic cancer and the response by health professionals in providing supportive care. The study was a retrospective review of the records of patients diagnosed with pancreatic cancer (N=99).

According to the Nova Scotia Cancer Registry, approximately 541 individuals were diagnosed with cancer of the pancreas. Slightly more than half were female (N=53). The mean age of all subjects was 69 years. Most patients were married.

At the time of admission to hospital 76 patients reported pain. The abdomen was the most prevalent pain site (N=43). Other symptoms included jaundice (N=35), diarrhoea (N=27) and constipation (N=22). Once hospitalised, pain continued to be the most common symptom experienced by nearly all patients (N=91). Other symptoms included nausea, vomiting and/or anorexia, alteration in bowel habit, and symptoms affecting the skin including jaundice. During hospitalisation 83% of patients experienced one or more gastrointestinal symptoms.

(Bakkevold et al, 1992)(116)

The study was designed to compare the symptoms and signs, and delays in diagnosis of pancreatic cancer at Norwegian hospitals. Information about the sensitivities of diagnostic investigations was obtained prospectively but data on signs and symptoms were extracted from the records. 472 patients with histologically verified carcinoma of the pancreas (N=442) or the papilla of Vater (N=30) were included. Patients with endocrine tumour,

cholangiocarcinoma, metastatic pancreatic tumour, cystadenocarcinoma, and histologically or cytologically unverified primary pancreatic tumour were excluded. Thirty-eight Norwegian hospitals participated in the study. The university and district hospitals diagnosed and treated 190 (40%) and 282 (60%) respectively. After preliminary investigations, the local hospitals referred their patients to larger hospitals for diagnosis and treatment.

Presenting symptoms and signs in patients with carcinoma of the pancreas or papilla of Vater were jaundice (47%), acute pancreatitis (5%), abdominal pain (72%), weight loss (58%), diabetes (8%), and other (49%). Jaundice without pain was present in 18%. The commonest nonspecific symptoms were dyspepsia (12%), diarrhoea/steatorrhoea (12%) and nausea (5%). Thromboembolism was seen in two patients (0.4%).

Jaundiced patients had less advanced tumours than non-jaundiced at staging ($P=0.0000$). In contrast, abdominal pain and/or weight loss predicted advanced disease ($P=0.0001$ and 0.004 respectively). Acute pancreatitis occurred more often in patients with tumours of the papilla of Vater (19%) than at other sites ($P=0.003$).

(Klamer et al, 1982)(117)

This US case series aimed to investigate epidemiologic factors, presenting symptoms, diagnostic strategies, site and extent of cancer, treatment approaches and survival data associated with pancreatic cancer. The charts of all 33 patients treated for cancer at Mount Sinai Medical Center between 1971 and 1978 were reviewed. Patients with cancers arising from periampullary and islet cell tissue were excluded. The 33 included patients had histologically confirmed duct cell carcinoma. No patient was aware of exposure to asbestos or other known carcinogens, and no patient had a previous history of pancreatitis. Fifteen gave a history of smoking, 11 of diabetes and five of alcohol abuse.

Seventeen patients were men and 16 women. The mean age was 63.3 years (range 40 to 89). Four patients were black, three of them women. The 29 white patients were nearly equally distributed by sex. All were city dwellers. Although most patients presented with more than one symptom, the most common complaint leading to hospitalisation was abdominal pain, which occurred in 23 (70%), followed by jaundice in 19 (57%), anorexia in 15 (45%), weakness in ten (30%), and nausea in eight (24%). Six patients (18%) complained of pruritis or diarrhoea. A range of diagnostic investigations were undertaken including radiography or radionuclide scanning, pancreatic scans, arteriography, ultrasound, computerised tomography and liver biopsy. Histologic confirmation was not obtained until autopsy in seven patients.

Risk Factors

Secondary studies

Oesophageal and gastric cancers

(Shaheen and Ransohoff, 2002)(118)

The evidence linking gastroesophageal reflux disease (GORD) and Barrett's oesophagus to oesophageal carcinoma was reviewed. A MEDLINE search was performed to identify all English language reports about GORD, adenocarcinoma, and Barrett's oesophagus from 1968 through 2001. Cohort studies demonstrated that symptoms of GORD occurred monthly in almost 50% of US adults and weekly in almost 20%. There were no prospective cohort studies of reflux patients to assess cancer risk. Three large case-control studies demonstrated a positive association between reflux symptoms and risk of adenocarcinoma of the oesophagus, with more prolonged and severe symptoms accentuating this risk. However, because of the low incidence of adenocarcinoma of the oesophagus and the ubiquity of reflux symptoms, the risk of cancer in any given individual with reflux symptoms was low.

Most studies on individuals with Barrett's oesophagus reported a risk ratio of cancer that was 40 to 125 times higher than that of the general population. Estimates of the absolute risk of oesophageal adenocarcinoma varied widely from 0% to almost 3% per patient year. Recent larger studies and a meta analysis suggested that a reasonable estimate was approximately 0.5% per-patient year, resulting in the risk of a patient with Barretts' esophagus developing cancer in a year as approximately one in 200.

(Tredaniel et al, 1997)(119)

A review and meta-analysis of 40 studies was undertaken to provide a quantitative estimate of the association between gastric cancer risk and tobacco smoking.

A total of 40 studies was included in the meta-analysis and 30 provided results on ever smokers; not all however, reported enough details to be included in the weighted analysis. In particular, the variance-weighted regression was restricted to the 20 studies providing risk estimates and confidence limits for men, since results for women were reported for only one study. The analysis weighted on number of cases showed a higher summary relative risk in men (1.59) than in women (1.11, P-value for difference, 0.04). All the cohort studies showed a significantly increased risk of gastric cancer of the order of 1.5 –2.5 for cigarette smokers. Evidence from case-control studies was less consistent. The results suggested a risk of stomach cancer among smokers of the order of 1.5-1.6 as compared to non-smokers.

A number of studies reported separate analyses for current and ex-smokers: the summary variance-weighted relative risk was higher in current smokers (1.47) than in ex-smokers (1.18, P value 0.27). A dose-response relationship was suggested by the analysis of studies reporting risk estimates for different levels of smoking: summary relative risks were 1.49 for smokers of up to 20 cigarettes per day and 1.67 for heavier smokers (P value, 0.43). The differences between current and ex-smokers and between light and heavy smokers persisted when the meta-analysis was stratified according to year of publication, sex, geographical region and study design.

(Wei and Saheen, 2003)(120)

Risk factors for oesophageal cancer and how these related to the increased incidence were reviewed by Wei and Saheen. They concluded that the most suspicious aetiologic factors associated with the current increase of oesophageal cancer were obesity, the use of lower oesophageal sphincter relaxing medications, possibly decreasing *H pylori* infection, changes in the

Western diet and the effects of smoking even when people have subsequently stopped. They also included increased age, male gender, white ethnicity, family history, and gastro-oesophageal reflux as risk factors but suggested that there was no evidence that any changes in these were associated with the current rise in oesophageal cancer.

Pancreatic cancer

(Lowenfels and Maisonneuve, 2002)(121)

This review of epidemiologic factors in pancreatic cancer identified the confirmed risk factors as being smoking, age and pancreatitis. Other potential risk factors were listed as being diabetes, peptic ulcer disease, gallstones, infections, salmonella, helicobacter pylori, obesity, diet, occupation, inherited and gene-environment factors. The relationship between smoking and pancreatic cancer has been studied extensively in case-control and cohort studies, the results indicating a consistent increased risk of pancreatic cancer in smokers. Most studies were reported to show a dose response, with heavy smokers having a higher risk than light smokers, and current smokers at increased risk compared with nonsmokers. The risk of pancreatic cancer was estimated to remain elevated for one to two decades after cessation of smoking.

Age was the strongest risk factor. Pancreatic cancer is extremely unusual in patients younger than age 30 and is rare before age 50. The mean age of onset was about 65. Underlying benign disease is known to increase the eventual risk of malignancy.

(Ahlgren, 1996)(122)

In this review, it was concluded that direct evidence linking specific dietary carcinogens to pancreatic cancer in humans was limited. Some studies have suggested that the risk of pancreatic cancer is increased in heavy alcohol users. However, most studies in which a relationship between alcohol and

pancreatic cancer has been sought have been negative. If an association between alcohol use and pancreatic cancer does exist, it has been suggested that the specific risk may be to the subset of alcoholics who develop chronic pancreatitis. However, studies of the chronic pancreatitis associated with alcohol consumption have not shown a major risk of pancreatic cancer. A confounding variable in some studies has been cigarette smoking, which is very frequent in heavy alcohol users, and is a known etiologic factor in pancreatic cancer. Thus, unless there is adequate control for cigarette smoking, studies of the relation between alcohol and pancreatic cancer cannot be considered reliable.

The environmental carcinogen which has been linked most closely to cancer is cigarette smoke. Considering all the evidence, cigarette smoking must be considered to be a significant risk factor for pancreatic cancer. Radiation may modestly increase the risk of pancreatic cancer, although the evidence is not conclusive. Familial clustering of pancreatic cancer has been reported, but a genuine association has thus far been established only for familial relapsing pancreatitis.

(Gold and Goldin, 1998)(123)

Incidence rates of pancreatic cancer increase steadily with age. Approximately 80% of cases fall between the age range of 60 and 80 years. Incidence and mortality rates from pancreatic cancer in blacks of both sexes are higher than in white and all other ethnic groups except Japanese. Pancreatic cancer occurs more frequently in men and higher rates have been reported among some low socioeconomic populations.

An apparent association between diabetes and pancreatic cancer has been reported although this was not a consistent finding. Diabetes and pancreatic cancer exhibited a declining sex ratio with increasing age, a phenomenon that is not observed for other digestive tract or other tobacco-related cancers. Although acute and chronic pancreatitis are related to alcoholism, the

relationship of either alcoholism or chronic non-familial pancreatitis to pancreatic cancer remained unresolved.

Various studies suggested that cigarette smoking increases the risk of cancer of the pancreas. The ratios for pancreatic cancer deaths in prospective studies of current cigarette only smokers compared with non smokers range from 1.6 in British physicians to 3.1 in Swedish men and were less than two in five of the eight studies. Most studies showed increasing pancreatic cancer risk with increased amounts of cigarettes smoked. However, not all of these studies demonstrated a dose-response relationship with number of cigarettes or with duration of smoking and some studies reported no significant association.

The evidence that related alcoholism to pancreatic cancer was fairly weak and inconsistent and the data available suggested that any increased risk from alcoholism was fairly small. Data from three case control studies in Europe were pooled and no association of alcohol with pancreatic cancer was found after controlling for gender, age, smoking and socioeconomic status and no evidence of a trend existed with the amount consumed.

The role that nutrition plays was addressed in a number of reviews. The results of the descriptive studies did not support an association of dietary fat intake with pancreatic cancer. However, descriptive studies were often limited by the quality of the cancer incidence data and the quality of the data on per capita intake and were confounded by other uncontrolled variables such as other dietary intake that may be closely correlated. Four cohort studies examined the relation of diet to pancreatic cancer but were of limited value due to the small number of pancreatic cancer cases.

Several ecologic studies showed a positive correlation between age-adjusted death rates for pancreatic cancer and per capita coffee consumption, although relationships by sex and race were inconsistent. Other studies, however, reported no association. The suggestion that coffee was a significant risk factor for pancreatic cancer remained an unresolved question, and if the

association did exist, it was weak. It was also reported to occur excessively among occupational workers exposed to coal gas or those employed in coke plants, metal industries and aluminium milling, but the small numbers reported in such studies should be interpreted with caution.

10.2 Investigations

10.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

10.2.2 Evidence Question:

In patients attending primary care services with symptoms that may be caused by cancer, which investigations when compared with the “gold standard” are predictive of a diagnosis of cancer, and which are not?

10.2.3 Evidence Statements:

Oesophageal and gastric cancers

Endoscopy and biopsy detect a greater proportion of cases of gastro-oesophageal cancers than radiography. (III)

The prescribing of H2 antagonists or proton pump inhibitors to people with gastro-oesophageal cancers prior to endoscopy and biopsy increases the risk of a false-negative test result. (III)

Pancreatic cancer

In pancreatic cancer, jaundice is usually obstructive and extrahepatic. (III)

Diagnostic investigations in pancreatic cancer include abdominal ultrasound which may be arranged in primary care, and more complex secondary care investigations, for example computed tomography, endoscopic retrograde cholangiopancreatography, and other specialist procedures. (III)

Introduction

Several studies included in the section on symptoms and signs also considered aspects of investigations, in particular upper gastrointestinal endoscopy with biopsy. The evidence statements above therefore were based

on the evidence presented in this section but also the evidence reported previously. The studies of pancreatic cancer reported a variety of investigations employed in secondary care, including laparotomy, ultrasonography, axial computed tomography, endoscopic retrograde cholangiopancreatography with or without cytology, percutaneous transhepatic cholangiography, fine needle aspiration cytology, and angiography (Bakkevold et al, 1992(116)).

Secondary studies

Oesophageal and gastric cancers

(Talley et al, 1998)(112)

This US review sought to determine the optimal method of investigating patients with dyspepsia. A MEDLINE and Current Contents search was performed up to April 1997 using the MeSH term 'dyspepsia'.

Endoscopy was reported as consistently providing superior diagnostic accuracy in comparison with radiography. Analysis of the results was limited to descriptions of the findings of oesophagogastroduodenoscopy in patients with dyspepsia although percentages of patients with cancer were reported. In the 36 studies of endoscopy of patients with dyspepsia, the proportion of patients found to have cancer ranged from 0% to 3.3%.

The authors concluded that endoscopy remained 'the gold standard approach because it is still the optimal means of establishing a firm diagnosis'.

Primary studies

(Voutilainen et al, 2003)(114)

Voutilainen and colleagues investigated the impact of clinical symptoms and referral volume of patients with dyspepsia on the detection of gastric and duodenal lesions. Data were collected prospectively on all patients referred

for upper gastrointestinal endoscopy by general practitioners in 1996. The included study population was 3378 patients; male to female ratio 1:1.3 and mean age 58 years. Of these, 20 (0.6%) of these were diagnosed with gastric cancer, of whom 14 were referred for with dyspepsia or alarm symptoms.

(Tatsuta 1989)(124)

The accuracy of gastrofiberscopic biopsy used in a Japanese hospital setting in the diagnosis of malignancies was evaluated by studying operative and postmortem findings. Gastrofiberscopic biopsy was performed during follow-up of all 1331 patients examined from 1968 until 1976, and the diagnosis was confirmed through histology. Biopsy materials and cytologic specimens were examined in two independent laboratories by different doctors without knowledge of the endoscopic diagnosis. Patients were referred to this hospital either because of a radiologic abnormality in the oesophagus, stomach or duodenum or because of persisting digestive complaints without radiological abnormalities and were found endoscopically to have some abnormality in the stomach.

There were 31 (3.7%) false-negative diagnoses of malignancy among 858 patients diagnosed as having benign lesions and three (0.6%) false-positive diagnoses among 473 patients diagnosed as having malignant tumours. The false-negative diagnoses were most frequent in cases of elevated types of early cancer, advanced cancer of type 4 and leiomyosarcoma, or in cases located in the posterior wall and in the antrum. The three benign lesions that were diagnosed as malignant by biopsy were all associated with active ulceration. From these findings the sensitivity and specificity of the gastrofiberscopic biopsy method for detection of gastric malignancies were calculated to be 93.8% and 99.6% respectively and the overall accuracy for all patients was 97.4%. Hence, a correct diagnosis was made in 1297 (97.4%) of 1331 patients with a satisfactory follow-up.

Related articles in health economics for endoscopy referral

Note: The following two articles consider cost-effectiveness of endoscopy in the investigation of dyspepsia, but not specifically in the investigation of suspected upper gastrointestinal cancer. Therefore, extrapolation of the findings to the costs incurred by urgent referral (as in suspected cancer) should be cautious.

(Delaney et al, 2000)(125)

The aim was to determine the cost effectiveness of initial endoscopy compared with usual management in patients with dyspepsia over age 50 years presenting to their primary care physician. 422 patients were recruited and randomly assigned to initial endoscopy or usual management. Primary outcomes were effect of treatment on dyspepsia symptoms and cost-effectiveness. Secondary outcomes were quality of life and patient satisfaction. Total costs were calculated from individual patient's use of resources with unit costs applied from national data.

In the 12 months following recruitment, 213 (84%) patients in the initial endoscopy group had an endoscopy compared with 75 (41%) of the controls. Initial endoscopy resulted in a significant improvement in symptom score ($P=0.03$), and quality of life pain dimension ($P=0.03$), and a 48% reduction in the use of proton pump inhibitors ($P=0.005$). The incremental cost-effectiveness ratio was £1728 (UK£) per patient symptom-free at 12 months. The incremental cost-effectiveness ratio was very sensitive to the cost of endoscopy, and could be reduced to £165 if the unit cost of this procedure fell from £246 to £100.

(Duggan,1999)(126)

A treatment algorithm for the management of upper gastrointestinal disease in general practice has been developed by an international group of general practitioners called the International Gastro Primary Care Group (IGPCG). The algorithm was evaluated to consider the overall cost per patient, showing

possible savings over current practice in the UK. Adjustments to the algorithm have been proposed, usually on the basis of variations in the place and timing of *Helicobacter pylori* testing and eradication, with or without endoscopy.

This paper evaluated the current cost of upper gastrointestinal disease in the UK, the base IGPCG algorithm and the five major alternative scenarios. The original IGPCG algorithm was the least costly option of all those considered, with additional *H. pylori* testing for all patients with suspected ulcer being the second least expensive option. Routine endoscopy for all patients or for all patients aged more than 45 years were the most expensive scenarios and would require a 16 or 13-fold increase, respectively, in the provision of endoscopy services in the UK. The use of routine endoscopy for all patients aged more than 45 years who were presenting with upper gastrointestinal symptoms for the first time was a mid-priced option, but would still require a five-fold increase in the provision of endoscopy services. The modelling process highlighted the fact that early stratification of patients into diagnostic and treatment groups, on the basis of history and symptom clusters is a less costly approach than that of early routine endoscopy or *H. pylori* testing. If *H. pylori* testing is to be used routinely, then the least costly approach is to select those patients who have symptoms that are more indicative of ulcer disease.

All the scenarios considered resulted in lower drug costs than current average UK drug costs per patient per year, and in fewer prescriptions and general practitioner surgery visits per patient. There are several ways in which the management of upper gastrointestinal disease in the UK could be improved with regard to costs and resource utilisation, some of which are presented here.

Before recommending routine endoscopy, however, it would be necessary to address the issue of provision of endoscopy services, since each scenario results in increased numbers of patients receiving endoscopy.

10.3 Delay and Diagnostic Difficulties

10.3.1 Key Clinical Question:

In people attending primary care services with upper gastrointestinal symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

10.3.2 Evidence Statements:

Presentation with 'alarm' symptoms such as weight loss and dysphagia was associated in some studies with reduced delay by patient and doctor (III).

Delay in diagnosis can be associated with having a normal endoscopy result in the past 12 months (III).

Clinical assessments by either general practitioner or specialist are poor predictors of gastric cancer, in comparison with endoscopy and biopsy (III).

Introduction

The fact that many studies examine factors related to the diagnosis of "early" gastric cancer (for example, cancers at an early stage) rather than early diagnosis has led to discussion amongst researchers about the benefits of prompt investigation. A large number of early cancers are clinically silent and therefore would not present for early investigation. Some of the studies exclusively examine the diagnosis of early gastric cancers, and hence observed survival may be influenced by *lead-time* biased. Most symptomatic cases appear to present as advanced disease, and there is at present no clear evidence that delay in diagnosis influences survival.

Secondary studies

No secondary papers were identified.

Primary studies

Oesophageal and gastric cancers

(Look et al, 2003)(127)

This Singapore-based study aimed to examine the symptoms of early gastric cancer, and to document in detail the time scale of symptoms and management delays. The authors retrospectively reviewed 44 patients with early gastric cancer treated at a surgical unit.

The median duration of symptoms at the time of diagnosis was 51 days, and 36.4% of the cases had symptoms for more than six months. Epigastric pain was the main presenting complaint in 63.3% of cases, gastrointestinal haemorrhage being the mode of presentation in 27.3% of cases.

The median patient delay, defined as the period from onset of symptoms to first medical consultation, was 30 days; it was more than six months and more than 1 year for 35.9% and 25.0% of the cases, respectively. The median doctor delay, defined as the period between initial medical consultation and definite diagnosis, was 21 days; in 11.4% of cases the diagnosis was delayed at this stage by four months or more.

Patient delay of more than six months was associated with patients being aged 50 or younger ($P = 0.04$), and with those in whom pain (rather than bleeding or other symptom) was the main complaint ($P = 0.05$). Doctor delay of more than four months was more likely when there was a previously negative gastroscopy or barium meal in the last 12 months ($P = 0.03$). The tumour size, location or histological subtype were not associated with the duration of patient and doctor delay.

(Irving et al, 2002)(128)

This UK study aimed to determine the impact of referral guidelines for upper gastrointestinal cancers on delays in the diagnosis in a specialised oesophago-gastric cancer unit.

All patients (N=90) underwent standard history taking by the clinical nurse specialist. The details of referral, investigation and treatment were all obtained, and the dates of a number of events (first symptoms, presentation to general practitioner, general practitioner referral, endoscopy, histological diagnosis, and treatment) were recorded for each patient.

46 (51%) patients were referred before the introduction of referral guidelines, and 44 (49%) were referred after the introduction; 65 patients were diagnosed with oesophageal cancer and 25 with gastric cancer. The overall median delay from the onset of symptoms to histological diagnosis throughout the study was 15.5 weeks. This was made up of patient delay in consulting a doctor (50%), delay in general practitioner referral (33%), and delay in diagnosis (17%).

The introduction of guidelines was associated with a significant decrease in referral time from first general practitioner consultation to endoscopy (median 7.25 to three weeks, $P = 0.005$). Only 11% (5/44) of patients waited more than four weeks from general practitioner referral to endoscopy compared to 35% (16/46) before the guidelines were implemented ($P = 0.008$). No significant reduction in total delay (median 25.0 vs. 17.5 weeks, $P = 0.11$) or change in the stage of disease at diagnosis was identified after the introduction of the guidelines.

(Haugstvedt et al, 1991)(129)

The purpose of this paper was to investigate factors influencing delay, and to evaluate the potential consequences of treatment delay on resectability rate and postoperative morbidity and mortality in patients with stomach cancer.

The study was a sub-study of a large prospective Norwegian multi-centre trial involving 51 surgical units. Out of a total of 1165 eligible patients, the authors had data on patient delay for 939 patients, on doctor delay for 964 patients, and data for total delay for 1000 patients.

The median total delay, defined as the interval between onset of symptoms and start of treatment, was 107 days. The patient delay, defined as the interval in days between onset of symptoms and the date the patient first consulted a physician, was 42 days. The doctor delay, defined as the time interval between the first consultation and start of treatment, was 37 days.

