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All efforts have been made to ensure the accuracy of information contained herein. However, errors may persist and clinical knowledge is frequently changing.

"A Systems Approach to Cancer" is a general guide for students and should not be used to inform the diagnosis or management of any individual patient.

Professor Yvonne Carter
(1958-2009)

Yvonne Carter was Dean of the Warwick Medical School from 2004 until July 2009 when she took early retirement due to ill health. Yvonne had fought a long battle with breast cancer and sadly passed away on 20th October 2009. She applied a tremendous personal energy to her research career as well as helping develop the first graduate-entry medical school in the United Kingdom. Her death from breast cancer is a sad illustration of the continued importance of this disease.

The current book – written largely by Professor Carter's students – combines her interests in research, publication, and the sharing of knowledge with future generations.

We hope she would have approved of our efforts in producing this volume.

DM   DB   BS

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Preface

Doctors have a duty to teach and share information. This applies at all levels of the medical hierarchy: from consultants supervising trainees to house officers supporting students on the wards. But the duty to share does not stop at teaching; medicine thrives on collaboration. Doctors collaborate with medical colleagues, allied health professionals, and with patients in every consultation.

A Systems Approach to Cancer represents collaboration between academics, clinicians, and student doctors. It addresses cancer – a disease which can only ever be beaten by collaborative partnerships, initiative, and commitment from the next generation of health professionals.

This book stands to achieve three goals. First, it will encourage students to take control of their own learning. Studying medicine requires a high degree of independence and students should not be afraid to think laterally when they perceive a deficit in existing study resources. Second, it demonstrates that genuinely useful outcomes can arise from students and teachers talking to, and working with, one another. Finally, it adds an additional resource – uniquely informed by the undergraduate perspective – to student textbooks on cancer. I wish the editors every success in realising these ambitions.

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Abbreviations

5-FU	5-fluorouracil
AAH	Atypical adenomatous hyperplasia
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
AP window	Aortopulmonary window
APC	Adenomatous polyposis coli (oncogene)
ATP	Adenosine triphosphate
BAD	British Association of Dermatologists
BAP	Benzo-a-pyrene
BCC	Basal cell carcinoma
BMA	British Medical Association
BTS	British Thoracic Society
BMI	Body mass index
BRCA	Breast cancer (oncogene)
CA125	Cancer antigen 125
CBT	Cognitive behavioural therapy
CEA	Carcino-embryonic antigen
CIN	Cervical intra-epithelial neoplasia
CML	Chronic myeloid leukaemia
CO_2	Carbon dioxide
COCP	Combined oral contraceptive pill
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
CT	Computed tomography
CYP1A2	Cytochrome P-450
DCIS	Ductal carcinoma *in situ*
DNA	Deoxyribonucleic acid
DTIC	Dacarbazine
ECM	Extracellular matrix
EGF	Epithelial growth factor
EGFR	Epithelial growth factor receptor
EMR	Endoscopic mucosal resection
EORTC	European Organization for Research and Treatment of Cancer
FAP	Familial adenomatous polyposis coli
FDG	18F-deoxyglucose

FIGO	International Federation of Gynecology and Obstetrics
FISH	Fluorescent *in situ* hybridisation
FNAC	Fine needle aspiration cytology
FOBT	Faecal occult blood testing
GALT	Gut associated lymphoid tissue
GORD	Gastro-oesophageal reflux disease
GSF	Gold Standards Framework
GVHD	Graft versus host disease
HER-2	Human epidermal growth factor receptor
HGD	High grade dysplasia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNPCC	Hereditary non-polyposis colorectal cancer
HPV	Human papilloma virus
HR	High risk
HRT	Hormone replacement therapy
IARC	International Agency for Research on Cancer
ICT	Intracavitary brachytherapy
IMA	Inferior mesenteric artery
JAK	Janus kinase
LCIS	Lobar carcinoma *in situ*
LGD	Low grade dysplasia
MAOI	Monoamine oxidase inhibitor
MAPK	Mitogen-activated protein kinae
MM	Malignant melanoma
MMP	Matrix metalloproteinase
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NCHSPCS	National Council for Hospice & Specialist Palliative Care Services
NICE	National Institute for Health and Clinical Excellence
NMSC	Non-melanoma skin cancer
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small-cell lung cancer
OUP	Oxford University Press
PDT	Photodynamic therapy
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
Ph	Philadelphia (chromosome)
PPC	Preferred place of care
PPI	Proton pump inhibitor
QOL	Quality of life
RB	Retinoblastoma

RGP	Radial growth phase
RNA	Ribonucleic acid
SCC	Squamous cell carcinoma
SCJ	Squamocolumnar junction
SCLC	Small-cell lung cancer
SH	SRC homology domain
SMA	Superior mesenteric artery
SRC	Sarcoma
SSRI	Selective serotonin reuptake inhibitor
STAT	Signal transducer and activator of transcription
SVCO	Superior vena cava obstruction
TGF-ß	Transforming growth factor ß
TNM	Tumour, node, metastasis
TS	Thymidylate synthetase
TZ	Transformation zone
UK	United Kingdom
UVA	Ultraviolet A
UVB	Ultraviolet B
UVR	Ultraviolet radiation
VEGF	Vascular endothelial growth factor
VGP	Vertical growth phase
WHO	World Health Organization
WLE	Wide local excision