Univariate analyses.

Patient delay was related to weight loss (increasing patient delay with greater loss of weight, $P < 0.0001$) and hospital level (patients referred to university hospitals had a shorter patient delay than those admitted to local or county hospitals, $P=0.025$). Doctor delay was longer for women than for men ($P=0.013$), and more advanced stages of disease were associated with a short doctor delay ($P=0.004$). Patients admitted to a university hospital had a longer doctor delay than those referred to country or local hospitals ($P=0.008$). The magnitude of weight loss did not affect the doctor delay. Women had a statistically significant longer total delay than men ($P= 0.045$), and the proportion of patients with a long total delay increased with increasing loss of weight ($P < 0.0001$).

Multivariate analyses.

Patients admitted to a university hospital had a shorter patient delay than those admitted to a local hospital ($P=0.03$). The patient delay was longer in those with excess weight loss ($P < 0.0001$). Women experienced a longer doctor delay than men ($P=0.003$). Total delay was associated with the disease stage ($P=0.003$) and weight loss ($P < 0.0001$). The findings, revealed by univariate analyses, that women had a longer total delay than men and that the association between disease stage and total delay was of no significance, were not confirmed in the multivariate analyses.

(Suvakovic et al, 1997)(130)

The aims of this UK study were to compare patients diagnosed as having gastric cancer at open access gastroscopy with patients referred through other channels (mainly outpatient clinics) to see whether open access gastroscopy did pick up more early tumours, and to analyse the effect of this on whole district figures. The study also attempted to analyse whether late stage disease was more common in patients with a longer history of symptoms prior to referral.

The authors undertook a retrospective review of patients diagnosed as having gastric cancer during a five year period (1989 to 1994). Patients had been diagnosed either at open access gastroscopy or through conventional referral channels. The retrospective analysis included presenting symptoms, general practitioner diagnosis, hospital records, operative findings, and histological findings in both groups. The primary health care records of 81 of these patients dying from gastric cancer were analysed for previous dyspeptic symptoms (e.g. excluding those leading up to referral and diagnosis), investigations, and acid suppression drug therapy. The findings were compared with 200 age and sex matched controls dying from non-malignant causes during that period.

181 cases were identified (39 cases were diagnosed following open access gastroscopy, 142 were diagnosed following clinic referral or emergency admission). The two groups were similar in terms of age and sex distribution. 21.1% of patients diagnosed through open access gastroscopy had early gastric cancer or stage I disease compared with 10.6% of patients diagnosed through conventional channels. This difference failed to reach significance ($\chi^2=3.149$; $P=0.05-0.1$). The overall incidence of earlier gastric cancer remained low at 13%, with 87% of patients having greater than stage I disease.

Worrying symptoms (dysphagia, anaemia, or weight loss) were present in 85% (120 patients) of those referred to clinic compared with only 51%

(20 patients) of those referred for open access gastroscopy ($\chi^2=17.43$; $P<0.001$).

Gastric cancer, as specified on the referral form, was suspected in only six patients referred for open access gastroscopy despite the fact that 20 patients had one or more worrying symptoms. General practitioner diagnosis was less clear from referral letters to clinic, but from the details given gastric cancer was a possibility in at least 49 patients ($\chi^2=4.42$; $P<0.05$). No differences in delay in diagnosis emerged between open access gastroscopy and clinic based referrals although not all cancers were diagnosed at the first gastroscopy (21 were not).

The primary care records of 81 patients dying from gastric cancer indicated a lifetime prevalence of dyspepsia necessitating a consultation with the general practitioner of 73%. This compares with only 22% of the 200 age and sex matched controls dying of non-malignant disease from the same practices ($\chi^2=56.23$; $P<0.001$). 22 patients had no previous history of dyspepsia. Of 59 patients with a previous history of dyspepsia, 19 had not been investigated. The diagnosis was suspected in only 20 patients at the time of referral. Just under half the patients had been investigated at some time in the past (40 patients). The average time between the onset of current symptoms and diagnosis was 32 weeks, equally split between the time the patient took to consult the general practitioner and the time the general practitioner took to refer the patient to hospital.

82% of patients with a previous history of dyspepsia had received some form of symptomatic treatment prior to a gastroscopy that did not reveal malignancy even though all patients were eventually found to have gastric cancer within three years.

(Martin et al, 1997)(131)

The aim of this UK based study was to examine the time taken to diagnose oesophageal or gastric cancer, identify the source of delay, and assess its clinical importance.

The authors undertook a study of all new consecutive patients (N=115) presenting to a surgical unit with carcinoma of the oesophagus over 16 months, starting in January 1994. Patients were interviewed at first presentation to the department. Dates were recorded according to the patients' recollection and cross-referenced with the patients' notes. Details of the patient's first symptoms, the number of visits to the general practitioner before referral to hospital, and of any relevant drug treatment were recorded. The authors then followed the patients' subsequent clinical course.

The overall delay in weeks was recorded for each patient and divided into four periods: 1) the time from first symptoms to the patient first seeking medical advice; 2) the time from first seeking medical advice to referral for investigation; 3) the time from referral to first attendance at hospital for investigation; and, 4) the time from first attendance at hospital to establishment of a definitive histological diagnosis.

88 patients had cancer of the stomach and 27 cancer of the oesophagus. The median age of the patients when they first developed symptoms was 66 years (range 31 to 89 years). The first symptoms or signs were dyspepsia or indigestion in 19 (17%), dysphagia in 41 (24%), abdominal or chest pain in 48 (28%), nausea or vomiting in 27 (16%), heartburn in 7 (4%), weight loss in 20 (12%), early satiety in 27 (16%), and anaemia in 19 (17%). Some patients experienced more than one symptom.

The median delay from the onset of symptoms to a definitive histological diagnosis was 17.1 weeks for patients with gastric cancer and 17.3 weeks for patients with oesophageal cancer. Overall, delay in consulting a doctor accounted for 29% of the total, delay in referral 23%, delay in being seen at hospital 16%, and delay in establishing the diagnosis at the hospital 32%.

The authors found no significant relation between the nature of the first symptoms and delay in diagnosis. Similarly no relation was found between diagnostic delay and tumour location. Use of an open access endoscopy service reduced the delay in diagnosis. Overall the median delay for the 65 patients referred directly to the open access dyspepsia clinic was 14 weeks compared with 25 weeks for the 50 who were more conventionally referred ($P<0.001$).

For patients with stomach cancer there was no clear relation between tumour stage and delay in diagnosis. For oesophageal cancer however, the median delay was 6.7 weeks in patients with stage I and II disease but 20.9 weeks in those with stage III and IV disease ($P<0.02$).

(Hallisey et al, 1990)(132)

The aim of this prospective study was to see whether investigation of dyspeptic patients aged over 40 after their first consultation with the general practitioner would increase the proportions with early and operable gastric cancers.

General practitioners in ten general practices were asked to refer all patients over 40 making their first attendance during the study period with any degree of dyspepsia. Patients were interviewed and examined by a member of the hospital team within two weeks at a dyspepsia clinic, their symptoms recorded, and endoscopy then performed within one week.

2,659 patients were seen at the dyspepsia clinics and 2,585 attended for investigation. Malignancy was detected in 115 patients (4%), of whom 57 had gastric adenocarcinoma, one had gastric lymphoma, and 15 had carcinoma of the oesophagus. All other malignancies were diagnosed after further investigations and included colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1), liver (1), and gallbladder (1), amongst others.

15 (26%) were of early gastric cancer, according to the rules of the Japanese Research Society for Stomach Cancer. High-risk lesions were identified in

19% (493) of patients, with 10 gastric cancers being identified during longer than 14-month follow up, six of which were early gastric cancers. One early case of gastric cancer was thus detected for every 177 patients examined. Neither the general practitioner nor the hospital doctor were accurate in diagnosing gastric malignancy at any stage of clinical diagnosis. For advanced lesions, the diagnostic accuracy of the macroscopic assessment of the lesion at first endoscopy was high (28 of 41 such cancers being correctly identified), whereas early lesions were reliably identified in only three of the 15 correctly diagnosed.

(Grannell et al, 2001)(133)

The study investigated public awareness of the potentially sinister significance of dysphagia. The authors conducted a community survey amongst healthy pedestrians (N=164) in a busy city centre using a questionnaire to evaluate the subjects' impression of the significance of dysphagia, and compare it with their perception of the significance of breast lump. The information sought was urgency of medical advice, options for care and the probable cause of the symptoms.

75% stated that they would visit the doctor within one week of developing dysphagia (82% of males, 68% of females). Only 17% felt that cancer was a probable explanation for dysphagia compared to 80% who felt that a breast lump could be due to cancer ($P < 0.001$).

Effect of acid suppression therapy on delay and diagnosis

(Bramble et al, 2000)(134)

The aim of this study was to ascertain the effect of acid suppression therapy, defined as the use of any H₂ receptor antagonist or proton pump inhibitor during the six months prior to the initial (index) gastroscopy, on the diagnostic process and findings for patients with upper gastrointestinal cancer.

The authors undertook a consecutive case study survey of the primary care records of all patients (N=133) who had died of upper gastrointestinal cancer during 1995-97 in one health district in the UK. The records were used to ascertain factors leading to the initial hospital referral for investigation by gastroscopy, including the time elapsed to investigation, any history of prior acid suppression therapy and any subsequent association between the use of acid suppression therapy and the diagnostic process. In the analysis patients were categorised into two groups: those who had been prescribed acid suppression therapy prior to gastroscopy and those who had not. Results were compared, where applicable, using the χ^2 test with P values (5% significance, 95% confidence limits, one degree of freedom).

85 patients (64%) had gastric adenocarcinoma, 31 (23%) oesophageal adenocarcinoma, and 17 (13%) squamous cell oesophageal carcinoma. Failure to reach the diagnosis of cancer at the index gastroscopy was associated with prior acid suppression therapy. Only one of 54 patients on no treatment or antacids alone was erroneously diagnosed as suffering from benign disease, whereas 22 of 62 patients treated with acid suppression were diagnosed as suffering from benign disease ($\chi^2 = 18.48$, $P < 0.00002$).

Of the 62 patients with upper gastrointestinal adenocarcinoma who were on acid suppression therapy, twenty of 45 patients taking a proton pump inhibitor had a delayed diagnosis compared with two of 17 taking an H₂ receptor antagonist. Overall, 67 patients (including 62 with adenocarcinoma) from the total of 133 had been prescribed acid suppression therapy and in 22 patients (33%) the adenocarcinoma was not diagnosed at the index gastroscopy. The risk of not detecting the true nature of endoscopically observed lesions or of not seeing any pathology at all was greater in patients prescribed proton pump inhibitors (20/45, 44%) compared with H₂ receptor antagonists (2/17, 12%; $\chi^2 = 4.42$, $P < 0.05$).

(Wayman et al, 2000)(135)

This small UK study reported the healing effect of proton pump inhibitors on early gastric cancer. The authors described a case series of patients (N=7)

with ulcerated gastric cancers macroscopically indistinguishable as malignant gastric ulcers at initial (index) endoscopy, and who were inadvertently prescribed a short course of a proton pump inhibitor prior to a second confirmatory endoscopy.

Patients had dyspeptic symptoms and had been referred from primary care physicians for upper gastrointestinal endoscopy. Histological examination of the first endoscopic biopsy specimens of these patients had confirmed the presence of malignancy or dysplasia.

In all cases the patient became asymptomatic, the endoscopic signs seen at the first endoscopy had resolved, and the lesions could not be recognised even by an experienced endoscopist.

(Wayman et al, 1997)(136)

The aim of the study was to investigate the hypothesis that proton pump inhibitor use can delay the diagnosis of gastric cancer. Patients with gastric cancer completed a questionnaire. The time, in weeks, from onset of new gastrointestinal symptoms until first seeking medical advice was recorded, plus the time taken from first attending the general practitioner until obtaining the diagnosis. Prescription for either proton pump inhibitors or H2 antagonists prior to diagnosis was recorded.

The mean presentation delay for all patients was 16.3 weeks and was not influenced by treatment. The mean time to diagnosis in the control group (N=57) from the time of initial consultation was 4.1 weeks compared with 15.5 weeks for cases when proton pump inhibitors were prescribed before diagnosis (P=0.0002). There was no significant difference in delay if patients received H2 antagonists, the mean time to diagnosis being 5.7 weeks (P=0.12).

Pancreatic cancer

No studies on the delay or difficulties in diagnosing pancreatic cancer in primary care were identified.

11 Lower gastrointestinal cancer

Number		Grade
General recommendations		
1	A patient who presents with symptoms suggestive of colorectal or anal cancer should be referred to a team specialising in the management of lower gastrointestinal cancer, depending on local arrangements.	D
2	In patients with equivocal symptoms who are not unduly anxious, it is reasonable to use a period of 'treat, watch and wait' as a method of management.	D
3	In patients with unexplained symptoms related to the lower gastrointestinal tract, a digital rectal examination should always be carried out, provided this is acceptable to the patient.	C
Specific Recommendations		
4	In patients aged 40 years and older, reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for 6 weeks or more, an urgent referral should be made.	C
5	In patients aged 60 years and older, with rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms, an urgent referral should be made.	C

Number		Grade
6	In patients aged 60 years and older, with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding, an urgent referral should be made.	C
7	In patients presenting with a right lower abdominal mass consistent with involvement of the large bowel, an urgent referral should be made, irrespective of age.	C
8	In patients presenting with a palpable rectal mass (intraluminal and not pelvic), an urgent referral should be made, irrespective of age. (A pelvic mass outside the bowel would warrant an urgent referral to a urologist or gynaecologist.)	C
9	In men of any age with unexplained ¹³ iron deficiency anaemia and a haemoglobin of 11 g/100 ml or below, an urgent referral should be made.	C
10	In non-menstruating women with unexplained ⁶ iron deficiency anaemia and a haemoglobin of 10 g/100 ml or below, an urgent referral should be made.	C

¹³ 'Unexplained' in this context means a patient whose anaemia is considered on the basis of a history and examination in primary care not to be related to other sources of blood loss (for example, non-steroidal anti-inflammatory drug treatment or blood dyscrasia).

Risk Factors

- 11** In patients with ulcerative colitis or a history of ulcerative colitis, a plan for follow-up should be agreed with a specialist and offered to the patient as a normal procedure in an effort to detect colorectal cancer in this high-risk group. **C**
- 12** There is insufficient evidence to suggest that a positive family history of colorectal cancer can be used as a criterion to assist in the decision about referral of a symptomatic patient. **C**

Investigations

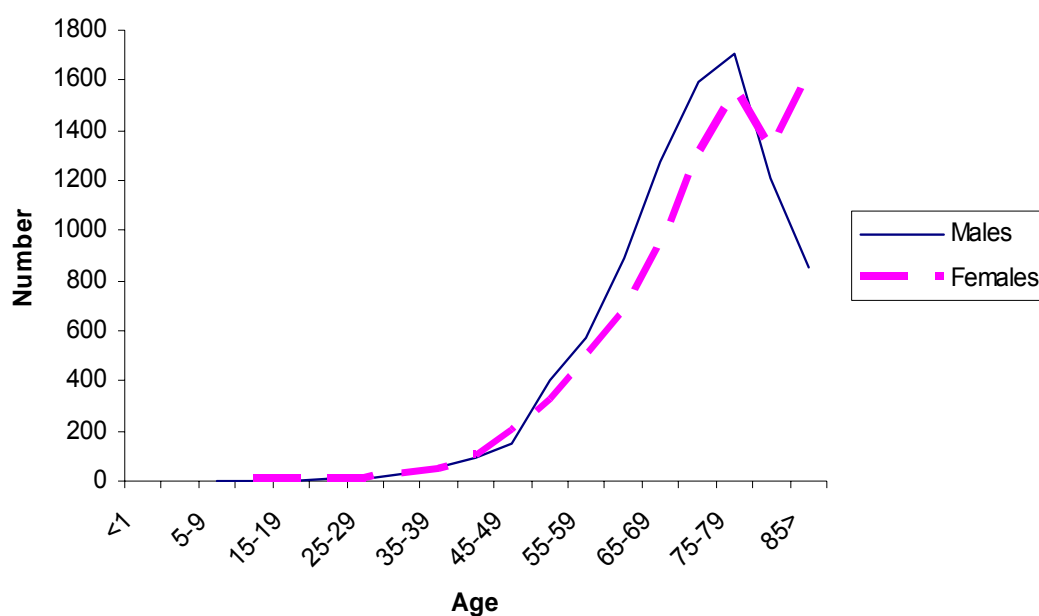
- 13** In patients with equivocal symptoms, a full blood count may help in identifying the possibility of colorectal cancer by demonstrating iron deficiency anaemia, which should then determine if a referral should be made and its urgency. **C (DS)**
- 14** In patients for whom the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be in accordance with local arrangements. **D**
- 15** In patients for whom the decision to refer has been made, no examinations or investigations other than those referred to earlier (abdominal and rectal examination, full blood count) are recommended as this may delay referral. **D**

Introduction

Incidence

Colorectal cancer (cancers of the colon and rectum) accounts for around 13% of all cancers in England and Wales. There were 15,535 new cases in 2001, Incidence is low in those aged 40 years and under, but increases with age in both males and females peaking in those aged 85 years and over.

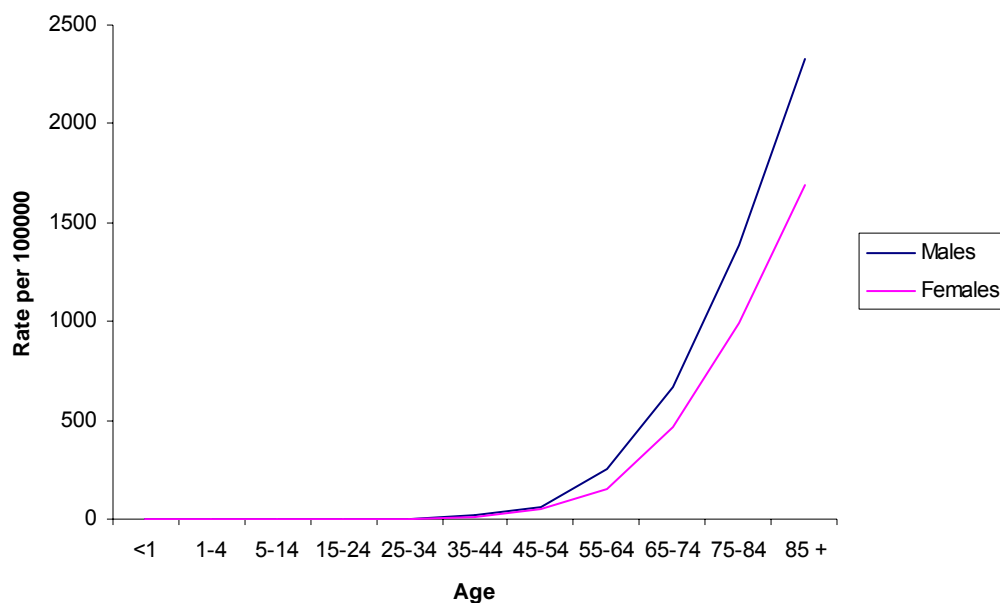
Figure 13 Newly diagnosed cases of malignant neoplasm of the colon in 2001 in England and Wales. (77)



Mortality

Mortality is low in those under 40 years in both sexes but increases steadily thereafter, peaking in those aged 85 years and over. The total mortality from colorectal cancer recorded in 2002 was 9504 of which 4,764 were in females and 4740 in males.

Figure 14 Mortality figures from cancer of the colon for 2002 in England and Wales. (78)



Audits of cancer referrals

The review of cancer referral audits(13) identified 71 audits that had evaluated referrals for lower gastrointestinal cancers. The proportion of two week wait

referrals that were found to be in accordance with the guidelines ranged from 53% to 91% (25 audits). The proportion of patients found to have cancer among the two week referrals ranged from 2% to 14% (30 audits). The percentage of two week referrals that were judged by the consultant to require a two week appointment ranged from 52% to 74% (six audits). The percentage of cancer patients that were referred under the two week wait system ranged from 0% to 46% (seven audits).

11.1 Symptoms and Signs

11.1.1 Key Clinical Questions:

How common is the disease in certain population groups, such as age, sex, ethnic groups etc?

Which symptoms, signs and other features raise a suspicion of cancer, and those that make cancer less likely as a diagnosis?

Does family history discriminate patients who should be referred?

What is the influence of co-morbidity on suspicion and referral?

11.1.2 Evidence Question:

In people attending primary care services with lower gastrointestinal, symptoms, which symptoms and signs and other features including family history when compared with the “gold standard” are predictive of a diagnosis of cancer; and which symptoms and signs are not?

11.1.3 Evidence Statements:

Colorectal cancer is very rare below the age of 40, and the incidence increases with increasing age thereafter. (III)

The incidence of colorectal cancer is higher in patients who have ulcerative colitis. The cumulative risk is 2.1% at 10 years, 8.5% at 20 years, and 17.8% at 30 years after diagnosis of ulcerative colitis. (III)

Among adults in the general population, rectal bleeding is relatively common (between 9% and 20% for bleeding in the past year in different studies). In most cases, cancer is not the cause (in two studies, the annual incidence was less than 1 per 1000 patients per year). (III)

Other lower gastrointestinal symptoms including change in bowel habit, abdominal pain, mucus, and tenesmus, are experienced relatively frequently

by people in the community. Symptoms other than rectal bleeding tend to be more common in people aged 70 or older. (III)

Individual symptoms are poor predictors of cancer. Blood mixed with or on the stool and change in bowel habit were the most consistent predictors of cancer. (III)

Use of a combination of symptoms/signs is more sensitive and specific than single symptoms or signs. The combination of age, bleeding mixed with or on stool, change in bowel habit and raised ESR tended to be most helpful in the studies reviewed. (III)

Iron deficiency anaemia can be the presenting sign of a colorectal cancer, although this diagnosis is not the most frequent cause of anaemia (in one study, cancer accounted for 7.7% of cases of iron deficiency anaemia). (III)

Rectal examinations undertaken in general practice do not detect all cases of rectal cancer, but a suggestive finding on rectal examination is a strong predictor of cancer. (III)

The primary care studies reviewed did not consider the significance of abdominal examination to detect abdominal masses. However, some patients with right sided cancers present with a mass. (III)

The significance of a family history in patients who present with symptoms potentially due to colorectal cancer is not clear. Family history of colorectal cancer or adenomas is associated with an increased risk of cancer among healthy people. (III)

There are differences between ethnic groups in the incidence of colorectal cancer, but the relevance of this finding to the assessment of symptomatic patients in England and Wales is not clear. (III)

In comparison with other cancers, we found a relatively large number of studies of the signs and symptoms of patients presenting to general practitioners who were diagnosed with colorectal cancer. However, most of the studies included only a small number of patients with cancer, and the ascertainment of all patients with lower gastrointestinal symptoms in the presenting population was often incomplete. Furthermore, different studies concentrated on different sets of symptoms and signs. Nevertheless, despite the patchy nature of the evidence, a reasonably consistent description of the symptoms and signs can be identified. With respect to some associated risk factors, several large case control studies have been undertaken, including systematic reviews of such studies.

An economic analysis of different referral options has been undertaken, and is included in Appendix C.

Guidelines

(SIGN, 2003)(137)

This clinical guideline made the following recommendations:

- Patients over the age of 50 years with any of the following symptoms over a period of six weeks should be urgently and appropriately investigated:
 - rectal bleeding with a change in bowel habit to looseness or increased frequency.
 - rectal bleeding without anal symptoms
 - palpable abdominal or rectal mass
 - intestinal obstruction. (Grade C)
- All patients with iron-deficiency anaemia (Hb<11g/dl in men or <10g/dl in post menopausal women) without overt cause should be thoroughly investigated for colorectal cancer. (Grade C)
- Patient groups at risk of colorectal cancer, especially those over 50 years of age, should be informed about significant symptoms and

encouraged to seek medical attention early should they develop such symptoms. (Grade D)

- General practitioners should perform a thorough abdominal and rectal examination on all patients with symptoms suspicious of colorectal cancer. (Grade D)
- When a patient presents with suspicious symptoms or signs, they should be urgently investigated and referred to a surgical unit with a declared interest in colorectal cancer. (Grade D).

Secondary studies

(Fijten et al, 1994)(138)

The review was undertaken to investigate the occurrence and significance of overt blood loss per rectum. The search covered 1984 to 1991, and used Medline and the Family Medicine Literature Index (FAMLI). Nine studies were found reporting the occurrence of rectal bleeding in the general population, all concerned with adult patients, although the precise age group varied between studies. Occurrence rates varied from 2% in the last two weeks to 20% in the last year. The positive predictive value of rectal bleeding in the general population was reported in four studies, varying from 3% to 8% for prediction of adenomas and 0% to 1% for carcinomas.

The review did not identify articles on the incidence of overt rectal blood loss among patients consulting in general practice. The authors therefore reviewed data from a national registration project in Dutch general practice that recorded diagnoses, or symptoms if a diagnosis was not reached. The incidence of rectal bleeding without a specified diagnosis was 0.4 per 1000 persons per year. The incidence of bleeding associated with the diagnosis of haemorrhoids was 6.8/1000 consulting persons per year, anal fissure or perianal abscess 3.2, diverticular disease 1.6, colitis 0.8, and cancer 0 per 1000 persons per year. No epidemiologic data on the diagnostic value of rectal bleeding in patients presenting in primary care were found.

The authors of the review estimated from the findings of a single Dutch study that around 0.8 per 1000 persons per year were referred with rectal bleeding by general practitioners to specialists. They went on to estimate the predictive values of rectal bleeding for colorectal cancer from the data they had identified of less than one in 1000 in the general population, two in 100 in general practice, and up to 36 in 100 referred patients. However, these estimates involved several assumptions and they cannot be taken as precise.

(Muris et al, 1993)(139)

A Medline search was undertaken for publications between 1982 and 1991 that investigated the diagnostic value of rectal examination in patients with abdominal pain and urinary complaints. Eight studies meeting the inclusion and quality criteria were identified, but none had been undertaken in a primary care setting. All the studies were carried out in populations selected by referral, adequate gold standards, based on histological evidence. The sensitivity of rectal examination for detecting rectal carcinoma in the two relevant studies were 50% and 24%; in one of these studies the specificity had been estimated as 95%, and likelihood ratio 4.8.

(Hamilton and Sharp, 2004)(140)

Medline and Embase were searched for studies of the common symptoms of colorectal cancer. The major single predictors of cancer were found to be rectal bleeding and change in bowel habit towards looser stools or increased stool frequency. One of these symptoms plus being over 60 was a strong predictor of cancer. Other symptoms in isolation had low predictive power. The review did not find evidence to support the delay of investigation of increased stool frequency for six weeks, and recommended that in the absence of a cause for the diarrhoea, referral should be immediate. Change in bowel habit was the symptom most associated with delay in diagnosis. The review also questioned whether constipation can be regarded as a low risk. It

was recommended that in people over aged 70, constipation should not be regarded as a low risk feature.

Primary studies

(Bellentani et al, 1990)(141)

This study was not included in Fijten et al's systematic review.(138) It involved 14 general practitioners in a local health care district in Italy, and the aim was to develop a scoring system for selecting patients at high risk of organic diseases of the colon. The system was intended to exclude organic disease and discriminate between irritable bowel syndrome and organic disease of the colon. Over one year, 254 (103 males and 151 females) consecutive patients who consulted one of the 14 general practitioners for chronic abdominal pain were asked to answer a guided questionnaire. An organic disease of the colon was found in the remaining 102 patients, with diverticulosis and polyps being most common (68.4%). 114 (44.9%) were referred to the gastroenterology service. In 152, (59.8%) the final diagnosis was irritable bowel syndrome, and ten patients had cancer.

Eleven items predicted the diagnosis of cancer in all ten cases. The items and the associated scoring scheme are shown below (note that the scoring system was designed to detect organic disease of the colon and not simply cancer). The mean score for patients with carcinoma was 240, range 123 – 315.

Table 27 Physical features and laboratory tests with associated scores(141)

Physical feature or laboratory test	Score
Visible distension of abdomen	-39
First degree relative with 'colitis'	-35
Feeling of distension	-34
Flatulence	-33
Irregular bowel movements	-26
ESR >17mm/hr	134
Blood in stool	112
Age >45	95
Leucocytosis > 10,000/cc	85
Fever 37-39°C	74
Neoplastic disease in first-degree relative	33

The mean score among patients with inflammatory bowel disease was 153 (range -26 to 332), polyps 136 (range - 60 to 374), and for diverticular disease 96 (range - 134 to 314). In predicting organic disease, the sensitivity of the scoring system was 82.4%, specificity 75.6%, and NPV 94.9%.

(Chapuis et al, 1985)(142)

A random sample of community living, well males aged over 50 years were invited to take part in a gastrointestinal survey. Each person was interviewed by a gastroenterologist and underwent flexible sigmoidoscopy. The examination was completed in 319 males (mean age 66 years). One subject had a colorectal carcinoma, and 12 had polyps of more than 10mm in diameter. Forty-four reported rectal bleeding, of whom six had small polyps, two melanosis coli, ten diverticular disease and 11 with haemorrhoids only. The patient with cancer did not report bleeding.

(Dodds et al, 1999)(143)

The sample consisted of patients with rectal bleeding referred to a specialist service in Portsmouth. Of 8438 patients, 252 had cancer. The positive

predictive value (PPV) for rectal bleeding plus change in bowel habit was 1:8, for change in bowel habit alone 1:17, rectal bleeding alone 1:18, and rectal bleeding plus perianal symptoms 1:148.

(Fijten et al, 1993)(144)

The aim of the study was to determine the incidence as well as the final diagnostic outcome of rectal bleeding presenting in general practice. 83 general practitioners identified 290 patients presenting to them because of rectal bleeding over a 19 month period (study A). However, because of wide variation in incidence between general practitioners, an additional study (B) was undertaken in which ten general practitioners took additional steps to maximise the catchment rate and ensure that younger patients were not excluded.

In study A, the incidence was 2.2/1000 persons per year (range between practices 1-8). In study B, the mean consultation incidence rate was seven per 1000 people per year. A follow up period of at least one year was applied to establish the final diagnosis. Colorectal cancer was found in 3% of patients with rectal bleeding in study A, and none in study B. The figure of 3% almost certainly is an overestimation of the proportion of people who present to general practitioners with rectal bleeding who will turn out to have colorectal cancer. In about 90% of patients rectal bleeding was related to minor ailments or self-limiting disorders.

(Fijten et al, 1995)(145)

This study was a further analysis of Fijten et al(144). The objective of the study was to determine the diagnostic value of combinations of signs, symptoms and simple laboratory test results for colorectal cancer in patients presenting with rectal bleeding to the general practitioner (83 general practitioners in the Netherlands). Age, change in bowel habit and blood mixed with or on stool independently discriminated between patients with low and high probability of colorectal cancer (see *Table 28*). The number of patients

with colorectal cancer was small (N=9), but Fijten et al reported from their analysis that colorectal was highly unlikely (1% or less) in patients who did not see blood on or mixed with stool, in patients who did see blood on the toilet paper, and in patients without change in bowel habit, with pain at night, with a family history of abdominal disease or with a previous history of rectal bleeding.

Nineteen patients recorded that a first degree relative had an abdominal disease and colorectal cancer (or polyps). However, the study questionnaire did not distinguish between a family history of colorectal neoplasm and other abdominal disease. The authors concluded that the combination of age, change in bowel habit and blood seen mixed with or on stool can serve as a useful diagnostic tool for the prediction of colorectal carcinoma (and overtly bleeding polyps).

Table 28 Diagnostic values of signs and symptoms for colorectal cancer in patients with rectal bleeding (P <0.1)(145)

Signs/symptoms	N	Sensitivity %	Specificity %	PV+ %	100- PV- %	Odds ratio	P
Blood seen							
mixed with stool only	14	40	95	14	1.3	5.9	*
on stool or mixed with only others	54	80	79	7	0.5	3.4	*
combinations unknown	122	20	53	1	3	0.1	**
Abdominal pain	54	44	81	7	2	3.4	*
Change in bowel habit	135	29	48	2	4	0.3	*
Pain at night	78	88	72	9	0.5	18.4	***
Decreased appetite	50	0	76	0	3	0	**
Nausea	42	11	84	2	4	0.7	**
Weight loss	68	11	74	2	4	0.4	***
Family history of abdominal disease	42	44	85	10	2	4.6	**
Previous history of rectal bleeding	83	0	62	0	6	0	*
Pale conjunctivae	96	0	63	0	5	0	**
Perianal eczema	6	13	98	17	3	7	*
Rectal palpation (n=208)	17	33	95	18	2	8.6	***
haemorrhoid	20	22	93	10	3	3.8	*
tumour	1	11	89	100	3	undefined	***

abnormal	2	11	99.6	50	3	31.8	***
prostate							
Proctoscopy	30	0	30	0	13	0.2	**
(N=45)							
abnormal							

N=269

Prevalence=3.3%

*0.1 > P ≥ 0.05

**0.05 > P ≥ 0.01

***P < 0.01

(Goulston et al, 1986)(146)

This article reports findings from a study also published in Mant et al(147). In this study undertaken in Canberra, Australia, 145 consecutive patients aged 40 years and over presenting to a general practitioner with rectal bleeding of less than six months were referred to a specialist for full investigation. Fifteen patients had colorectal cancers (one patient had two cancers). The general practitioners' assessment of the likelihood of cancer as the source of bleeding based on description of symptoms and clinical examination was inaccurate (PPV 20.7%). If they had followed their normal practice on referral, four of 16 cancers would have been overlooked.

(Helfand et al, 1997)(148)

Patients were recruited from those attending walk-in and general medical clinics in Palo Alto, USA. Of the 297 with visible rectal bleeding, 201 underwent double-contrast barium enema, rigid sigmoidoscopy and follow up for up to one year. Ten years later, the diagnosis was verified by review of the medical records. Thirteen (6.5%) of the 201 patients had colon cancer. Two clinical predictors had statistically significant association with cancer – age and duration of bleeding less than two months. Among the 143 patients older than 50 years, the risk of cancer was higher when bleeding had been present for less than two months (18% vs. 6%, P=0.03), but six of the cancers

occurred among individuals who had experienced bleeding longer than two months.

(Mansson et al, 1999)(149)

In this retrospective study, the medical records of all subjects from one community (Kungsbacka, in Sweden, with about 46 500 inhabitants) with colorectal, pulmonary, breast or prostate cancer, reported to the Swedish Cancer Registry were reviewed to obtain information about initial symptoms, diagnostic procedures, outcome of diagnostic procedures, level of care, and doctor delay.

There were 42 patients with colorectal cancer, and the presenting symptoms are shown below:

Table 29 Presenting symptoms of patients with diagnosis of colorectal cancer(149)

	N	%
Change in bowel habit	18	43
Tiredness, dizziness etc	17	40
Blood with stool	12	29
Pain	9	21
Gas formation	4	10
Other	5	12

A palpable lesion of the rectum or the observation of a tumour on proctoscopy was a diagnostic sign in 21% of patients with colorectal cancer. However, physical symptoms were not always specified in the records. Nine patients were referred to hospital as a result of the first consultation.

Doctor delay was defined as the interval between first visit at which the symptoms and signs could be attributable to cancer and the time when the diagnosis was clinically confirmed as documented in the records. Median doctor delay for colorectal cancer was four weeks, for breast cancer two weeks, for pulmonary cancer five weeks and for prostate cancer eight weeks.

Twelve cancers were located in the rectum, twelve in the sigmoid colon, seven in the transverse colon, six in the ascending colon, and five in the caecum. Two rectal cancers were diagnosed by means of palpation and two by means of proctoscopy. The remaining rectal tumours were not found at the patient's initial visit in spite of symptoms which could have been related to the tumour.

(Mant et al, 1989)(147)(see also Goulston et al, 1986)(146)

Fifty-five general practitioners in Australia referred all patients aged 40 years and over who presented to them with rectal bleeding. A detailed history was taken followed by investigations that included colonoscopy. 145 patients were eventually fully investigated, 15 (10.3%) being found to have colorectal cancers. Few symptoms and patient characteristics were related to final diagnosis. Patients reporting blood mixed with the stool had a 21% probability of colorectal cancer, a 35% probability of cancer or polyp, and a 44% probability of bleeding coming from a colorectal rather than anal source.

(Metcalf et al, 1996)(150)

This was a prospective study of consecutive patients aged over 40 years who presented with rectal bleeding to 17 general practices in Newcastle upon Tyne. In patients in whom rectal bleeding was the primary reason for the consultation, general practitioners completed a detailed questionnaire to record the presence or absence and duration and features of bleeding, diarrhoea, mucus, change in bowel habit, abdominal pain, weight loss, meleana, and family history of bowel disease. Patients were then referred for colonoscopy. 99 patients were included in the analysis.

Eight (8.1%) patients were found to have carcinoma, 25 (25.3%) polyps, 11 (11.1%) inflammatory bowel disease, 16 (16.2%) diverticular disease, 28 (28.3%) haemorrhoids, and 11 (11.1%) no abnormality. The following symptoms were significantly more likely in cases with serious disease

(carcinoma, polyps and inflammatory bowel disease): blood mixed with stool ($P<0.001$), change in bowel habit ($P<0.01$), abdominal pain ($P<0.05$).

However, the sensitivity and specificity of these symptoms were low (sensitivity 25-68%, specificity 25-53%). The high proportion of patients in this study who were found to have serious disease suggests that participating general practitioners failed to enrol all patients presenting with rectal bleeding to the study.

(Muris et al, 1993)(151)

This was a prospective, descriptive study of 578 consecutive patients with non-acute abdominal pain presenting to 11 general practices and followed for 15 months. After 15 months, three of the authors examined the medical records of all patients to collect details of outcomes and further treatment.

In the younger age groups relatively more females consulted their general practitioner with abdominal complaints. Eighty percent of the 578 patients enrolled in the study visited their general practitioner three times or less for abdominal complaints during the follow up period. The duration of pain before the patient presented for the first time varied from some days to more than one year. Eighty-three percent were managed entirely in the practice and 64% received a prescription. Only 20% were investigated in any way by the general practitioner.

No firm diagnosis was made in 47% of patients with symptoms lasting seven days or less, and in 43% of those with symptoms lasting longer than seven days. Irritable bowel syndrome accounted for 11.9% of cases, and no other condition accounted for more than 9%. Only three (0.5%) cases of malignant colorectal diseases were detected. Ninety percent of patients were not having active treatment after 15 months.

(Muris et al, 1995)(152)

This was a one-year prospective study in 80 general practices in the Netherlands. General practitioners notified patients presenting with non-acute abdominal complaints. 933 patients aged 18-75 were included in the study. Information was collected about 23 symptoms and four investigations (white blood cell count, ESR, haemoglobin, faecal occult blood). The symptoms included blood in stool, pain, change in bowel habit, weight loss, vomiting, mucus per rectum and significant past history. Five items were found to predict neoplasms: male sex (OR 2.4), greater age (OR 1.1), no specific character to pain (OR 5.7), weight loss (OR 4.4) and ESR greater than 20 mm/hour (OR 3.0).

(Norrelund and Norrelund, 1996)(153)

In the first stage of this study, 96 general practitioners in Denmark reported information about 208 patients who consulted with rectal bleeding. In the second stage, 112 general practitioners reported information about 209 patients. In the first study, 32 patients had cancer, in the second 13 had cancer. When the findings of both studies were combined, only age (OR 40-69 1.0, 70-79 5.4, 80+ 4.1) and change in bowel habit were associated with cancer (change in habit OR 1.0, no change 0.44). Caution is required in extrapolating these findings to all patients in general practice with rectal bleeding since it is likely that the study general practitioners reported only patients with symptoms they regarded as significant.

(Curless et al, 1994)(154)

The symptoms of 273 patients with colorectal cancer were compared to symptoms reported by a matched sample of 273 people in the community. The sample was divided into two groups: 'young' (under 70 years) and 'old' (70 or above). Among controls, the old group compared with the young more often reported abdominal pain ($P < 0.05$), mucous discharge ($P < 0.01$), faecal incontinence ($P < 0.05$), and change in flatus production ($P < 0.05$). There were no significant differences in regularity and frequency of bowel habit by age

group. The old group tended to report the following symptoms more often: tenesmus, change in bowel habit and subjective weight loss, although the differences did not reach statistical significance. Rectal bleeding was the only symptom reported less often by old controls although this did not reach statistical significance.

Table 30 shows the odds of colorectal cancer associated with particular symptoms in the young and old samples. Since the control old patients experienced more symptoms, the odds ratios are lower in the old group. Aspects of this study are also reported in Curless et al.(155)

Table 30 Comparison of the reported frequency of gastrointestinal symptoms within the last year by colorectal cancer cases v community controls by age group ('young' <70 years; 'old' 70 years or greater). Expressed as odds ratio 7AB(154)

	'Young'			'Old'		
	Cases (N=150)	Controls (N=148)	OR (CI)	Cases (N=123)	Controls (N=125)	OR (CI)
Change in bowel habit	111	0	418.4* (169.2-1034.7)	83	4	64.4 (30.0-138.4)
Abdominal pain	81	6	27.9 (14.0-55.2)	59	14	7.3 (4.0-13.5)
Faecal incontinence	27	0	32.3* (8.5-121.9)	23	8	3.4 (1.5-7.6)
Tenesmus	68	7	16.7 (8.4-33.1)	30	14	2.6 (1.3-5.2)
Mucus per rectum	53	3	26.4 (11.0-63.2)	27	13	2.5 (1.2-5.0)
Rectal bleeding	93	21	9.9 (5.8-16.7)	49	13	5.8 (3.0-11.0)
Change in flatus	70	12	9.9 (5.4-18.1)	39	21	2.4 (1.3-4.3)
Anorexia	52	5	15.2 (7.0-33.0)	66	14	9.2 (5.0-16.8)
Weight loss	70	8	15.3 (7.9-29.6)	59	14	7.4 (4.0-13.7)
Bloating	68	17	6.4 3.6 – 11.2	38	28	1.5 0.9 – 2.7
Malaise	57	25	3.0 (1.8-5.1)	60	40	2.0 (1.2-3.4)

(*Estimated OR when cell = 0)

(Stellon and Kenwright, 1997)(156)

This study was undertaken in one small general practice over a period of five years. All patient aged over 50 years found to have iron deficiency anaemia were included. In addition to history and examination, patients underwent faecal occult blood testing, upper Gastro Intestinal endoscopy, flexible sigmoidoscopy and double-contrast barium enema. Patients were followed up for five years. Of the 26 patients investigated, one was found to have a

tubulovillous adenoma of the rectosigmoid junction and one had caecal carcinoma.

(Trilling et al, 1991)(157)

This study was undertaken to determine how frequently patients in primary care who present with haemorrhoids also have other significant colorectal disease. Information was obtained from the clinical records of 173 patients of a family practice centre in the USA who had consulted with haemorrhoids. Only one patient had also been diagnosed as having colorectal cancer (detected by the family physician before referral). During the same period, eight colorectal cancers were detected in patients without haemorrhoidal disease. The authors concluded that haemorrhoidal disease is rarely associated with other anorectal disease. It should be noted, however, that in this US population, most patients had undergone examinations (sigmoidoscopy, proctoscopy) leading to a definite positive diagnosis of haemorrhoids.

Risk Factors

Several potential risk factors for colorectal cancer have been identified, but there is no evidence to suggest they are helpful in identifying patients who may need referral.

Secondary studies

Ulcerative colitis

(Eaden et al, 2000)(158)

This study was a meta-analysis of the risk of colorectal cancer in patients with ulcerative colitis, and involved a literature search using Medline to identify 194 studies of which 116 met the inclusion criteria. 54,478 patients in total were included in the identified studies, and these had a total of 1698 colorectal cancers. 9846 patients had total colitis, among whom 700 cancers were found.

The overall prevalence of colorectal cancers in any ulcerative colitis patient, based on 116 studies, was estimated to be 3.7% (95% CI 3.2-4.2%). For patients with total colitis (pancolitis) the overall prevalence of cancer was 5.4% (95% CI 4.4-6.5%). Colitis duration was reported in 41 of the 116 studies. From these, the overall incidence rate was 3/1000 person years duration (95% CI 2/1000 to 4/1000). The corresponding annual incidence rate in the general population given by the Office of National Statistics is 0.6 per 1000 population. 19 studies reported incidence stratified into ten year periods. For the first ten years, the incidence rate was 2/1000 person years duration, (95% CI 1/1000 – 2/1000), for the second decade 7/1000 person years duration (95% CI 4/1000 – 12/1000), and in the third decade 12/1000 person years duration (95% CI 7/1000 – 19/1000). These incidence rates correspond to cumulative probabilities of 2% by 10 years, 8% by 20 years, and 18% by 30 years. Six of the 19 studies reported data for patients with total colitis. Decade specific incidence rates corresponded to a cumulative risk of 2.1% (95% CI

1.0-3.2%) at 10 years, 8.5% (95% CI 3.8-13.3%) at 20 years, and 17.8% (95% CI 8.3-27.4%) at 30 years.

The overall incidence rate for any child was 6/1000 patient year duration (95% CI 3/1000 to 13/1000).

A regression analysis was conducted using data from 21 studies to determine whether age at onset of ulcerative colitis (over 20 years) affected the log incidence rate of colorectal cancers. Overall, a negative trend emerged indicating that a younger age at onset in adults was associated with a slightly increased risk of developing cancer, but this was not statistically significant ($z = -1.61$, $P = 0.11$). A further meta regression analysis of 11 studies that reported the age at onset of ulcerative colitis together with the risk at ten yearly intervals also showed that age at onset in adults appeared to have no statistically significant bearing on cancer risk.

This was a good quality review, although some reservations about the primary studies should be noted. Many of the studies in the meta analysis were population based and their inclusion did not rely on contact with gastroenterologists. However, there was a greater likelihood that cancers were detected among those having active follow up as a majority of cases came from surveillance programmes or tertiary referral centres, and very few studies included in the meta analysis used national cancer registry data.

Table 31 Summary of estimated cancer risks(158)

			Unstratified Data				Stratified Data			
			All patients	Total	UC	Children	All patients	Total	UC	
			(41 studies)	(26 studies)		(5 studies)	(19 studies)	(6 studies)		
Cancer incidence rate			3/1000	4/1000		6/1000	2/1000	2/1000		
at 10 years/1000 pyd			(2 to 4/1000)	(3 to 6/1000)		(3 to 13/1000)	(1 to 2/1000)	(1 to 4/1000)		
Cumulative cancer risk (%)			3	4.4		5.5	1.6	2.1		
at 10 years			(2.2-3.8)	(2.0-6.8)		(2.5-12.3)	(1.2-2)	(1.0-3.2)		
Cancer incidence rate			3/1000	4/1000		6/1000	7/1000	7/1000		
at 20 years/1000 pyd			(2 to 4/1000)	(3 to 6/1000)		(3 to 13/1000)	(4 to 12/1000)	(3 to 14/1000)		
Cumulative cancer risk (%)			5.9	8.6		10.8	8.3	8.5		
at 20 years			(4.3-7.4)	(4.0-13.3)		(4.8-23.1)	(4.8-11.7)	(3.8-13.3)		
Cancer incidence rate			3/1000	4/1000		6/1000	12/1000	11/1000		
at 30 years/1000 pyd			(2 to 4/1000)	(3 to 6/1000)		(3 to 13/1000)	(7 to 19/1000)	(4 to 28/1000)		
Cumulative cancer risk (%)			8.7	12.7		5.7	18.4	17.8		
at 30 years			(6.4-10.9)	(6.0-19.3)		(7.2-32.6)	(15.3-21.5)	(8.3-27.4)		

Values are mean (95% confidence intervals)

Pyd, person years duration.

Family history – hereditary nonpolyposis colon cancer (HNPCC)

(Burke et al, 1997)(159)

Studies of cancer risk, surveillance and risk reduction in individuals genetically susceptible to colon cancer were sought through a search of MEDLINE 1990-1995. Hereditary nonpolyposis colon cancer criteria include (1) at least three relatives with histologically verified colorectal cancer; (2) at least two successive generations should be affected; (3) in one of the relatives, colorectal cancer should have been diagnosed before age 50 years. The condition is genetically heterogeneous, and four genes are estimated to account for 73% of the families with the condition.

The risk of colorectal cancer in people with confirmed HNPCC was estimated to be 68% to 75% by age 65, although the average age at diagnosis is 45 years. The risk of a new primary after limited resection for a first cancer was also high at 30% after ten years. Endometrial cancer was the second most common cancer seen in HNPCC.

Skin tags

(Radack and Park, 1993)(160)

A systematic review was undertaken of articles identified by search of Medline for all relevant studies from 1983 until January 1992 to assess the clinical utility of skin tags (skin appendages occurring on almost any part of the body, especially the axilla, neck, or groin) as a biomarker for colonic polyps. The article aimed to identify subjects at increased risk of adenomatous colonic polyps (a predisposing factor in colon cancer) that could lead to earlier recognition of either polyps or colon cancer. Of the 15 reports, ten with sufficient data were eligible for analysis. Only four of the ten studies reported a statistically significant association between skin tags and colonic polyps; the remaining studies reported outcomes indicating no association.

Significant statistical heterogeneity across studies indicated sharp differences in the direction and magnitude of the odds ratios for the association between skin tags and colonic polyps (Chi square test of homogeneity = 37.42, nine degrees of freedom; $P < 0.005$). The marked disparity prevented meaningful pooling of the individual data.

Limitations potentially responsible for the varying outcomes included lack of blinded ascertainment of clinical information, noncomparability of subjects, differing diagnostic investigations of the colon, and uncontrolled confounding. All but one study were performed in a tertiary care setting, seriously limiting the relevance of the results to the “average” subject seen in primary care settings. There was variability in study populations, methods of diagnostic evaluation and the control of possible confounders (for example age and sex) that could affect the potential relationship. For these reasons, the review did not provide a reliable estimate of any association between skin tags and polyps.

11.2 Investigations

11.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

11.2.2 Evidence Question:

In people attending primary care services with lower Gastro Intestinal symptoms, which investigations when compared with the “gold standard” are predictive of a diagnosis of cancer, and which are not?

11.2.3 Evidence Statements:

Biochemical markers, including CEA, are not sufficiently sensitive or specific to be used as a diagnostic aid (III)

The principal investigations are double contrast barium enema, colonoscopy, and flexible sigmoidoscopy (III).

Competence in colonoscopy and flexible sigmoidoscopy improves with experience (III).

In symptomatic patients, the sensitivities, specificities, and positive predictive values of faecal occult blood tests are too low to make these tests helpful (III).

Laboratory tests (haemoglobin, ESR, white blood cell count) have low sensitivity in detecting colorectal cancer (III).

Symptom score questionnaires have been investigated for use among referred patients, but insufficient evidence is available about their use in primary care (III).

Two relevant secondary studies and two primary studies were identified. No study was entirely satisfactory for our needs. Several related to investigations in referred patients, and extrapolation to primary care attenders requires caution. No primary care study included adequate numbers of patients with and without rectal cancer, a full range of presenting symptoms (i.e. inclusion of patients with symptoms other than rectal bleeding, or an adequate 'gold standard' (colonoscopy)).

Secondary studies

(Duffy et al, 2003)(161)

These guidelines of the European Group on Tumour Markers (EGTM) were an extensive review of relevant evidence. The most widely used biochemical marker was carcinoembryonic antigen (CEA), a high molecular weight glycoprotein that has been implicated in cancer metastasis. CEA was not sufficiently sensitive (30-40%) or specific (87%) to be used as a diagnostic aid. For example, it can be elevated in the absence of malignancy. CA 19-9 is the most widely investigated gastrointestinal tumour marker, but is less sensitive than CEA in the detection of colorectal cancer. Other markers including CA 242, tissue polypeptide antigen (TPA), tissue polypeptide-specific antigen (TPS), and TIMP-1 were under investigation, but there was insufficient evidence to indicate whether they have a role either singly or in combination in the early detection of colorectal cancer. Preliminary investigation of cell and tissue markers such as cellular oncogenes and tumour suppressor genes suggested that these may be sensitive and specific markers for use in early detection, but confirmation is required in further research. However, these markers were unlikely to be specific for colorectal cancer, but would probably occur in other cancers.

(NHS Centre for Reviews and Dissemination, 1997)(162)

This review was undertaken to support the NHS Service Guidance on Colorectal Cancer, and was focused on management, although it included

some consideration of diagnostic methods. The methods discussed did not include blood tests for anaemia or raised erythrocyte sedimentation rate (ESR). The review concluded that the large bowel may be completely examined by one of two methods: colonoscopy, or sigmoidoscopy plus double-contrast barium enema. These methods have similar yields and costs, although their equivalence depends on operator competence. Colonoscopy can produce reliable results if the tip of the colonoscope reaches the caecum or proximal end of the colon ('completion'). Completion rates of up to 85% have been reported in studies, although rates achieved in routine practice may be lower. Colonoscopy technique improves with practice; in one study of training, physicians were normally able to achieve a completion rate of 80% after 50 colonoscopies, rising to 95% after 200.

Competence in flexible sigmoidoscopy can be achieved after 24-30 examinations.

Primary studies

(Steine et al, 1994)(163)

Information about the investigations undertaken prior to referral for barium enema was obtained from patients and referral letters (83% from general practitioners). The study does not contain information about the utility of tests, but does show that 76% of patients had a haemoglobin test, although a rectal examination was performed in only 45%.

(Muris et al, 1995)(152)

This was a prospective observational study in 80 general practices in the Netherlands. 933 patients presented to their general practitioner with new non-acute abdominal complaints lasting two or more weeks. A structured history was obtained, an examination performed, and the following laboratory tests undertaken: haemoglobin, white blood cell count, ESR, faecal occult blood (three times, with peroxidase-free diet). 24 (2.6%) of the sample of 933

were diagnosed to have cancer during the following year. Multiple logistic regression was used to estimate the odds of cancer given certain symptoms, signs and investigation results. Only an ESR greater than 20mm/hour was associated with a diagnosis of cancer (odds ratio 3.0 [95% CI 1.1-8.2]). The paper did not report sufficient data to enable the sensitivity or specificity of a raised ESR to be calculated.

(Pierzchajlo et al, 1997)(164)

This study reports a case series of 751 colonoscopies performed by a family physician in the US. Completion was achieved in 91.5%. Only three cancers were identified. No patient suffered a complication resulting in death or necessitating surgery.

(Meyer et al 2000)(165)

In this study, a random 5% sample of Medicare claims relating to gastrointestinal endoscopy were investigated to compare patients examined by generalists and specialists. Only 7.7% of colonoscopies were performed by generalists, although they performed higher proportions of rigid sigmoidoscopies (35.2%) and flexible sigmoidoscopies (42.7%). Specialists were more likely to perform the procedure to investigate cancer.

(Rodney et al 1987)(166)

An educational course on flexible sigmoidoscopy was delivered to 114 physicians. After the course, the physicians reported undertaking more examinations. The study was limited to a simple survey of course participants, and gives no information about the sensitivity or specificity of flexible sigmoidoscopy by family physicians for the detection of lower colorectal cancer.

(Fijten et al, 1995)(145)

This study was a further analysis of Fijten et al, (1993)(144). The objective of the study was to determine the diagnostic value of combinations of signs, symptoms and simple laboratory test results for colorectal cancer in patients presenting with rectal bleeding to the general practitioner (83 general practitioners in the Netherlands). The tests were haemoglobin, erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and faecal occult blood. The sensitivity, specificity and positive predictive value (PPV) of these tests are shown in *Table 32*. In a multiple logistic regression that included symptoms and signs, none of the tests were significant independent predictors of colorectal cancer in patients with rectal bleeding.

Table 32 Diagnostic values of laboratory test results for colorectal cancer in patients with rectal bleeding (Fijten et al 1995(145))

Laboratory test results	N	Sensitivity %	Specificity %	PV % ⁺	Odds ratio	P
Haemoglobin						
low (♀<7.5mmol/l, ♂<8.5 mmol/l)	14	33	95	14	8.8	***
ESR						
high (♀>28mm/h, ♂>12mm/h)	23	40	91	9	6.3	**
high (>30mm/h)	12	40	96	17	14	***
White blood cell count (n=219)						
high (> 10 ⁹ /l)	25	75	90	12	26.3	***
Haemoccult ≥ 1 positive out of 3	41	50	82	5	4.6	*

n = 225; Prevalence = 2.2%; *0.1 > P ≥ 0.05; **0.05 > P ≥ 0.01; ***P < 0.01.

(Sorensen et al, 1992)(167)

The number of proctoscopies performed by general practitioners and the Duke's stage at diagnosis of rectal cancer were compared using information on a central register of general practitioner activities and a cancer register. No association was identified between numbers of proctoscopies performed per year and the stage of cancer. The study did not collect patient-level data about proctoscopy examinations.

(Church, 1991)(168)

This study included 269 patients presenting to a colorectal surgery department. Bleeding was categorised into outlet (bright red blood during or after defaecation, on the toilet paper or in the bowl, with no family history of colorectal neoplasia and no change in bowel habit), suspicious (dark red blood and/or blood mixed with stool, any bleeding with a family history or past history of colorectal neoplasia, bleeding in association with a change in bowel habit or the passage of mucus), haemorrhage (large bleed needing urgent admission and transfusion of one or more units of blood), and occult (rectal bleeding and anaemia, or positive stool occult blood test). All patients underwent colonoscopy. The findings of colonoscopy were compared to the results of barium enema in a group of patients who had undergone radiology before referral. With colonoscopy as the gold-standard, sensitivity of barium enema was 75%, specificity 43%, PPV 71% and NPV 47%.

(Tate et al, 1990)(169)

Three different faecal occult blood tests (Haemoccult, Fecatwin, E-Z Detect) were compared in a sample of patients referred for investigation by double-contrast barium enema (used as the gold standard). The sensitivities of the tests were 80.0%, 93.3% and 57.1% respectively; the specificities were 88.8%, 71.6%, and 88.9%; the PPVs were 32.7%, 13.3% and 19.0%. The authors concluded that a negative Haemoccult test should not influence the management of symptomatic patients because treatable disease would be missed. Fecatwin is more sensitive, but the number of false positives was high (a positive result in a symptomatic patient would have just over a 1:8 chance of being due to colorectal cancer).

11.3 Delay and Diagnostic Difficulties

11.3.1 Key Clinical Questions:

In people attending primary care services with lower gastrointestinal symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a woman/man who presents with lower gastrointestinal symptoms/signs may or may not need urgent referral with suspected cancer?

11.3.2 Evidence Questions:

In people attending primary care services with lower gastrointestinal symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a woman/man who presents with lower gastrointestinal symptoms/signs may or may not need urgent referral with suspected cancer?

11.3.3 Evidence Statements:

Delay

There are no associations between personal characteristics such as age and social class and patient delay. Personal advice to go to the doctor is important in reducing delay. (III)

Delay in consulting for rectal bleeding is unrelated to age, sex, ethnic origin, competence in English, length of schooling, social status, availability of social

support, measured psychological traits, and to the belief that the cause might be cancer. (III)

Overall delay does not differ significantly between male and female patients, although men are more likely to have patient-related delay. (III)

Patient delay can be the result of not knowing the importance of bowel symptoms. (III)

The most common reason for delay or failure to consult is thinking that the bleeding is not serious, or is caused by haemorrhoids. (III)

The second most frequently reported reason for delay or failure to seek care is the fear that the resultant tests will be unpleasant or embarrassing. (III)

Patients consult more quickly if their symptoms produce considerable initial discomfort and embarrassment, or have abdominal pain, nausea or vomiting. (III)

Colorectal patients with more advanced disease at diagnosis have more noticeable symptoms and are less likely to delay, as are also those with another chronic disease. (III)

No association is demonstrated between general practitioner delay and patient social class, age, physical isolation, or the regular consulting rate of the patient. (III)

Failure to investigate iron deficiency anaemia, and perform rectal examination at first consultation have been linked with inappropriate referral and increased delay. (III)

Not recognising symptoms suggestive of colon carcinoma increases delay. (III)

Initial referral to a non-surgical specialty appears to contribute to delay. (III)

Failure to undertake a rectal examination of patients with rectal symptoms is associated with delay in referral of patients with rectal cancer (III).

Diagnostic Difficulties

Lower gastrointestinal symptoms are common in people attending primary care, and symptoms become more frequent with increasing age (III).

Most general practices do not undertake sigmoidoscopy; a few do not undertake proctoscopy (III).

A family history of colorectal cancer is common among people attending primary care (III).

Delay

Introduction

In establishing a diagnosis of colorectal cancer there are three stages that may be associated with delay: the time from initial symptoms to the first visit to a doctor (patient-related delay), the time from the first visit to referral for specific investigations (general practitioner-related delay), and the time from referral to final diagnosis and treatment (hospital-related delay). This paper outlines the evidence surrounding the psychosocial and socio-demographic factors - including age, sex, ethnicity and socio-economic status - that influence both patient-related and general practitioner-related delay. Hospital delay is usually related to the positive predictive value of diagnostic investigations (covered elsewhere), or either to organisational aspects of secondary care that are beyond the scope of these guidelines. It is, however, not always possible for a given study to clearly distinguish between general practitioner and hospital related delay because of imprecise definition of the study outcomes.

All evidence we have identified is exclusively based on observational studies of similar grade of evidence. Most studies evaluate the factors that cause delay within a relatively small sample of patients, and information about the psychosocial and socio-demographic profile of patients is usually either absent or incomplete. It appears from the evidence that follows that delay in diagnosis is mostly related to the symptoms patients experience and their beliefs about them, and the readiness of general practitioners to examine patients at the first consultation, together with their suspicion thresholds. The few studies that have examined the relationship between socio-economic status or ethnicity and diagnostic delay have generally identified a non-significant association. More research into this issue may be warranted.

Secondary studies

(NHS Executive, 1997)(170)

The authors of this guidance undertook a systematic review of studies that examined reasons for the delay between the onset of symptoms of colon or rectal cancer and treatment. They identified 12 retrospective observational UK studies that gave figures for delay. Relatively short delays by clinicians appeared to be linked with active encouragement to investigate all cases in which there is any suspicion of cancer. Some general practitioner delay appeared to be due to misdiagnosis, most commonly the assumption that symptoms were caused by haemorrhoids. Inadequate investigation, notably of anaemia, could increase delay. There was evidence of failure by some general practitioners to carry out adequate rectal examination, leading to delay. In studies that investigated patients' reasons for delaying consulting, respondents were most likely to report that they did not consider that their symptoms were likely to signify serious illness. Hospital delay may be caused by false negative results of investigations such as barium enema and endoscopy.

Primary studies

(Young et al, 2000)(171)

This retrospective observational study sought to assess the incidence and reasons for delay in the diagnosis of colorectal cancer, and the effects of delay, gender, age and tumour site on the stage of disease. Delay was defined to have occurred if more than a three month period had lapsed from the time when initial symptoms were clearly established to the time of operation.

For 100 patients presenting with colorectal cancer to a hospital based colorectal unit during a one year period, the authors collected data on principal presenting symptoms, time to first presentation to a doctor, time to diagnosis and treatment, reasons for delay, diagnostic procedures, tumour site, operation, and Australian clinicopathological stage of the tumour. Only symptomatic patients with invasive adenocarcinoma who underwent excisions of their tumours were included in the study.

34 patients were diagnosed and treated more than three months from the onset of symptoms. The overall distribution of delay did not differ significantly between male and female patients, although men were more likely to have patient-related delay (31% of men vs. 10% of women; $P=0.011$). The mean age of the delay group was not significantly different to the non-delay group (mean: 69.4 vs. 71.0 years; $P=0.53$). In the 18 patients with patient-related delay alone, 16 were due to a delay in presentation. Reasons why these patients had presented late were not easy to quantify, but included: not seeking medical help until the symptoms (bleeding, abdominal pain, anaemia) were severe (4); not being concerned by symptoms (change in bowel habit, abdominal pain) (4); assuming that bleeding was due to haemorrhoids (2), hoping that the bleeding would go away (1), and no reason at all (5). The other two patients in this group had refused investigations recommended by their doctors after initial visits, and both delayed for 24 months.

Of the 13 patients with doctor-related delay alone, in seven patients symptoms had not been adequately investigated. Five had an incorrect original diagnosis (haemorrhoids, N=2; peptic ulcer, N=1; biliary colic, N=1), and for two patients the doctor was slow to investigate symptoms. Three patients experienced delay because an initial rectal examination was not performed. One sigmoid cancer was missed on barium enema with a resulting 11.5 month delay; another cancer was missed on colonoscopy with an 11 month delay. One other patient failed to be diagnosed on both colonoscopy and barium enema which resulted in a 12 month delay. All 13 patients with doctor-related delay alone had presented within three months from the onset of symptoms.

For the three other patients with both patient-related and doctor-related delay (>six months total delay), the delay was a combination of the patient's failure to seek help early enough because of competing pressures or misperception of the symptoms' significance, and the doctor's incorrect initial diagnosis or slowness to investigate.

(Robertson et al, 2004)(140)

This study reviewed the presentation of cases of colorectal and breast cancer in three Scottish health boards, 1997-8. A total of 1071 cases of colorectal cancer were included. The mean time from presentation to treatment was 138 days for colorectal cancer, but was faster for those in the 50-64 age group and for women. A history of abdominal pain, tenesmus or presence of an abdominal mass decreased the time to treatment. People with a history of anxiety and depression were only half as likely to be treated within 90 days, and those on iron therapy at presentation were more likely to be treated quickly.

(Potter and Wilson, 1999)(172)

This was a one-year retrospective audit carried out in a specialist teaching hospital to calculate the time to diagnosis for colorectal cancer from first

hospital attendance, and to identify any remedial factors felt to contribute to an undue delay in diagnosis.

The authors inspected the hospital records of 59 patients who were undergoing surgical resection for colorectal carcinoma. Twenty patients (34%) waited more than 30 days for their diagnosis. Incomplete examination or initial referral to a non-surgical specialty appeared to contribute to this delay. Rectal examination was documented in 23 (39%) general practitioner referrals and 52 (88%) the hospital case notes at initial consultation. The reason for the delay in diagnosis was deciding on an alternative diagnosis leading to no initial gastrointestinal investigation in 13 patients; in seven patients, despite initial suspicion of colorectal cancer with gastrointestinal investigation, the diagnosis was missed (of these patients, four were incompletely investigated as recommended by guidelines current at the time of the study). The general practitioner had organised a colonoscopy or barium enema for 13 patients (22%) prior to referral. The same investigations were arranged after first hospital consultation in 34 (58%) patients.

(Crossland and Jones, 1995)(173)

The aim of this study was to determine the prevalence of rectal bleeding in the community, and to examine factors that lead patients to consult their general practitioners about rectal bleeding. 1,200 patients completed a questionnaire on whether they had consulted a doctor for any of a variety of lower bowel symptoms. 287 admitted to having noticed rectal bleeding at some time in their lives, and 231 had noticed it within the previous 12 months. Bleeding was most commonly reported by those aged under 50. Only 118 (41%) respondents who had noticed rectal bleeding had sought medical advice. Patients aged over 60 were most likely to have consulted a doctor, and those aged 40-60 were least likely to have done so (56% vs. 34%, $P < 0.022$). Patients with blood in their stools were more likely to have consulted a doctor than were those who had seen blood on the paper only (53 vs. 64, $P < 0.001$).

Sixty of the respondents (30 consulters, 30 non-consulters) who had experienced rectal bleeding in the previous 12 months were then interviewed in order to assess their reasons for consulting or not consulting a doctor. The most common reason given for consulting a doctor was worry that rectal bleeding might be a sign of serious disease, the next most common reason given was that the bleeding and associated symptoms were causing pain, discomfort or embarrassment. For others the consultation arose while consulting for another reason. The main reason for not consulting a doctor was the belief that the bleeding was not serious. Most non-consulters thought that haemorrhoids were the cause of their bleeding. Haemorrhoids were recognised as the most common cause for rectal bleeding by respondents in the two groups, while cancer was recognised as the second most important cause, also in both groups. Most respondents, whether they had consulted a doctor or not, had also discussed their rectal bleeding with a relative or friend before consulting a doctor.

(Goodman and Irvin, 1993)(174)

The case records of 152 consecutive patients with carcinoma of the right colon admitted to a single surgical unit were examined to assess the incidence of delays in the treatment, reasons for the delay and effects on survival. Treatment of right-sided colonic cancer was delayed for more than 12 weeks in 61 patients (40%). The factors involved in delay included late presentation to the general practitioner (17 patients), failure of the practitioner to investigate or refer the patient (18), and failure of hospital clinicians to investigate or diagnose the illness (36). The most common error on the part of general practitioners was failure to determine the cause of iron-deficiency anaemia (16), which was also a frequent error (17) during hospital management if the anaemia was an incidental finding during treatment of another illness.

(Byles et al, 1992)(110)

The aims of this study were to estimate the incidence of rectal bleeding in the community, and to determine the proportion of individuals who delay or fail to seek medical advice after a first episode of rectal bleeding. The authors interviewed 1,213 individuals who had taken part in a large-scale general population survey of the health practices and attitudes of individuals, and who had admitted to a first episode of rectal bleeding within the last five years.

239 people (20%) reported noticing rectal bleeding at some time in their life. Of the 77 individuals who had noticed a first occurrence of rectal bleeding more than three months but less than five years prior to the interview, 23 (30%) had either not sought medical advice or had only done so after a period of delay. The most commonly reported reason (52%) for delay or failure to consult was thinking that the bleeding was not serious and would clear up by itself. The second most frequently reported reason (13%) for delay or failure to seek care was the fear that the resultant tests would be unpleasant or embarrassing.

(Dent et al, 1990)(175)

The aim of this study was to identify demographic or psychological factors, or beliefs or behaviours related to delay in presentation of rectal bleeding. The authors interviewed 93 patients, aged 35 years and older, who consulted their general practitioners because of rectal bleeding. Delay ranged from 0 to 249 days with a median of seven days; 29% delayed more than 14 days. Delay was unrelated to age, sex, ethnic origin, competence in English, length of schooling, social status, availability of social support, psychological traits, and to the belief that the cause might be cancer. The proportions delaying more than 14 days were statistically significantly elevated among those who were not worried by the bleeding (47% delayed), those who did not regularly look at their faeces or the toilet paper after use (37%), and those who took some other action before presenting to their general practitioner (43%). The main reasons given for delay were that the patient believed the bleeding was caused by haemorrhoids, it was of minor concern, and that it was not convenient to see a doctor when the bleeding first occurred.

(Mor et al, 1990)(176)

In this study, patients with a hospital diagnosis of lung, breast, and colorectal cancer were requested to participate in one home and two telephone follow-up interviews over the one-year period following diagnosis in an attempt to investigate the determinants of cancer symptom recognition and delay in seeking medical care.

24.6% of patients who reported noticing symptoms prior to diagnosis delayed longer than three months in seeking medical care. No demographic or social support factors were predictive of symptom recognition or delay, with the exception that older patients with colorectal cancer were less likely to notice symptoms, but also less likely to delay (patients in the youngest age category were almost three times more likely to delay than patients in the oldest age category; OR=2.76; 95% CI=1.10,6.91). Patients with more advanced disease at diagnosis were less likely to delay ($P<0.5$), as were also those with another chronic disease ($P<0.5$).

(Ratcliffe et al, 1989)(177)

The aim of this study was to examine delay in patients with colorectal cancer, those with risk factors and those with diverticular disease, and to assess the influence of delay on stage of disease at presentation, and patient survival. Patients with large-bowel cancer, as recorded in three consultant surgeons' databases, were interviewed about the history and duration of symptoms, and family history. The site of the tumour and Duke's staging were recorded from the operation notes. Left-sided cancers had a significantly shorter general practitioner delay. There were no significant differences between total delay times for patients with risk factors, family history or diverticular disease and those patients without risk factors or diverticular disease (patients with risk factors had previously had a colon cancer or adenomatous polyps removed, or the diagnosis of ulcerative colitis, or Crohn's disease established). There was no significant difference in delay times between the three Duke's stages.

(Funch, 1988)(178)

Data from a sample of 294 patients with colorectal cancer were used to examine factors influencing symptom reporting. The number of symptoms reported spontaneously by the subjects in response to open-ended questions was compared with the total number of symptoms reported using this technique plus a variety of other techniques. Of the symptoms reported, 54% were reported spontaneously by the subjects. Subject and symptom characteristics were examined for an association with symptom reporting patterns. Subject characteristics associated with spontaneous reporting were higher socio-economic status, better prior health status, and psychological status (more depressed) at the time of the interview; age and sex were not related to symptom characteristics, with symptoms that were severe, unusual, and developed quickly being reported more often. Incomplete symptom reports also were associated with inaccurate estimates of patient delay.

(MacDonald and Freeling, 1986)(179)

The aim of this study was to determine from a group of people aged 55 years and over their present experience and beliefs concerning bowel habit, their understanding of the terms “regular”, “diarrhoea”, “constipation”, and what they would do if they had a change in bowel habit. The authors mailed a questionnaire to a randomly selected 10% (266) sample of patients, aged 55 years and above, registered at a group general practice. The questionnaire consisted of both structured and open questions.

10% of the respondents reported no predictable frequency of movement, with women more likely to report so (14% vs. 5%). 79% believed that a daily movement is important and 90% that “regularly” is necessary for good health. 14% were dissatisfied with their bowel habits and 16% regularly self-treated. 95% gave reasonable definitions of “regular” and “diarrhoea”, 10% were unsure about the definition of “constipation”. Although 76% believed there were bowel symptoms that require immediate medical attention, 98% would in

the first instance treat themselves for constipation, 90% for diarrhoea, and 25% for rectal bleeding. Bowel symptoms for which a doctor should be seen without delay included passing blood (41%), pain (19%), constipation (16%), diarrhoea (12%), and “anything unusual” (9%). A third of respondents had in fact consulted a doctor about their bowels at some time prior to the questionnaire. A greater proportion (42%) of those aged 65-74 years had done so than those in other age groups. The reasons for which they consulted were: constipation (25%), pain (21%), bleeding (12%), diarrhoea (12%), and piles (9%). All comparisons are significant at the $P < 0.05$ level.

(MacArthur and Smith, 1984)(180)

127 patients with large bowel cancer were interviewed shortly after having received treatment to identify factors associated with delay in presentation, diagnosis, and referral for treatment (patient delay, general practitioner delay, and hospital delay). Further data were obtained from general practitioners and abstracts from case notes.

Of those patients included in the study, 45% had consulted within a month, although few did so within a week of first noticing their symptoms. 28% delayed more than three months before consulting a doctor. The authors found no associations between personal characteristics such as age or social class and patient delay. Personal advice to go to the doctor was important in reducing delay. Patients with abdominal pain, or nausea and vomiting as an initial symptom, went more quickly to the doctor; those with both these symptoms went most quickly. Symptoms associated with long delay were loss of weight and rectal discomfort or pain. Patients with cancer of the colon were more likely to experience the symptoms of abdominal pain and vomiting, and this explains why they delay less than patients with rectal cancer.

Only 32% of patients in this study were referred to a specialist immediately. 30% of the patients were delayed for longer than three months. Mean delay was 120.5 days and median delay 25.3 days. There was a little more delay in patients with cancer of the rectum than colon. The nature of the symptoms the

patient presented to the doctor did not play a large part in affecting this phase of delay; patients with constipation were referred a little more quickly than patients with diarrhoea or those with only one symptom. Patients from the manual social classes also waited a little longer than middle class patients. Examination of patients by the doctor at the first consultation was found to be associated with the speed of referral. Median delay for patients who had been examined was 1.5 compared with 89.5 days in the 42 cases where no physical examination took place. A longer duration of symptoms did not seem to prompt the doctor into more immediate action.

Most patients (90.5%) reported that they had not considered cancer as a possible cause of their symptoms and had delayed consulting their doctor until such symptoms became either more severe or more persistent. The only patients who consulted quickly were those whose symptoms produced considerable initial discomfort.

(Holliday and Hardcastle, 1979)697}

The authors of this study interviewed 200 patients admitted to hospital with colon or rectal carcinomas. They recorded data on the following: total duration of symptoms, delay in presentation to the family doctor, number of visits to the family doctor, type of clinical examination performed, and department to which the patient was referred.

Mean delay between the onset of symptoms and treatment was 30.5 weeks in a hundred patients with colon carcinoma, and 38 weeks in a hundred patients with rectal carcinoma. Most of this delay occurred outside hospital, and delays attributable to the patient and family doctor were almost equal in duration. Patient delay was largely the result of not knowing the importance of bowel symptoms, while delay with the family doctor was the result of not examining patients with possible rectal carcinomas and not recognising symptoms suggestive of colon carcinoma. There was no relation between the duration of symptoms and the Duke's stage of the tumour.

(Macadam, 1979)(181)

The author of this study interviewed 150 patients admitted to hospital with gastrointestinal cancer as soon after admission as possible with the aim of exploring their presenting symptoms, and delay in diagnosis and treatment. Responses were contrasted with hospital records and general practitioners' recollections. In approximately 50% of cases there was an interval of weeks between the patient consulting the general practitioner and being referred for hospital investigation. No association was demonstrated between delay and social class, age, physical isolation, or the regular consulting rate of the patient.

(Jones, 1976)(182)

The author undertook a survey in a group of over 40-year-olds in an attempt to derive information on people's beliefs and perceptions of what constitutes "normal bowel habit". The sample was randomly selected from a local population database, and all respondents were personally interviewed about a standard set of outcomes. The majority of respondents had a set pattern for their bowel habit; of these 80% had one bowel motion per day; the majority realised that a severe change in bowel habit should lead them to consulting a doctor, 24% had noticed blood on their bowel motions and 32% had noticed blood on the toilet paper. There were deficiencies in the understanding of the terms diarrhoea and constipation. The majority of patients treated themselves for slight changes in bowel habit.

(Rowe-Jones and Aylett, 1965)(183)

200 consecutive patients with carcinoma of the colon or rectum who attended a hospital clinic were interviewed and their case notes analysed to examine where diagnostic delay occurred. The authors recorded the main presenting symptom together with its date of onset, the date the patient first sought medical advice with symptoms referable to the disease, and the date of first attendance at any hospital. Both patient and doctor (general

practitioner/hospital) related delays were examined. Doctor related delay was defined as failure to diagnose within two months of the patient presenting with symptoms.

For patients with colon cancer, symptoms were on average present for seven months with a standard deviation of 5.3 months (patient delay). Medical delay occurred in 22% of the patients, 68% of those at the hospital and 32% (seven patients) with the general practitioner. The average delay was 7.8 months, hospital delay 7.9 months, general practitioner delay 7.7 months. Of the seven cases with general practitioner delay, rectal examination was only carried out in one patient. In patients experiencing medical delay, a more advanced stage of disease was statistically significantly more likely ($P=0.025$) at the time of treatment.

For patients with rectal cancer, symptoms were on average present for 10.3 months (standard deviation 8.82 months) before seeking medical advice. Medical delay occurred in 22% of cases. In contrast with cancer of the colon, the delay in rectal carcinoma was mainly with the general practitioner. In 82% of those experiencing delay, the delay was due to the general practitioner, and in the remaining 18% to delay at the hospital. The principal reason for general practitioner delay was that in 18 patients with bowel symptoms, only two underwent a rectal examination, although all returned at least once to their general practitioner with continuing symptoms of bleeding, or constipation, or diarrhoea, or with a lump. The commonest problem was the presumptive diagnosis of haemorrhoids as the cause of bleeding without any examination. As in patients with colon cancer, a more advanced stage of disease at the time of treatment was significantly more common in those who experienced medical delay ($P<0.025$).

Diagnostic Difficulties

Introduction

We were unable to identify studies that directly investigated the reasons why primary care professionals experience difficulties in suspecting cancer in

some patients. Qualitative studies involving interviews of professionals would have been one suitable study design; the direct observation of consultations with real or simulated patients would have been another. Neither did we find randomised controlled trials of interventions to improve professionals' ability to detect colorectal cancer.

Primary studies

(Bankhead et al, 2001)(184)

A postal questionnaire was sent to 909 practice nurses in four English health authorities, and 600 (66.0%) replied. 49.8% collected information about a family history of colorectal cancer in new patient appointments, 45.6% in well person appointments, and 22.7% in chronic disease clinics. Only 33.2% expressed confidence in making a basic risk assessment in the case of colorectal cancer, 25.0% felt confident in reassuring those at low risk, and 61.1% felt confident in advising on relevant symptoms

(Henningan et al, 1990)(185)

A postal questionnaire was sent to 859 general practitioners in London, and 609 (71%) responded. 279 general practitioners did five or fewer rectal examinations a month, 211 did six to ten, and 96 did more than ten. Factors associated with doing fewer examinations were a small partnership and being a female general practitioner, and expectation that the examination would be repeated. Lack of time in the surgery and an urgent outpatient appointment waiting time of less than two weeks were also important. The reasons given for deciding not to do a rectal examination in symptomatic patients were reluctance of the patient (278 respondents, 45.6%), the expectation that the examination would be repeated after referral (141, 23.2%), lack of time (132, 21.7%), or lack of a chaperone (39, 6.4%). General practitioners who thought they had been poorly taught, were more recently qualified, or worked in inner London were significantly more likely to be deterred by one or more of these factors.

12 Breast cancer

Number		Grade
General recommendations		
1	A patient who presents with symptoms suggestive of breast cancer should be referred to a team specialising in the management of breast cancer.	D
2	In most cases, the definitive diagnosis will not be known at the time of referral, and many patients who are referred will be found not to have cancer. However, primary healthcare professionals should convey optimism about the effectiveness of treatment and survival because a patient being referred with a breast lump will be naturally concerned.	C
3	People of all ages who suspect they have breast cancer may have particular information and support needs. The primary healthcare professional should discuss these needs with the patient and respond sensitively to them.	D
4	Primary healthcare professionals should encourage all patients, including women over 50 years old, to be breast aware ¹⁴ in order to minimise delay in the presentation of symptoms.	D
Specific Recommendations		
5	A woman's first suspicion that she may have breast cancer	C

¹⁴ Breast awareness means knowing what your breasts look and feel like normally. Evidence suggests that there is no need to follow a specific or detailed routine such as Breast Self Examination, but women should be aware of any changes in their breasts. See <http://cancerscreening.org.uk/breastscreen/breastawareness.html> for further information.

is often when she finds a lump in her breast. The primary healthcare professional should examine the lump with the patient's consent. The features of a lump that should make the primary healthcare professional strongly suspect cancer are a discrete, hard lump with fixation, with or without skin tethering. In patients presenting in this way an urgent referral should be made, irrespective of age.

- 6 In a woman aged 30 years and older with a discrete lump that persists after her next period, or presents after menopause, an urgent referral should be made. **C**
- 7 **Breast cancer in women aged younger than 30 years is rare, but does occur. Benign lumps (for example, fibroadenoma) are common, however, and a policy of referring these women urgently would not be appropriate; instead, non-urgent referral should be considered. However, in women aged younger than 30 years with:** **C / D**
- a lump that enlarges, **[C]** or
 - a lump that has other features associated with cancer (fixed and hard), **[C]** or
 - in whom there are other reasons for concern such as family history. **[D]**
- an urgent referral should be made.**
- 8 The patient's history should always be taken into account. For example, it may be appropriate, in discussion with a specialist, to agree referral within a few days in patients reporting a lump or other symptom that has been present for several months. **D**
- 9 In a patient who has previously had histologically confirmed **C**

breast cancer, who presents with a further lump or suspicious symptoms, an urgent referral should be made, irrespective of age.

- 10** In patients presenting with unilateral eczematous skin or nipple change that does not respond to topical treatment, or with nipple distortion of recent onset, an urgent referral should be made. **C**
- 11** In patients presenting with spontaneous unilateral bloody nipple discharge, an urgent referral should be made. **C**
- 12** Breast cancer in men is rare and is particularly rare in men under 50 years of age. However, in a man aged 50 years and older with a unilateral, firm subareolar mass with or without nipple distortion or associated skin changes, an urgent referral should be made. **C**
- Investigations**
- 13** In patients presenting with symptoms and/or signs suggestive of breast cancer, investigation prior to referral is not recommended. **D**
- 14** In patients presenting solely with breast pain, with no palpable abnormality, there is no evidence to support the use of mammography as a discriminatory investigation for breast cancer. Therefore, its use in this group of patients is not recommended. Non-urgent referral may be considered in the event of failure of initial treatment and/or unexplained persistent symptoms. **[B (DS)]**

Introduction

Pathology

Breast carcinoma develops from the epithelial cells within the terminal duct/lobular unit (186). It is categorised as either *'invasive'* or *'in situ'*. Before malignant cells breach the basement membrane the cancer is *'in situ'*, but once that membrane has been breached the cancer is *'invasive'*.(186). Breast cancers can be classified as either 'ductal' or 'lobular' on the basis of carcinoma type. The terms 'ductal carcinoma *in situ'* (DCIS) and lobular carcinoma *in situ'* (LCIS) are widely used but carry no more relevance than *invasive* cancer.(186)

Staging breast cancer

Staging is used to classify cancers on their anatomic extent. Tumour staging is based on size and the whether there is fixation of the cancer to surrounding tissue(186). The TNM staging system (Table 33) was developed from work in the 1940s by Pierre Denoix and is now the most widely used system of cancer classification.(187)

Table 33 TNM classification and stage grouping for breast tumours ((186))

TNM classification		Stage grouping			
Tis	In Situ	Stage 0	Tis	N0	M0
T1	≤2 cm	Stage I	T1	N0	M0
		Stage IIA	T0	N1	M0
			T1	N1	M0
T2	>2 to 5 cm	Stage IIB	T2	N0	M0
			T2	N1	M0
T3	>5 cm	Stage IIIA	T3	N0	M0
T4	Chest wall/skin		T0	N2	M0
			T1	N2	M0
		T2	N2	M0	
N1	Mobile axillary nodes involved	Stage IIIB	T3	N1, N2	M0
			T4	Any N	M0
			Any T	N3	M0
N1	Mobile axillary nodes involved	Stage IV	Any T	Any N	M1

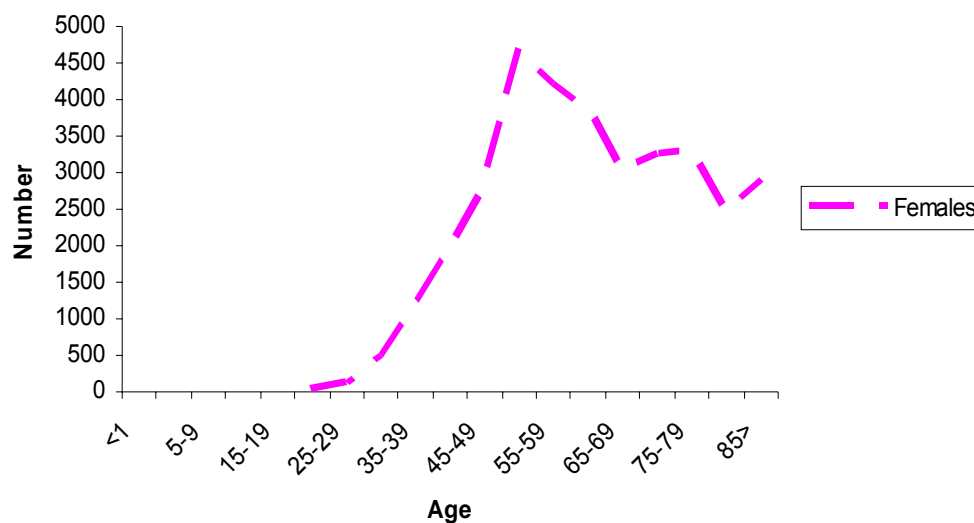
N2	Fixed axillary				
N3	Internal axillary				
M1	Distant metastases				

T = Tumour; N = Node; M = Metastasis.

Incidence

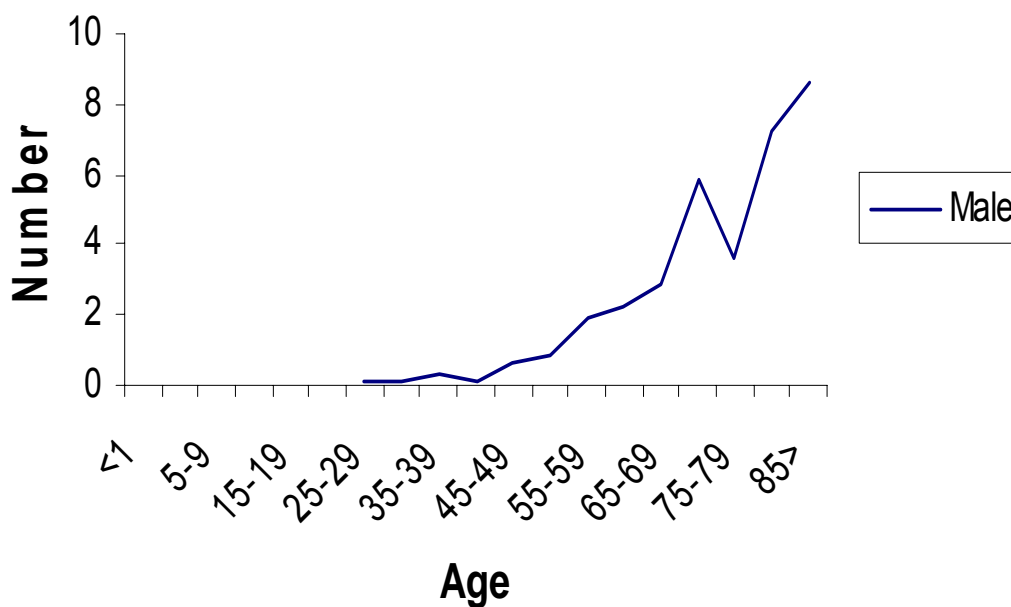
Breast cancer is the most common malignancy in women, accounting for almost 30% of female cancers. A general practitioner can expect to encounter one new case of breast cancer approximately every 11 months. It is estimated that more than 75% of cases present symptomatically and not through screening programmes. In 2001 there 40,740 cases in women.

Figure 15 2001 Registrations of Malignant Neoplasm of the Breast in England and Wales. (77)



Breast cancer in males is rare occurring approximately 100 times less than in women(128). The distribution of incidence by age is shown in *Figure 16*.

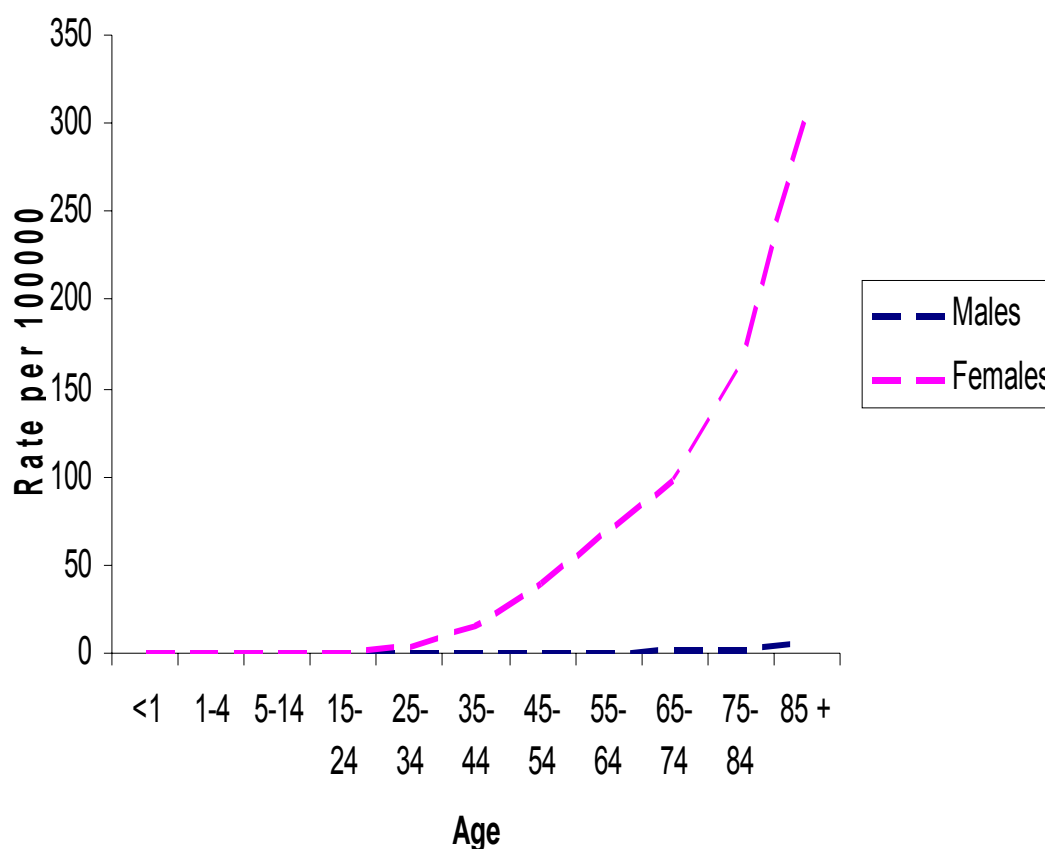
Figure 16 2001 Registration rates of Malignant Neoplasm of the Breast in Males in England and Wales. (77)



Mortality

Despite increased incidence rates, mortality among women from breast malignancies has been falling since 1990 decreasing from approximately 38 to 32 per 100,000 population between 1971 and 1999. In 2002, there were 11,476 deaths among women and 81 among men (Figure 17).

Figure 17 2002 Mortality rates per 100,000 population from Malignant Neoplasm of the Breast in England and Wales. (78)



Review of cancer referral audits

The review (CRD, 2004) identified 72 clinical audits. The proportion of two week referrals in accordance with the symptoms listed in the Department of Health (2000) guidelines ranged from 65% to 99% (20 audits). The proportion of patients found to have cancer who had been referred under the two week system ranged from 0% to 34% (37 audits). The proportion of patients

referred as 'urgent' but not under the two week system ranged from 4% to 20% (five audits). The proportion of patients found to have cancer who had been referred non-urgently ranged from 0% to 10%. Of the patients found to have cancer, between 4% and 83% had been referred under the two week system (nine audits). The proportion of two week referrals considered by the consultant to be appropriate or warrant an urgent appointment ranged from 18% to 96%.

Demographic information

(ONS, 2001) (17)

Breast cancer is the most common cancer in women worldwide, although cervical cancer is more frequent in some developing countries. It accounts for about 30% of all malignancies in women in England and Wales and recorded rates are higher in women in western, developed, countries. Breast cancer in men is extremely rare.

In 1997 there were 33,100 new registrations of breast cancer in women in England and Wales (Table 34), almost 30% of all cancers in women, and more than twice as many as for the second most common site, colorectal cancer. Worldwide, the highest recorded incidence rates occur in the USA and other western, developed countries. Rates in Japan, China and India are only about a quarter of those in the USA.

Table 34 Breast Cancer incidence and mortality, England and Wales, 1997 (ONS, 2001. (17))

Total number of new cases	33,100
Rate / 100,000	124.6
Mortality	11,500
Mortality / 100,000	43.3

Before the introduction of screening, incidence rates rose with age from the late 20s, but slowed at around 45-54 years, the age of the menopause. The effect of breast screening has been to raise the incidence in women aged 50-54, because many women were being screened for the first time with cancers being detected at an earlier stage. Rates in women aged 55-64 also rose during the early years of screening, but have since returned to levels expected based on the earlier trends. Incidence in women aged 65-69 has fallen in recent years: many cancers in these women will have been detected at earlier ages during screening; their rates in 1995-97 were lower than those in women aged 50-64.

As the incidence of breast cancer is high and survival is relatively good compared with many other cancers, there are large numbers of women alive who have been diagnosed with breast cancer. About 81% (75,000) of those diagnosed in 1990-92, and 62% (168,000) of those diagnosed in 1983-92 were still alive at the beginning of 1993.

One-year survival rates for patients in England and Wales diagnosed in 1991-93 was 92%; five-year survival was 74%. Women aged under 40 at diagnosis had worse survival than those aged 40-49. In the late 1980s, mortality in England was not only higher than in most western European countries, it was among the highest in the world. However, survival has improved steadily over time, and in all regions. Five-year survival rose by 14% points between the early 1970s and the late 1980s and by a further 6% for patients diagnosed in 1991-93. The five-year survival from breast cancer in the UK is now 75.9%, (www.cancerresearchuk.org/aboutcancer/statistics/survival). and for screen-detected cancers five-year survival is 94.1% (<http://www.cancerscreening.nhs.uk/breastscreen/publications/ba00-01.html>).

12.1 Signs and Symptoms

Women

12.1.1 Key Clinical Question:

Which symptoms, signs and other features raise a suspicion of cancer in women consulting in primary care and those that make cancer less likely as a diagnosis?

12.1.2 Evidence Question:

In women attending primary care services with breast symptoms, which symptoms and signs and other features when compared with the “gold standard” are predictive of a diagnosis of cancer; and which symptoms and signs are not?

12.1.3 Evidence Statements:

The incidence of breast cancer in women in England and Wales rises sharply with age and is rare in women aged under 30 (III).

In studies of risk factors associated with a diagnosis of breast cancer, age is the only factor consistently reported in association with breast symptoms and a diagnosis of cancer (III).

Women with breast symptoms commonly consult general practitioners. In one study, the typical general practitioner was consulted by one woman with breast symptoms every two weeks (III).

Among women presenting in general practice with breast problems, the most common presenting features are a lump and/or pain (III).

Women who attend primary care with the following features have an increased likelihood of having breast cancer:

Palpable mass

Skin or nipple change (III)

The likelihood of having a diagnosis of breast cancer is highest in women who present to primary care with a palpable mass. However, the absence of a palpable mass does not rule out the possibility of cancer (III).

There is little or no research evidence on the characteristics of breast lumps among women presenting in primary care and the likelihood of cancer. Benign lumps are said to be more likely to be smooth and well demarcated, whereas less mobile lumps with poorly defined margins are more likely to be malignant (IV).

Guidelines

(Austoker and Mansel, 2003) (188)

These guidelines quoted Barclay et al (1991) and Cochrane et al (1997). Cochrane et al (1997) reported that of 2332 new patients presenting to a breast clinic, 147 had symptomatic carcinomas. The symptoms and signs reported by the general practitioners in patients referred with carcinoma were:

lumps 90%

painful lumps 21%

nipple discharge 3.4%

nipple change 10.2%

skin contour change 4.8%

any family history 6.1%.

The guidelines recommended urgent referral for patients with a discrete lump in the appropriate age group, or definite signs of cancer such as: ulceration, skin nodule, skin distortion (<3 months). Nipple discharge or pain in the

absence of a lump were said to be much less common presentations of breast cancer.

(All Wales Minimum Standards, 2000) (189)

Standard 10 stipulated that there should be a mechanism to provide general practitioners with rapid access to an appropriate specialist, urgent referrals being seen within ten working days of receipt of the referral by the hospital. The Standards did not include guidance on the presenting symptoms or signs.

(Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998) (190)

This publication is a Canadian evidence-based guideline to assist decisions in excluding or confirming the presence of cancer when a breast lump is detected. The guidelines were based on published evidence supplemented by expert opinion. Articles were identified through a database search using MEDLINE (from 1966) and CANCERLIT (from 1985) to January 1996. A non systematic review of breast cancer literature continued to January 1997. The guidelines made recommendations on how to establish a reliable diagnosis using the minimum of procedures. Evidence graded I-III was used as far as possible, but when experimental evidence was weak or lacking, the opinion of respected authorities (level IV) was employed. The conclusions arising from the review are outlined below.

Most lumps are not caused by cancer, but the possibility of malignancy must always be considered. The first step is to obtain a clinical history and carry out a physical examination. When necessary, this is followed by further diagnostic procedures (mammography, fine needle aspiration [FNA], ultrasonography) and, if uncertainty still remains, by tissue biopsy (core or open surgical). The clinical history should establish how long the lump has been noted, whether any change has been observed and whether there is a history of biopsy or breast cancer. Risk factors for breast cancer should be noted, but the

guidelines advised that their presence or absence should not influence the decision to investigate a lump further.

The presence of certain factors increases the likelihood of breast cancer. These include a history of a biopsy of either breast showing atypical hyperplasia, lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS), a history of resected carcinoma or radiation treatment for Hodgkin's disease in childhood, or a strong family history of breast cancer (level III evidence). Although known risk factors, including ageing, all increase the risk of breast cancer, they do not substantially influence the probability that any particular lump will be malignant. The fact remains that most women in whom breast cancer is diagnosed have no identifiable risk factors and breast cancer does not develop in most women with common risk factors.

The physical examination of the breast should aim to identify those features that distinguish malignant from benign lumps. Breast examination should be accompanied by a thorough examination of the axilla and supraclavicular areas to check for nodal involvement. Premenopausal women are best examined one week after the onset of the last menstrual period when engorgement of the breast is at a minimum (level IV evidence).

Paget's like lesions of the nipple are frequently caused by breast cancer. The condition may resemble a benign dermatitis that is sometimes moist and eczematous or sometimes dry and psoriatic and usually accompanied by thickening of the nipple-areolar complex. These features usually reflect centrifugal spread of cancer cells from the ductal epithelium into the overlying skin of the nipple. Biopsy is indicated when the condition fails to respond rapidly to topical treatment.

Smooth, well demarcated lumps are usually benign (level IV evidence). These are either cysts or fibroadenomas. Lesions that are less smooth and less mobile, with poorly defined margins, increase the suspicion of carcinoma.

Nipple discharge is not a common feature of cancer. Persistent unilateral discharge may be due to cancer in 4% to 21% of cases. The discharge may be watery, sanguineous, serosanguineous or serous. A non-bloody discharge is unlikely to be caused by cancer, and even a sanguineous discharge is often not due to cancer. Also, a bilateral discharge is unlikely to be caused by cancer.

Breast cancer may or may not be painless. Although breast cancers are usually painless, the cancer may be accompanied by discomfort. Thus, the presence or absence of pain and tenderness should not influence the investigation of a suspicious lump.

(SIGN, 1998)(191)

The SIGN guidelines recommended referral of patients who presented with any new discrete lump, a new lump in pre-existing nodularity, asymmetrical nodularity that persist at review after menstruation, an abscess or breast inflammation which does not settle after one course of antibiotics, or a cyst persistently refilling or recurrent cyst (if the patient has recurrent multiple cysts and the general practitioner has the necessary skills, then aspiration is acceptable). It was also recommended that pain in association with a lump, or that was intractable or unilateral in a post-menopausal women should be an indication for referral, and nipple discharge is also an indication for referral in women over the age of 50 and also under 50 if the discharge is blood stained, persistent single duct or sufficient to stain clothes.

Secondary studies

(Centre for Reviews and Dissemination, 2002)(192)

This Service Guidance Evidence Review did not find any studies of the effectiveness of routine physical breast examination in self-presenting well women in the primary care setting. The review identified two large randomised

controlled trials, a non-randomised trial, two cohort studies and three case control studies but no reliable evidence to suggest that breast self-examination (BSE) among asymptomatic women reduces mortality rates from breast cancer. In fact some evidence suggested that BSE can do harm through increased rates of biopsy for benign lesions (grade of evidence I [systematic review of randomised controlled trials] and III [systematic review of non-randomised controlled trials]).

(Levine et al, 2001) (193)

In this systematic review undertaken by the US Agency for Healthcare Research and Quality, studies published from 1994 to 1999 were searched using Medline and Current Contents databases. The review included observational studies, randomised and non-randomised trials, and uncontrolled case series. The first question addressed in the review was 'What are the recommendations for evaluation of breast symptoms, mammographic findings and other suspicious findings based on menstrual status, use of hormone replacement therapy (HRT), pregnancy, age, and family history?'

Information about the association of symptoms and signs and a diagnosis of breast cancer could only be drawn from those studies that reported individual rather than aggregated data. Patients who presented with palpable masses were much more likely to be diagnosed with cancer than those with non-palpable masses, nipple discharge or breast pain. Ten studies reported the number of patients with palpable masses who developed cancer. Of a total of 2027 patients with masses, 303 (14.9%) had cancer. Six studies reported patients with 'lesions' as clinical findings; of 1094 with lesions, 358 (32.7%) were cancer. Four studies reported on nipple discharge, and among the total of 570 patients with discharge, 18 (3.2%) had cancer. Only two studies reported the incidence of cancer in association with breast pain, the proportions being seven of 216 (3.2%) in one study, and four of 221 (1.8%) in another. However, it should be noted that the reviewed studies included samples of women after referral.

Primary studies

There were few studies of the symptoms and signs associated with breast cancer among women presenting to primary care. Most studies involved only a small number of practices and patients, and consequently the numbers of women with cancer were usually too few to draw any meaningful conclusions about the predictive value of symptoms and signs in primary care. Since general practitioners encounter around one new patient with breast cancer per year, studies of presentation in primary care would require the participation of a large number of general practitioners.

The gold standard used in several studies was referral rather than subsequent diagnosis. One study provides more detail (Barton et al, 1999(194)), and this is described at greater length. There are several studies of the symptoms and signs of women attending specialist services, and we have included two of these only to highlight the different patient features found among a specialist service in contrast to primary care. Considerable caution is needed, therefore, in extrapolating from studies undertaken in specialist clinics to patients presenting to primary care.

Studies of patients presenting in primary care

(Newton et al, 1999) (195)

In this case series, data were collected prospectively from 508 women consulting 248 general practitioners in Sheffield over a four week period between January and July 1995. The general practitioners used a standard pro-forma to record information about women consulting primarily for a breast problem. The pro-formas were not completed for women who had a breast examination as part of a consultation for any other reason.

Table 35. Presenting features among 508 women consulting with breast problems (Newton et al, 1999 (195))

Presenting symptoms	Referred
Lump - 218	126 (57.8%)
Pain -196	33 (16.8%)
Nipple discharge – 21	7 (33.3%)
Skin/nipple change -21	3 (14.3%)
Family history -7	4 (57.1%)
Other – 45	13 (28.9%)
Total 508	186 (36.6%)

Referral rates increased according to patient age: 16-39 32.6%, 40-49 38.7%, 50-64 40.6%, 65+ 50.0% (*Table 35*). The mean number of consultations was 2.05 over the four week period, suggesting that a general practitioner would see 15.8 women with new breast problems in one year. However, this figure excludes women who consulted for primarily other problems but also had a breast problem.

(Nichols et al, 1980) (196)

In this case series, 193 general practitioners were recruited in Southampton to record in a booklet all women seen with breast symptoms over four weeks. There were 331 consultations recorded by 323 women for breast conditions (mean: 3.5 per general practitioner). Of those consultations 241 were for new episodes (*Table 36*).

Table 36. Presenting features among 323 women consulting with breast problems (Nichols et al 1980)

New episodes	Referred
1 lump only – 29	18 (62.1%)
2+ lumps - 7	3 (42.9%)
Pain only - 125	7 (5.6%)
Other - 24	24 (20.8%)
Lump and pain - 29	14 (48.3%)
Lumps and pain – 19	11 (57.9%)
1 lump + other – 1	1 (100%)
2+lumps + other– 1	0
Pain and other - 6	2 (33.3%)
Total – 241	61 (25.3%)

(Bywaters, 1977)(197)

This study involved six general practitioners in one UK practice recording 451 consultations for breast problems by 180 women. Details of consultations were recorded and a list was created of women consulting with breast complaints between October 1972 and December 1974. The presenting features are summarised in *Table 37*.

28 of the 180 had cancer (18 new cases -10%); All these were aged 30 or over. Of 57 patients seen with a discrete lump, 32 (56.1%) were referred immediately.

Table 37 Presenting features among 180 women consulting with breast problems (Bywaters 1977).

Feature	Number
Lump	68 (38%)
Pain	51 (28%)
Nipple discharge	8 (4.4%)
Change in shape	8 (4.4%)
Post-mastectomy –	5 (2.8%)
Anxiety	4 (2.2%)
Cosmetic	3 (1.7%)
Ulceration	2 (1.1%)
Other	7 (3.9%)

(Roberts et al, 1987)(198)

This was a study to ascertain the effects of a recent health campaign on the number of general practitioner consultations for breast problems. The study involved giving each patient consulting with breast problems a questionnaire; women having a breast examination associated with contraceptive care or routine cervical cytology tests were not included. 262 women returned questionnaires from five UK general practices over 18 months. Their symptoms and referral rates are shown in *Table 38*.

In addition, the study suggested that public health campaigns had little measurable affect on consultation rates.

Table 38 Presenting features among women consulting at primary care with breast problems (Roberts et al, 1987 (198))

Presenting symptoms/signs	Referrals
Pain – 124	54 (43.5%)
Lump – 93	63 (67.7%)
Discharge – 3	3 (100%)
Other – 40	19 (47.5%)
Total – 262	total 132 (50.4%)

Studies of referred patients

(Seltzer, 2004)(199)

This study reviewed data on 10 000 consecutive new surgical referrals for breast complaints in the US. Female patients referred between 1987 and 1999 completed a comprehensive medical history form. The aim of the study was to demonstrate those situations which are likely to yield a cancer diagnosis.

Across all ages, 9% of patients presenting with lump yielded cancer; 16% of those presenting with pain; 4% of those presenting with discharge; 11% of those found by mammogram and 5% presenting with miscellaneous complaints.

(Campbell, 2004)(200)

This study reviewed prospective audit data from patients referred to a symptomatic breast unit in the UK. The patients with a breast lump were significantly more likely to have breast cancer than patients without a lump (OR = 5.0765, CI = [3.06662-8.4047], $p < 0.001$). The likelihood of breast cancer increased with age (OR = 1.0808, CI = [1.0712-1.0906], $p < 0.001$). Pain was the least likely to indicate the presence of cancer (OR = 0.1351, CI = [0.0664-0.22749], $p < 0.001$), as was breast lumpiness (OR = 0.3192, CI = 0.1718-0.5930], $p < 0.003$), nipple discharge (OR = 0.5337, CI = [0.1821-1.5647], $p > 0.05$), HRT use (OR = 0.6995, CI = [0.4431-1.1042], $p < 0.05$) and signs of cancer (OR = 0.6842, CI = 0.4156-1.1265], $p < 0.003$). Family history was not found to be statistically significant within their model.

(Patel et al, 2000)(201)

This study was prospective case series involving new patient referrals from general practitioners to a specialist breast clinic in Glasgow. Of the 321 patients referred, 10% had breast cancer and 90% had either benign disease

or no pathology. The study concluded that one third of the referrals were inappropriate (*Table 40*).

Table 39. Features among 321 women referred to a breast clinic (Patel et al 2000)(201).

i) 10% with breast cancer	
Lump/nodularity –	21 (91%)
Nipple change –	2 (6%)
Axillary lump	1 (3%)
ii) 90% without cancer	
Lump –	175 (60%)
Pain –	55 (19%)
Nipple discharge/change	22 (8%)
Family history only	12 (4%)
Anxiety only	3 (1%)
Other	22 (8%)

(Barclay et al, 1991)(202)

In this case series, information was collected about women referred to breast or surgical outpatient clinics in Dundee between 1979 and 1989. During this period, 940 women presented with new breast cancers and 3,500 were referred with benign conditions. The features at presentation among the patients with cancer are shown in *Table 40*. The median age of those with benign disease was 35 years, but for those with cancer the median age was 57 years. The majority (91%) of referrals to the breast unit for benign disease occurred in patients under 55 years.

Among those with cancer, a visible abnormality was noted in the left breast in 362 patients, and the right breast in 320 patients. The most common observed abnormalities were asymmetry (68%), nipple abnormalities (43%) and skin changes (7%).

Of those diagnosed with breast disorders, 15% reported a family history of breast cancer, compared with only 18% of the 940 who had cancer reporting family history.

Table 40. Features at presentation among 940 women with breast cancer (Barclay et al 1991).

	Cancer n (%)	Benign conditions n (%)	
		Right breast	Left breast
Lump only	459 (50)	519 (29)	579 (26)
Pain only	26 (3)	301 (17)	373 (17)
Lump and pain only	124 (13)	316 (17)	371 (17)
Nipple discharge only	14 (1)	64 (4)	75 (3)
Nipple retraction only	29 (3)	13 (1)	27 (1)
One other symptom only	45 (5)	160 (9)	174 (8)
Combination of symptoms	259 (28)	445 (26)	597 (27)

(Barton et al, 1999) (194)

This US population-based retrospective cohort study was undertaken at a large health maintenance organisation in New England over a ten year period. The study sought to determine 1) how often women presented with breast symptoms to primary care providers 2) how these symptoms were evaluated, and 3) how often symptoms led to a diagnosis of breast cancer. The study population was 2400 women aged 40-69 years, sampled in a random age stratified manner and from people who had been continuously enrolled in the health maintenance organisation (HMO) from July 1983 to June 1993. For this sample, information was abstracted on all breast related encounters and diagnoses of cancer subsequent to presented symptom(s) were recorded.

Patient symptoms were classified as 1) mass (a single lump or nodule); 2) pain (a report of pain or tenderness in either breast or bilaterally), 3) skin or nipple change (including nipple discharge) 4) multiple lumps or nodules often described by clinicians as 'fibrocystic' or 'diffuse cystic change', or 5) other symptoms (such as increasing breast size). Clinicians' diagnostic interpretations were classified as normal (even if fibrocystic), abnormal-benign (no further follow up required), indeterminate (record of firm or fixed lumps, or

follow up by surgeon recommended, or suspicion of cancer noted). The meaning of such terms as benign or normal had to be inferred because clinicians did not use a standard taxonomy to describe their examination findings nor a standard metric to convey level of concern.

Over the ten year period, 372 (16%) of the HMO population presented with a breast symptom (22.8 presentations per 1000 person years). Women younger than 50 years of age presented nearly twice as often as older women ($P=0.0001$). Rates did not differ by ethnic group. Women with a family history of breast cancer were more likely to present with breast symptoms than those without a family history (22% compared with 14%; $P=0.001$).

The most common symptom was pain, followed by a mass, skin or nipple change, lumpiness and other symptoms. Two symptoms were noted in 59 episodes (13%); the most frequent combinations were pain and mass (31 episodes [7%]) and pain and skin or nipple changes (14 episodes [3%]). In 69 episodes, no specific symptom was documented. Presenting symptoms and signs varied by age. A mass was the most common feature among women in their 40s, and pain was the most common feature among women in all other age groups. Pain was unilateral in 91% of episodes and bilateral in 9% of episodes.

On physical examination, the clinicians found a mass in 184 episodes (34%), skin changes or nipple discharge in 43 episodes (8%), fibrocystic changes in 112 episodes (21%) and other findings in 32 episodes (6%). More than one finding was documented in 45 episodes and no specific findings were documented in 214 episodes (40%). Of the 196 episodes in which a patient reported a mass, the clinician confirmed the mass in 160 (82%). Of the 343 episodes in which mass was not one of the patient's symptoms, the clinician documented a mass in 24 (7%).

Clinicians interpreted physical findings as normal in 33% of episodes, abnormal-benign in 27%, indeterminate in 35%, and suspicious for cancer in 6%. Breast cancer was diagnosed in 23 of the 372 women who presented

with breast symptoms (6.2%); 21 had invasive disease (six with stage 1 disease, 14 with stage 2 disease, and one with stage 3 disease) and two had ductal carcinoma in situ.

Of the 23 women with cancer, 11 (6.4%) presented while in their 40s, six (4.4%) while in their 50s, three (4.4%) while in their 60s, and three (8.3%) in their 70s. Clinicians had found a mass in 22 (96%), skin findings in two (9%), fibrocystic changes in three (13%) and other findings in three (9%).

The 23 women with symptomatic breast cancer had higher tumour stages at diagnosis than 58 women whose breast cancer was detected by screening mammography during the study period ($P=0.02$). The likelihood of breast cancer varied by symptom or sign. A report of a mass was associated with a 10.7% chance of breast cancer and a likelihood ratio of 65, whereas a report of pain led to a diagnosis of cancer in 1.8% of episodes, with a likelihood ratio of 10. A mass accompanying any other symptom or sign increased the risk for cancer. At the same time, each symptom or sign alone was associated with a significantly higher risk for cancer than in the population at large.

Although younger women presented more frequently with breast symptoms or signs, cancer rates did not vary significantly by age group. The study indicated that 4.3% of breast symptom or sign episodes led to a diagnosis of breast cancer, but it should be noted that the incidence of cancer may be lower in this study than in an unscreened population because of the use of screening mammography in the study population. A mass was the feature most often associated with breast cancer. Only two of 23 women (8.7%) who were found to have cancer presented with pain as the only feature.

It should be noted in interpreting these findings that the study did not include women younger than 40 years of age, and that a relatively high proportion (18%) had a family history of breast cancer.

(Chalabian and Dunnington, 1998) (203)

This study involved 66 graduating primary care physicians, assessing the link between observed breast examination skills during an objective structured clinical examination (OSCE) and ability to detect lumps in silicone models. The correlation detected between lump detection and examination skills, although statistically significant, was only 0.34. No relationship was found between breast model sensitivity and specificity. Although the authors commented that thorough clinical breast examinations are imperative as they can identify 10% of breast cancers not visible on mammograms (204), no specific manoeuvres or techniques could be recommended.

(Khan and Apkarian, 2002a) (205)

In this study, a modified version of the McGill Pain Questionnaire was administered to 271 women with breast pain but without breast cancer. 134 women had cyclic breast pain and 152 non-cyclic. Cyclical breast pain tended to be a diffuse, heavy ache, most prominent towards the end of the cycle, although may also be severe during menstruation. It may occur in one breast, but commonly in both. However, there are very few studies of women with breast pain in primary care, and the significance of pain as an indicator of cancer is difficult to determine.

(Khan and Apkarian 2002) (206)

This study was a retrospective case controlled investigation into the relationship between breast mastalgia and cancer studying a population of 5463 women aged over 30 attending a New York breast care centre. Of those women, 861 were diagnosed with breast cancer, of whom 141 (16.4%) reported breast pain (mastalgia). Of the 4602 women who did not have cancer, 1391 (30.2%) reported mastalgia. Breast pain was reported as an incidental complaint at first visit to the centre by 1532 (28%) of all the women in the study.

This investigation found that within their study population, women who experienced breast pain were less likely to be diagnosed with breast cancer than those without, regardless of age or other risk factors. Additionally the study found that risk factors associated with breast cancer (age, age of menarche, age at first full term pregnancy, age at menopause, family history, alcohol use) were associated with a decreased frequency of breast pain, with the exception of exogenous hormone use.

Risk Factors

Evidence Statements:

Epidemiological studies have reported a number of risk factors as being associated with an increased probability of developing breast cancer. Such risk factors include: age; family history of breast cancer; age of having first child and use of hormone replacement therapy. (III)

In a woman who presents to a medical practitioner with a palpable breast lump, the presence or absence of any given risk factor has no significant effect on the likelihood of that woman having breast cancer. (III/DS)

There is no evidence that information on risk factors is of use in selecting those symptomatic women who should be referred (III)

Guidelines

(NICE: The Classification and care of women at risk of familial breast cancer 2004) (207).

This evidence based guideline is limited to women over 18 who have not been previously diagnosed with breast cancer. The evidence searches were wide ranging and papers were graded according to NICE specifications, while quality of studies was assessed using modified SIGN checklists.

The guideline states that although most breast cancer occurrences are random, in 16-19% of cases a family history of the disease is identifiable. The probability of a 20 year old woman developing breast cancer by 80 increases with the incidence of breast cancer within her family. With no affected relatives the risk is 7.8%, with one 13.3%, and with two 21.1%(207).

The evidence used in assessing the specific risk factors of breast cancer evaluated by the guideline was of varying quality and a summary of the findings and subsequent recommendations follow.

Family history

Risk increases with the proximity of the relationship to an affected relative, the number of affected relatives and with the decrease in age of those relatives at the time of developing breast cancer. The high risk genes BRCA1 or BRCA2 account for only a small amount of this increased risk. However, the risk of carrying one of these mutated genes is related to the strength of the family history, and risk of breast cancer is increased by their occurrence (BRCA1 60-80% risk, BRCA2 40-80% risk).

Hormone Replacement Therapy (HRT)

The risk of breast cancer is increased and continues to increase in association with the duration of HRT use. Increased risk reduces once treatment is stopped and risk returns to same level as a woman who has never taken HRT after five years. Thus, it was recommended that treatment time is restricted to short term (no definition of short term was given) in women with familial risk, and alternative treatments should be considered and the woman informed of the increased risk.

Oral Hormonal Contraceptives

Evidence concerning ever-use, current use, duration, and cessation of oral contraceptive use is contradictory and inconsistent. Ever-use was not associated with increased risk in breast cancer in women of any age. Findings on current use and duration of use were inconclusive and contradictory as some studies suggested an increase in risk and some did not. A 16% increased risk was observed within the first four years after stopping oral contraceptive use and a 7% increase between five and nine years. After ten years no increased risk was observed. A statistically significant increase in risk was found in women using oral contraceptives prior to their first full term pregnancy (72%). No specific increase in risk was recorded among those with familial risk taking oral contraceptives. One study identified carriers of the

BRCA1 mutation gene as having a 20% increased risk when using oral contraceptives, but no increased risk in carriers of the BRCA2 mutation gene.

Breastfeeding

Breastfeeding has a protective affect against breast cancer, which is proportionate to the total duration of breastfeeding. There is a 4% reduction in risk for every 12 months of breastfeeding and the risk is similar in women with familial risk. It was recommended that women be advised to breastfeed.

Alcohol consumption

Risk increases with alcohol consumption by 7.1% per 10g daily intake and is unaffected by familial risk. It is recommended that information is provided to women with familial risk.

Smoking

Evidence reviewed reached different conclusions ranging from no association of smoking with increased risk of breast cancer, to significant increases in both current or former smokers, with additional particularly high risks in premenopausal women or those who began smoking very early. The guideline concludes that as scientific studies have produced inconsistent findings a relationship is merely speculative.

Weight and physical activity

No specific link between diet and familial risk of breast cancer was found, although moderate exercise was thought to confer a decrease in risk of cancer. However, high BMI was associated with an increase of risk in postmenopausal breast cancer. Thus it was recommended that women are informed of the increase in risk associated with being overweight.

Menstrual/reproductive factors

Menstrual and reproductive factors carry the same risks among women with or without a family history of breast cancer. In both groups of women, older age at first birth and earlier menarche were associated with increased risk.

Risk decreases with the number of live births. It was recommended that the practitioner should provide information about hormonal risk factors.

Secondary studies

(Levine et al, 2001) (193)

This review undertaken by the Agency for Healthcare Research and Quality is outlined in the section dealing with symptoms and signs above. Age was the only risk factor consistently reported in association with symptoms and cancer diagnosis. The influence of family history varies depending on the age of the patient and the closeness of the affected relative(s), the ages at which the relatives developed cancer, the number of relatives with breast cancer, and the number with other gynaecological or other cancers. Women whose mother or sister had breast cancer before the age of 40 had the highest risk (relative risk 2.2, 95%CI 1.5-4.2). HRT was reported as not significantly increasing the risk among women who have a family history.

Risk of breast cancer increases with duration of oestrogen exposure. Women who had an early menarche are at increased risk (before age 12 RR 1.1-1.3), as are those with a late menopause (after age 55 RR 2.0). Women who delay their first child until after age 30 have an increased risk (RR 1.3-1.9). The impact of pregnancy is not well understood, since there is an increased risk for up to 10 years after delivery.

The review did not consider the impact of smoking, diet, alcohol, lactation or genetic factors on risk of breast cancer.

(Collaborative Group on Hormonal Factors in Breast Cancer, 2002) (208)

The authors analysed individual data from 47 epidemiological studies in 30 countries to estimate the association between breastfeeding patterns and childbearing with breast cancer. For women who had never breastfed, the relative risk of breast cancer declined by 3% for each year younger they were

when their first child was born. The relative risk of breast cancer decreased by 4.3% for every 12 months of breastfeeding (not necessarily consecutively) in addition to a decrease of 7% for each birth. The size of the decline in the relative risk of breast cancer associated with breastfeeding did not differ significantly for women in developed and developing countries, and did not vary significantly by age, menopausal status, ethnic origin, the number of births or age when the first child was born. It is estimated that the cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6.3 to 2.7 per 100 women by age 70, if women had the average number of births and lifetime duration of breastfeeding that had been prevalent in developing countries until recently.

Primary studies

(McPherson et al, 2000)(78)

This paper reviews the risk factors for breast cancer in the UK, the findings are summarised in *Table 44* below.

Table 41 Established and probable risk factors for breast cancer

Factor	Relative Risk	High Risk Group
Age	>10	Older people
Geographical location	5	Developed country
Age at Menarche	3	Menopause before age 11
Age at first full pregnancy	3	First child in early 40s
Family history	>2	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight:		
Premenopausal	0.7	Body mass index >35
Postmonopausal	2	Body mass index >35
Alcohol consumption	1.3	Excessive intake
Exposure to ionising radiation	3	Abnormal exposure in young females after age ten
Taking exogenous hormones:		
Oral contraceptives	1.24	
HRT	1.35	
Diethylstilbestrol	2	

12.1.2 Men

12.1.2.1 Key Clinical Question:

Which are the symptoms, signs and other features that raise a suspicion of cancer in a man presenting with a breast abnormality, and those that make cancer less likely as a diagnosis?

12.1.2.2 Evidence Question:

In men attending primary care services with breast symptoms, which symptoms and signs and other features when compared with the “gold standard” are predictive of a diagnosis of cancer; and which symptoms and signs are not?

12.1.2.3 Evidence Statements:

A subareolar mass is the most common presenting sign in men with breast cancer. Less common signs include nipple retraction, local pain, nipple ulceration, discharge or bleeding (III).

In men, breast cancer is more common, but not confined to, those over 50 years of age (III).

There are several risk factors for breast cancer in men, but their significance in estimating the likelihood of cancer among men presenting with symptoms is unclear (III).

Secondary studies

(Giordano et al, 2002) (209)

This is an up to date systematic review. The authors sought articles published between 1942 and 2000, and used CancerLit, Medline and study bibliographies to identify articles. They included studies on the epidemiology,

risk factors, genetics and pathology of breast cancer in men. The review reports the following conclusions.

The incidence of breast cancer in men has remained stable in the past 40 years, and the median age at diagnosis is 68 (compared to 63 in women). However, the disease has been reported in males from ages 5 to 93 years. The incidence increases exponentially with age. Breast cancer in men may be hormonally driven, as in women. The risk factors include: testicular abnormalities (undescended testis, congenital inguinal hernia, orchidectomy, orchitis, testicular injury); infertility; Klinefelter syndrome; positive family history; benign breast conditions (nipple discharge, breast cysts, breast trauma); radiation exposure; increasing age; Jewish ancestry. The rate of gynecomastia in men with breast cancer is similar to the rate in the general population.

Approximately 90% of all breast tumours in men are invasive carcinomas, the remaining 10% being non-invasive (most being ductal carcinoma in situ). Approximately 85% (ranging between 50-97% in different studies) of affected men present with a painless subareolar mass. Other common signs include nipple retraction (10-51%), local pain (4-20%), nipple ulceration (4-17%), nipple discharge (1-12%), and nipple bleeding (2-9%). Men are more likely than women to have a delay between the onset of symptoms and diagnosis. Mammography is reported as being helpful in distinguishing a benign from a malignant lesion, and fine needle aspiration has been found to be sensitive and specific.

No primary studies are included in this evidence review as the systematic review of Giordano et al (209) is recent and comprehensive.

12.2 Investigations

12.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

12.2.2 Evidence Question:

In women attending primary care services with breast symptoms, which investigations when compared with the “gold standard” are predictive of a diagnosis of cancer; and which are not?

What investigations to diagnose a suspicious breast lump are available to primary care practitioners in the UK?

12.2.3 Evidence Statements:

Evidence from studies in Britain and Sweden indicate that decisions on whether to refer women presenting with breast symptoms are commonly made at the first consultation, and without recourse to investigations (III).

There is no evidence that laboratory tests have a role in initial investigation of women presenting with breast lumps in primary care (III).

In some countries, some primary care physicians undertake FNA for cytological examination. However, success in obtaining a satisfactory sample is dependent on the skill of the physician. There is no evidence on the role of FNA in primary care in the UK (IV).

There is no evidence from the UK to suggest that a policy of investigation with mammography and/or FNA accelerates referral to secondary care of patients with cancer. It is possible that use of these investigations would delay referral (IV).

Women presenting to primary care with breast pain and in whom cancer is not suspected but who are referred for a mammogram are unlikely to have a suspicious mammogram. (III)

Background

Established management of women suspected of having breast cancer includes the triple assessment of physical examination, mammography and percutaneous biopsy (also referred to as fine needle aspiration – FNA).

We found very few studies of the role of investigations in women presenting with breast symptoms in primary care. The majority of studies of investigations involved women who had been referred, and since the findings cannot be extrapolated to the population of symptomatic women before referral, these studies have been excluded.

Guidelines

(Austoker and Mansel, 2003).(188)

These guidelines did not suggest any primary care investigations before referral in patients presenting with a breast lump, breast pain, or severe cyclical mastalgia. In the case of nipple discharge in women less than 50 years of age, a test for blood was advised if the discharge is from multiple ducts. Referral was recommended when the test is positive. Other investigations, including triple assessment, were restricted to patients who had been referred, the investigations being carried out by the specialist.

(All Wales Minimum Standards, 2000) (189)

Standard 11 requires that all diagnostic tests are carried out in one visit. The standard related to patients referred to and attending specialist services.

(Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998) (190)

These guidelines were based on a systematic review of evidence (Medline from 1966, Cancerlit from 1985, through to 1996). However, the studies cited were not confined to those involving patients in primary care. Mammography was found to be unlikely to give useful information in younger women, although is more useful from aged mid-30s. The overall level of sensitivity of mammography was reported as possibly no higher than 82% (level III evidence), and therefore a normal mammogram cannot exclude cancer. The guideline indicated that fine needle aspiration can be carried out in office settings, and that cytologic examination should be ordered if the obtained fluid is bloody. Success in obtaining satisfactory samples, however, is operator dependent. The false negative rate in one reviewed study had been 15.2%. When physical examination, mammography and cytology are combined, the diagnosis is likely to be confirmed in 99% of cases in which all three tests are positive; cancer will be found in 0.5% of cases if all tests are negative.

(Royal Australian College of General Practitioners 1997) (210)

These guidelines are reported as based on a review of evidence, although there is insufficient information to judge the extent and quality of the review. The guidelines encourage the use by general practitioners of imaging and fine needle aspiration. Ultrasound is recommended in place of mammography in women under age 35.

Secondary Studies

(Kerlikowske, 2003)(211)

A review of papers found on Medline between January 1966 and March 2003 to determine the most accurate and least invasive means to evaluate an abnormal mammography result and palpable breast abnormality.

This study found that a diagnostic mammography is most helpful in deciding whether a nonpalpable breast lesion should be biopsied but not whether a palpable breast abnormality should be. For palpable masses, fine needle aspiration biopsy or core-needle biopsy were preferred. However in order to determine whether a lesion is a simple cyst and therefore benign, core needle biopsy or needle localisation with surgical biopsy was usually preferred.

Primary studies

(Duijm et al, 1998a) (212)

In a study of 987 women with a painful breast referred to the radiology department of a Netherlands hospital between 1992-1996, follow up was undertaken for two years. The gold standard was a recorded diagnosis of breast cancer during follow up. 84.1% of the sample had been referred by general practitioners. The findings were compared with a control sample of 987 asymptomatic women undergoing a screening mammogram. Four (0.4%) of the women with pain were diagnosed with cancer, in comparison with seven (0.7%) of the controls. Mammograms were classified as suspicious or malignant in only 1.2% of the symptomatic cases.

(Mansson et al, 2001) (213)

This study was undertaken in four primary health care centres in Sweden 1995-1997, and investigated the diagnostic actions of general practitioners in relation to colorectal, pulmonary, breast and prostate cancer. The total patient population in the area served by the health centres was 9556, and 125 women were recorded as presenting with breast problems. In most, no laboratory test had been performed, although 80 mammographies were undertaken, with a yield of three cancers. Seven breast cancers were diagnosed in total, six at the first consultation; one was interpreted as a benign tumour, and six were referred to a surgeon. Two patients had haemoglobin tests, one ESR, and four various other tests not related to breast cancer (e.g. urine dipslide). The study did not indicate whether these

laboratory tests served a useful role in the initial assessment of the patients with breast cancer.

(Mansson and Bengtsson, 1992) (214)

The primary care records of all 62 women with a diagnosis of breast cancer between 1981 and 1983 in Kungsbäcka in Sweden were reviewed. Information was collected about the investigations ordered before diagnosis. The article does not report the number of women who underwent laboratory investigations, but notes that 12 (19%) were found to have an elevated erythrocyte sedimentation rate, eight (13%) had anaemia, and six (10%) had a leucocytosis. However, in another report from this study (Mansson et al, 1999), it was reported that 59 (95%) had a haemoglobin estimation and 57 (92%) an erythrocyte sedimentation rate estimation. The authors concluded that haematology and erythrocyte sedimentation tests did not assist in the diagnosis of breast cancer.

12.3 Delay and Diagnostic Difficulties

12.3.1 Key Clinical Question:

What influence do age, gender, social class and ethnicity have on the differential at presentation?

What diagnostic difficulties do primary care professionals themselves report in determining whether a woman/man who presents with breast symptoms/signs may or may not need urgent referral with suspected cancer?

12.3.2 Evidence Question:

In women attending primary care services with breast symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation of breast cancer?

What diagnostic difficulties do primary care professionals themselves report in determining whether a woman/man who presents with breast symptoms/signs may or may not need urgent referral with suspected cancer?

12.3.3 Evidence Statements:

Delay

There is strong evidence of an association between older age and delay by patients, and strong evidence that marital status is unrelated to delays by patients (III).

There is an association between socioeconomic status and survival (III)

There is moderate evidence for an association with delay by patients with five other factors:

- fewer years of education
- presenting with breast symptoms other than a lump
- not disclosing the breast symptom to another not attributing the breast symptom to breast cancer (III).

Younger age and presentation with a breast symptom other than a lump were strong risk factors for delays by health professionals. There is moderate evidence that ethnicity does not influencing delay by providers. (III)

Diagnostic Difficulties

Primary care professionals report that detection of the possibility of breast cancer is often straightforward, but in some cases is difficult (III).

A past history of benign breast conditions, young age, and presentation without a palpable lump are features that can make the detection of possible cancer more difficult (III).

Primary care professionals' referral decisions are influenced by their own and their patients' anxiety. Past experience of a delayed or missed diagnosis can lower the professional's referral threshold (III).

Delay

The following section addresses the influence that socio-demographic and psychosocial factors have on the women's decision to seek help when confronted with symptoms and signs suspicious of breast cancer. The four that will be considered are:

- Psychosocial factors
- Socio-economic status
- Age
- Ethnicity.

(Sainsbury et al, 1999)(215)

An retrospective analysis of 36,222 patients with breast cancer listed on the Yorkshire Cancer Registry between 1976 to 1995, in order to investigate whether delay in referral from primary care influences survival. Patients were grouped according to time taken from family-physician referral to treatment (<30 days / 30-59 days / 60-89 days and 90> days).

Results demonstrated no evidence that delay up to three months (90 days) adversely influenced survival. From 1976 to 1995 the time from family-physician referral varied very little with a median of 10 vs.13 days. However the time from first visit to until the patient received treatment doubled for the same time period going from 7-13 days. Of the women included in the study, those who presented early and were in less than 30 days actually had significantly worse outcomes ($p<0.001$).

Secondary studies

(Ramirez et al, 1999) (216)

The authors undertook a systematic review of 23 papers to assess the quality and strength of evidence on risk factors for delays by patients and providers. There was strong evidence for an association between older age and delay by patients, and strong evidence that marital status was unrelated to patient delays. There was moderate evidence for an association between patient delay and five other factors: fewer years of education, non-white ethnic origin, presenting with breast symptoms other than a lump, not disclosing the breast symptom to another, and not attributing the symptom to breast cancer. Younger age and presentation with a breast symptom other than a lump were strong risk factors for delays by providers. There was moderate evidence against non-white ethnic origin influencing delay by providers.

Primary studies

A. Papers that explore the influence of more than one factor

(Grunfeld et al, 2002) (217)

This study investigated the influence that women's age and socio-economic status play on delayed presentation. 996 women, randomly selected through the postal address file were interviewed by the authors to elicit their knowledge of breast cancer risk, breast cancer symptoms, and their perceptions of the management and outcomes associated with breast cancer. Older women were particularly poor at identifying symptoms of breast cancer, risk factors associated with breast cancer and their personal risk of developing the disease. Professional women and women classified as intermediate had a greater knowledge of risk factors than women from lower socio-economic groups. 32% of professional and intermediate women reported reduced risk compared to 10-15% of partly skilled and unskilled women, and women who were unskilled or had never worked identified significantly fewer symptoms than the other socio-economic groups.

(Grunfeld et al, 2003) (218)

This study primarily investigated the influence of psychosocial factors but in relation to women's age. The authors recruited a sample of 546 women as the second phase of a previous study (Grunfeld et al, 2002 (217)). All women completed a postal questionnaire about beliefs regarding the symptoms, causes and outcomes associated with breast cancer, attitudes towards help seeking and beliefs about one's ability to seek help. The inability to correctly identify a range of potential breast cancer symptoms was a significant predictor of intention delay in seeking help across all age groups. For women aged 35-54, negative attitudes towards medical help seeking for breast symptoms and a negative belief in one's ability to seek help were additional predictors of intention not to seek help. Holding negative beliefs about the consequences of breast cancer (i.e. that the disease could be potentially

disabling or disfiguring) was found to be an important additional predictor of delay in help seeking among women aged over 65 years.

(Nosarti et al, 2000) (219)

This paper examined the influence exerted by women's symptoms, psychosocial, socio-economic status and ethnicity. The authors interviewed 692 women referred to a London breast clinic to identify factors associated with delay in presentation. Sixty per cent of women with a breast lump presented to their doctor within 27 days from symptom discovery, compared to 34% of those without a lump. Of patients with breast tenderness or pain, 76% presented to their doctor within 27 days from symptom discovery, compared to 62% of those without pain. Thirty-five per cent of the women delayed presentation 4 weeks or more (median 13 days). The most common reason was that they thought their symptom was not serious. Others thought their symptom would go away or delayed presenting because they were scared. Delay was associated with psychiatric morbidity but not age. Median system delay was 18 days. Patients who thought they had cancer and those so diagnosed were seen more promptly (median 14 days). Most socio-demographic factors, including socio-economic status and ethnicity, were non-contributory to delay.

(Nichols et al, 1981) (220)

In this UK study, women with breast symptoms referred to a specialist outpatient department were interviewed to ascertain the interval between first noticing a breast symptom and consulting a doctor. The largest component of delay was patient delay, with 20% of women delaying longer than 12 weeks. Long delays were related to age and symptoms other than lumps.

B. Papers that explore the influence of psychosocial factors

(Burgess et al, 2001) (221)

The authors interviewed 46 women in the UK with newly diagnosed breast cancer to explore the factors that influence general practitioner consultation by women with breast cancer symptoms. The main factors that influenced help seeking behaviour were: the identification the woman made of their symptoms as suggestive or not of breast cancer; their attitudes to requesting an appointment with a general practitioner; their beliefs about the consequences of cancer treatment; the effect of competing events and difficulties that could be prioritised over and above their personal health; and influences or experiences that functioned as triggers to action.

(Burgess et al, 2000) (222)

In this UK study, 158 women were interviewed five months after diagnosis to examine the influence of adverse life experiences and mood disorders on delayed presentation of breast cancer. The study did not identify statistically significant associations between these factors and delay, and suggested that neither adverse life events nor mood disorders in the year before symptom discovery increased the risk of patients with symptoms of breast cancer delaying their presentation to their general practitioner.

C. Papers that explore the influence of socio-economic status

(Malik and Gopalan, 2003)(199)

This is a prospective study of 138 recently diagnosed (within three months) breast cancer patients who had initially presented with breast lump in Pakistan. The majority (85%) of the patients discovered the lump accidentally, 10% were identified by a family physician and 5% as part of regular self examination. These patients took an average of 8.7 weeks to inform members of their family and 17.2 weeks until their first physician visit.

The initial perceptions of the lump included milk clots, trauma, infection benign growth, other and cancer (however only 17% perceived it as cancer). Of those patients included in the study 73 (52.9%) were recorded to have delayed seeking medical advice. The reasons given were; antecedent use of complimentary/alternative therapies (34%), lack of significance attached to the lump (23%), fear of surgery (22%), conflicting personal commitments (7%), fear of cancer (5%) and other reasons (8%).

(MacLeod et al, 2000b) (223)

This was a UK population-based review of the case records of 417 women under 75 with breast cancer. Women living in deprived areas (according to the Carstairs Index) were more likely to present with large, locally advanced cancers or with metastatic disease than those living in affluent areas. There were no major differences in pathological prognostic factors at presentation between socio-economic groups. Although stage at presentation accounts for some of the differences in survival between affluent and deprived women, other unidentified factors adversely affect survival in deprived women.

(Thomson et al, 2001) (224)

The authors analysed two datasets relating to breast cancer patients in Scotland (23,866 women). Survival differences of 8.7% at five years and 10.2% at ten years between affluent and deprived women were observed

across all age groups. No differences were observed in tumour size or nodal status at presentation between the deprivation groups. Although deprived women were more likely to have oestrogen receptor negative tumours, this difference explained only about a third of the difference in survival between affluent and deprived women. Women aged under 65 with non-metastatic disease were more likely to have breast conservation than mastectomy if they were affluent (45%) than deprived (32%); the affluent were also more likely to receive endocrine therapy (65%) than the deprived (50%). However, differences in treatment between affluent and deprived women do not seem to account for their different survival.

(Carnon et al, 1994) (225)

The authors carried out a retrospective analysis of data from a cancer registry within the catchment areas of two large hospitals in Glasgow, and attempted to explain socio-economic differences in survival from pathology and biochemistry records for 1361 women diagnosed with breast cancer. They could find no significant relation between socio-economic deprivation and four pathological prognostic factors at presentation: tumour size, negative nodes, tumour grade, and low oestrogen receptor concentration.

(Schrijvers et al, 1995) (226)

The authors explored the association between deprivation and survival from breast cancer in 29,676 women aged 30 and over. There was a clear gradient in survival that increased slightly with time since diagnosis, with better survival for women from more affluent areas. At all ages, women in the most deprived category had a 35% greater risk of death than women from the most affluent areas after adjustment for stage at diagnosis, morphology and type of treatment. In younger women (30-64 years), the survival gradient by deprivation category cannot be explained by these prognostic factors. In older women (65-99 years), part of the unadjusted gradient in survival can be explained by differences in the stage of disease: older women in the most deprived category were more often diagnosed with advanced disease. Other

factors, so far unidentified, are responsible for the gradient in breast cancer survival by deprivation category.

(Quinn et al, 2001) (17)

Data from National Statistics provide some information about incidence and survival according to level of deprivation. In 1993, there was a negative gradient in the incidence of breast cancer by Carstairs deprivation category, the rate being about 30% higher in the most affluent groups. In contrast, mortality was not related to deprivation, implying that survival is better in the more affluent groups. The gap in survival between deprived and affluent groups in the 1980s was 6% at one year after diagnosis, and 9% at five years.

(MacLeod et al, 2000) (227)

The authors reviewed hospital and general practice case records of 821 women with invasive breast cancer. Women living in affluent areas did not receive better NHS care for breast cancer than women in deprived areas. Admissions to hospital for problems not related to breast cancer were more common in those living in deprived areas, as also were the number of consultations with their general practitioners in the two years following diagnosis.

D. Papers that explore the influence of age

(Kroman et al, 2000) (228)

The authors undertook a retrospective cohort study in Denmark based on 10,356 women who were less than 50 years old when diagnosed with breast cancer to investigate the effect of young age on prognosis, and the influence of tumour staging and treatment on such association. Young women with low risk disease who did not receive adjuvant treatment had a significantly increased risk of dying than the women who did, and the risk was increased with decreasing age at diagnosis. This increased risk remained when women

were grouped according to presence of node negative disease and by tumour size.

E. Papers that explore the influence of ethnicity

We have not found any relevant papers that exclusively investigated the influence of ethnicity in delayed presentation of women with breast cancer since the publication of the systematic review by Ramirez et al (1999) (216). Most recent identified studies that explore this factor have studied the experiences of African-American women. Caution is required when extrapolating results from these studies to England and Wales because of the different characteristics of the UK and US health care systems.

(Velikova, 2004)(229)

This retrospective UK study examined population based data on 16,879 women with breast cancer diagnosed between 1986 and 1994 with an aim to evaluate patient and provider delays of South Asian patients. Of those included in the study, 120 (0.7%) were South Asian and the standardised incidence rate ratio of South Asian with non-South Asian was 0.56 (95% CI 0.46-0.66).

Asian women were significantly younger than non-Asian at the time of diagnosis with a greater proportion being diagnosed before 50 years of age. The mean age at diagnosis of Asian and non-Asian was 49.7 years compared to 62 years respectively. A significantly higher proportion of South Asian patients presented with tumours larger than 2cm. Asian patients had a longer period of delay between symptom onset and presentation to a general practitioner with a median of 61 days compared to 31 days for non-Asian women which could not be explained. However no significant difference in delay was recorded between general practitioner visit and first hospital visit.

(Coates, 1992)(230)

This study collected retrospective data over 410 black women and 325 white women who were newly diagnosed with invasive breast cancer in 1985 or 1986 in the US in order to evaluate racial differences in delayed presentation.

The study found that black women were diagnosed more commonly at later disease stage. They were twice as likely to be diagnosed with Stage IV breast cancer and one and a half times as likely to be diagnosed with Stage III than white women. Additionally black women were only half as likely to be diagnosed with Stage I breast cancer. Black women were also found to be twice as likely as white women to be diagnosed with tumours larger than 5cm.

There was a low but statistically significant (15%) difference in the rate with which black women obtained initial consultation compared to white women and the median time between symptom recognition and consultation was 16 days for black women and 14 days for white women. The study concluded that although there were significant differences in delay, the differences were small and therefore unlikely to account for differences in survival rates.

(Bassett et al, 1986) (231)

This study used data from the Western Washington cancer surveillance system, and examined the influence of social class and race as predictors of survival in breast cancer in 1506 women in the first 11 years after diagnosis. Although survival was poorer among African-Americans, in regression analysis, the difference between them and whites was largely explained by socio-economic status.

F. Paper that explore the influence of where people live.

(Robertson, 2004)(232)

This study evaluated data from 1097 patients with breast cancer and 1223 with colorectal cancer in the UK between January 1997 and December 1998

to assess delay in diagnosis in those living further away from treatment centres.

The geometric mean time from presentation to treatment was 42 days. However, it was found that women living further away were treated faster than those living closer ($P=0.011$) although multilevel modelling discovered that this may be attributable to then receiving earlier treatment at hospitals other than the cancer centres. This study also found that older people were treated more quickly but that deprivation was not a significant factor. Under multilevel model evaluation only one organisational variable remained significant: that treatment was quicker for those referred to general hospitals than for those referred to cancer centres, and quicker still for those referred to private hospitals.

Diagnostic Difficulties

In a comparison of survival of women with breast cancer in 12 countries in Europe, the lowest five year survival rates were in Spain, the UK, Estonia and Poland (55-64%) (Sant et al, 1998 (233)). In the period 1985-1989, one year and five year survival rates in the UK had improved, but were still below the European average (by 3-4% and 6-9% respectively), although were higher than in Slovakia, Poland or Estonia (Quinn et al, 1998 (234)). Variation in survival between regions in the same country were observed, a finding that may in part be related to socio-economic indicators.

However, survival rates in the UK have continued to improve, and recent UK data indicate that five-year survival is now 75.9% among women who present with symptoms [(www.cancerresearchuk.org/aboutcancer/statistics/survival). (<http://www.doh.gov.uk/nhsperformanceindicators/hlpi2002/NationalDocument.pdf>)], and 94.1% among women who have cancer detected at screening (<http://www.cancerscreening.nhs.uk/breastscreen/publications/ba00-01.html>).

No relevant, good quality systematic reviews were identified.

Primary Studies

(Ruston, 2004)(33)

This study draws information from 85 women newly referred to four specialist breast clinics and their referring general practitioners in the UK in order to understand the referral decision-making process. The data was collected through semi-structured interviews with the patients and then separately with their matched doctor.

The study reported that the general practitioners felt under pressure from a 'cloud of medical litigation' that surrounds breast cancer and symptoms associated with it to refer all cases. Only 25 of the 85 cases reported trying to deal with the patient in primary care. There were three main categories identified where general practitioners would refer, the first that in the professional opinion of the practitioner the symptoms were indicative of cancer and urgent referral required. The second was that the nature of the lump was 'sinister' and referral decision was affected by patient anxiety, family history and medico-legal concerns over the implications of not referring the patient. The third category was that the practitioner felt that the symptoms were probably benign and referral was based on patient anxiety and concern over medico-legal consequences.

(The Bridge Study Group, 2002) (235)

The BRIDGE study evaluated the effects on patient management of breast disease guidelines issued to all general practitioners in the UK in January 1996. The practices in the BRIDGE study were randomised to receive either the breast lump or the breast pain guideline. During the study, general practitioners and practice nurses in the participating 34 practices were invited to take part in discussion seminars. The views of the participants were sought on the management of women with breast symptoms, the problems encountered, and influences on decisions about treatment. The transcripts of the recorded discussions were analysed to identify primary health care professionals' views about patients presenting with breast problems. Referral

decisions emerged as an overarching theme, which set the context for discussions with participants about the nature of clinical presentation.

The “easy” presentation was characterised by a single problem of the breast, where the clinical findings did not conflict with the history, in a woman with no or few preceding breast problems. The “difficult” presentation usually concerned a woman who had presented on numerous previous occasions, and who may have had previous investigation or surgery. Many practitioners expressed considerable uncertainty in establishing diagnoses for patients with breast symptoms on clinical grounds alone. For example, there was a reluctance to make an essentially histological diagnosis on the basis of palpation.

Doctors reported high levels of anxiety running through these consultations, not all confined to the patient. This sometimes resulted in cautious management strategies, perhaps with negative consequences for patients who were exposed to radiation during mammography, but it calmed the general practitioner’s own anxieties. The high level of patient and doctor anxiety about breast symptoms appeared to be a pervasive context for managing women presenting with these conditions. These levels of anxiety reflected underlying perceptions of risk, mainly of breast cancer. There are medico-legal issues about the liability for a delayed or missed diagnosis of breast cancer. Other comments however, suggested that both doctors and patients overestimated the predictive value of symptoms for breast cancer and also did not relate presentation and diagnosis to the overall natural history of the condition.

There was variation between general practitioners about the effects of their past experiences on current practice. Some were open about the fact that adverse previous experiences had had a major impact on subsequent referring behaviour. For example, a young woman with cyclic breast pain, who later had cancer, reduced a general practitioner’s referral threshold. Others highlighted a change in clinical practice resulting from having previously missed a diagnosis. For instance a lump was only suspected as being

cancerous when a patient returned with the same complaint, and a lymph node was detected in the axilla after a more thorough examination. There was particular concern about “atypical” presentations, especially those in younger women or those that had culminated in a patient’s death. A case many years previously sometimes continued to have a strong effect on a clinician’s practice.

Risk factors were mentioned frequently, especially a family history of breast cancer. A positive family history was seen as a factor likely to raise anxiety in a woman presenting with a breast problem, and make it more difficult for the general practitioner to reassure her.

The availability and use of investigations in specialist clinics may undermine attempts to rationalise referrals. General practitioners do not deny the need to assess patients, but on occasions they view it as legitimate to arrange referral purely for reasons of reassurance. These general practitioners may be resistant to changing their clinical practice as they feel that they are making ‘safe’ choices.

Management of breast cancer is often complex and is an area in which general practitioners do not feel they have special skills. A single, and often atypical, case may have a profound influence on the way general practitioners manage their patients. Decision making about referral is often a consequence of a negotiation between patient and doctor. Attempts to modify clinical management of women presenting with breast symptoms must take account of these contextual issues, especially the high levels of patient and doctor anxiety.

(Watson et al, 2002) (71)

This cluster randomised controlled trial of educational interventions on general practitioner management of familial breast and ovarian cancer involved 688 general practitioners in 170 UK practices. Group A were provided an information pack and in-practice educational session, group B were mailed an

information pack, and group C received no intervention at all. All general practitioner referral letters between March 1999 and December 2000 were audited and classified as appropriate or inappropriate referral.

The appropriateness of referrals improved among general practitioners who either received the guidelines alone (68.7% of referrals appropriate), or reinforced with an educational session (75.0% appropriate). In the group that did not receive the guideline or any other intervention, only 52.6% of referrals were judged appropriate.

(Burgess et al, 1998) (236)

In an interview study of 185 patients referred to a London breast clinic, referral did not occur at the first general practitioner consultation in 32 (17%). Delayed referral was observed more frequently among patients who were not aware of a lump at the time of presentation to the general practitioner (accounting for 44% of all cases of general practitioner delay). Patients experiencing general practitioner delay were younger (49 years vs. 55 years).

(McLeod et al, 1999) (237)

In this New Zealand study, 30 general practitioners were interviewed in depth to identify the key issues relating to the early detection and diagnosis of breast cancer in primary care. Following the interviews, a postal survey of a national random sample of 639 active general practitioners was undertaken, of whom 524 (82%) returned completed questionnaires.

The general practitioners reported that they were limited in their management of symptomatic women by the availability of services such as mammography and fine needle aspiration, and access to specialist breast surgeons or clinics. In some isolated rural communities, distance to services was a limiting factor. Some general practitioners used investigations to confirm the presence of a lump, or the nature of a lump. In the postal survey, 137 (27%) general practitioners personally aspirated cysts and 39 (8%) personally performed fine

needle aspiration for diagnostic purposes. Most considered referral should occur either when a lump was palpated or after abnormal test results, although would refer women over aged 50 more promptly. In younger patients, recall and review were more likely.

Risk was viewed as associated with family history, although the definition of family history varied between respondents. There was a tendency to over estimate the impact of a first degree relative with breast cancer on the risk of cancer.

The key area of difficulty was reported as being the management of young women with lumpy breasts. Concern about the possibility of missing a malignant lump had to be balanced with the risk of causing unnecessary worry. Some general practitioners requested more information on the management of breast pain and nipple discharge.

12.4 Support and Information needs

12.4.1 Key Clinical Question:

What are the relevant patient vulnerability factors? These factors concern the psychological and social factors that influence the patient's ability to manage the consequences of referral for suspected cancer.

12.4.2 Evidence Question:

In women attending primary care services with breast symptoms, which patient vulnerability factors, when compared with patients without vulnerability factors, are associated with the need for psycho-social support; and which are not?

12.4.3 Evidence Statement:

There is little evidence about the support and information needs of women at referral. Before diagnosis, women are anxious and focused on quick referral and diagnosis (III).

General recommendations about the support and information needs of patients undergoing referral for suspected cancer are included in Chapter Seven. This section is confined to a consideration of the particular needs of women being referred with suspected breast cancer. There are very few studies of the needs of women suspected of having breast cancer at the time of referral, although many more studies have been undertaken relating to the time of diagnosis and after diagnosis. We discuss below a review that drew on studies undertaken at or after diagnosis, and also include information from the small number of studies that do consider the stage of referral.

Secondary studies

(Centre for Reviews and Dissemination, 1996) (232)

An Effective Health Care bulletin by the Nuffield Institute for Health and NHS Centre for Reviews and Dissemination (1996) offers a review of relevant trials that explore the information and communication needs of patients with breast cancer, as well as the psychosocial support required.

Information giving

The most common complaints by patients were about poor communication and inadequate information. Focus groups of patients revealed that they wanted information in both verbal and written forms about their cancer, treatment options, the likelihood of treatment success and possible side effects. Patients who are given more complete information showed greater satisfaction without an increase in anxiety.

Studies of consultations suggest that patients and their doctors may disagree about the adequacy of information given. Patients often feel they are not given sufficient information, while doctors tend to overestimate the amount of information they provide. Younger, better educated women, and those with better prognoses, tend to get more detailed information. Patients are likely to get more complete information when it is given in a structured way. They consistently find audiotapes of their consultation and information booklets about treatment helpful (grade of evidence range I-IIc).

Participation in decision-making

The fact that women want to be properly informed does not, however, imply that they want to be responsible for the final treatment decisions. The degree to which women wish to take an active role in decision-making varies between individuals and is affected by age, education and other social and cultural factors.

One study exploring the effects of choice between mastectomy and breast conservation surgery suggested that offering such a choice could cause distress (grade IIA). Other studies reported that a significant proportion of women found the process of making a choice problematic (grade IIA and IIC).

Psychosocial support

The bulletin identified 13 studies that assessed the effects of a range of psychotherapeutic interventions and also two critical reviews of the literature. These studies showed that psychotherapeutic counselling and educational interventions can improve quality of life and may possibly improve immune function and increase life expectancy. In general, interventions that focussed on past problems, as in the psychoanalytic model, were not found to be effective, whereas those that dealt with the woman's current problems were more likely to be helpful. A more definitive statement about the impact of psychosocial interventions was not possible because of the poor quality of the studies, which were often small and poorly controlled. The multiplicity of types of intervention and outcomes made comparisons between studies difficult.

Cognitive/behavioural interventions

Cognitive/behavioural interventions, including psychotherapy, relaxation training, systematic desensitisation, guided imagery, pain control training, biofeedback and physical exercise, have mainly been used to reduce side-effects of cancer therapy such as nausea. They have been assessed in 21 RCTs. 16 of these studies demonstrated some degree of benefit, while the rest were equivocal.

Effectiveness of follow-up policies

The bulletin also reviews trials that explore the effectiveness of different follow-up strategies. Two RCTs from Italy and one from Britain compared general practitioner-based with hospital follow up. Results from both trials suggested that patients followed up by their general practitioners experience the same quality of

life as those cared for by specialist clinics, and that general practitioner follow-up was acceptable to both patients and general practitioners.

The provision to women of a contact number for the breast care nurse has been shown to lead to better quality of life and lower levels of psychological and physical morbidity than either routine care or support from a local voluntary agency.

(Centre for Reviews and Dissemination 2002) (192)

The Service Guidance Evidence review did not identify trials of interventions to improve communication between professionals and patients leading up to referral.

Primary Studies

We have very little evidence on need for information and support of women who are referred. There are studies of the reasons for delay in presentation of symptoms, and in reaction to investigation and diagnosis (Oktay, 1998), but the needs of women who are referred have not been adequately studied.

(Breakthrough Breast Cancer 2002) (238)

A qualitative study involving individual and group interviews was undertaken and did consider this question. Women had different levels of knowledge about breast cancer. The pre-diagnosis stage was distressing because of fear; women were extremely sensitive to what was said to them and how health professionals behaved. The focus at this stage was on quick referral for testing and diagnosis. Although no recommendation from the study dealt specifically with initial presentation and referral, it was recommended that women be given clear

expectations of services. Highlighted in the study as particularly beneficial was 24-hour access to information, advice and psycho-social support pre-diagnosis and beyond and, in particular, encouragement to use such services.

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