Molecular Pathology of Cancer

Alan Morris
DPhil

Cancer is a disease in which normal cells, over a period of time, cease to behave in an orderly and controlled manner. Instead, they grow in an unregulated manner, fail to do the jobs they are supposed to do, and migrate from their proper homes to other sites of the body. This is the process of carcinogenesis. Observations over many years, both clinical and experimental, indicate that carcinogenesis is a multistep process with evolution by stepwise changes towards an ever more malignant phenotype. These changes always involve alterations in genes: activation or inactivation of gene expression, or alterations in gene sequence resulting in changes to the functioning of its protein gene product. These genetic alterations may be relatively small scale, large as in deletion of a region of a chromosome, or may not involve sequence changes at all. These epigenetic changes most commonly involve methylation of the bases of the DNA of a gene so that it is not transcribed into messenger RNA. The result is gene silencing.

Many genes may be subverted in a cancer although there may be relatively few (five or six) key alterations. One of these may be inherited, resulting in an accelerated process of carcinogenesis in syndromes such as familial adenomatous polyposis coli (FAP) in which the key gene *apc* is mutated. However, most alterations occur in somatic cells. Cancer almost always starts with a single cell with a mutation in a single gene which may lead to increased cellular division. As the cell proliferates, further changes may occur in individuals of its progeny leading to greater growth advantage, loss of function, and migration: hence the stepwise progression. Factors which stimulate cell division, such as exposure to irritants (*e.g.* tobacco smoke) also favour carcinogenesis, but the main stimuli are genotoxins which damage DNA. Factors which drive carcinogenesis are collectively known as carcinogens. Most prominent are chemical carcinogens of one sort or another present in the environment, but there are endogenous carcinogens, within the organism, such as reactive oxygen species which are genotoxic, and hormones which drive cell division.

That somatic genetic change results in cancer was first postulated by Boveri who noted that the chromosomes of cancer cells were often disorganised. We have now identified many genes which are altered in cancer, and usually the roles in cancer of their protein products are understood. Hence we can describe the molecular pathology of cancer in some detail. The following sections outline the molecular pathology of cancer with examples of the most relevant genes/proteins. Most of the discussion will be about carcinomas, derived from epithelial cells, since these comprise the majority of cancers.

TARGET GENES IN CANCER

A bewildering number of genes are involved with cancer. One distinction is that some are activated in carcinogenesis – oncogenes – whilst others are inactivated – tumour suppressor genes. This is not in fact terribly useful because it tells us little of the function of the genes. Hence it is probably better to think of these genes in terms of the particular stage or process in carcinogenesis that they affect. A functional classification of cancer genes could be into those that affect:

- mutation
- cell proliferation
- cell death
- angiogenesis
- cell position control and motility (metastasis)
- immune responses

These phenomena collectively comprise carcinogenesis.

Mutation

Failure of mechanisms to control gene mutation leads to genetic instability and so mutation in other genes more directly involved in carcinogenesis. It is increasingly thought that the acquisition of genetic instability (also known as the mutator phenotype) underlies cancer.

Mutation is caused by damage to DNA: a chemical such as benzo-a-pyrene (BAP, present in tobacco smoke) or aflatoxin (a mould metabolite in mouldy grains) combine with DNA and, by disrupting DNA replication, cause mutation. These compounds often require metabolic activation via oxidative process before they can interact with DNA. One important enzyme for this is the cytochrome oxidase

CYP1A2 which is present in elevated levels in the lungs of smokers and so there is augmented activation of BAP.

Damage to DNA can be repaired. This depends first on the damage being recognised and then the activation of enzymes that repair damage. The nature of the damage of course determines the nature of the repair systems, *e.g.* single-strand or double-strand breaks. One gene frequently altered in cancer is involved in DNA repair: *p53* ("Guardian of the Genome") is normally activated when DNA damage is sensed and sets off a process resulting in repair or, if this is not possible, cell death. Inactivation of *p53* is one of the commonest events in cancer. The well-known genes *brca1* and *brca2* whose mutation results in breast cancer are both involved in repair of double-strand DNA breaks. It appears that *brca* genes are not often mutated in somatic cells but there is evidence they are susceptible to gene silencing which may be common in sporadic (*i.e.* not inherited) breast cancers. Failure to repair mismatched bases in the microsatellite instability (MSI) variant of large bowel cancer is due to somatic loss of mismatch repair (MMR) genes *hmlh1* or *hmsh2* whose mutation is inherited in the Lynch syndrome.

Cell proliferation

Proliferation of mammalian cells is controlled through external factors and through internal check points governing progression of the cell through the division cycle (G1, S, G2 and M: Gap 1, (DNA) Synthesis, Gap 2 and mitosis respectively). Failure of these control mechanisms results in unlimited cell proliferation, one of the hallmarks of cancer.

Growth factors The external factors may be diffusible (*e.g.* growth factors) or may be associated with the extracellular matrix (ECM). Mammalian cells do not divide in the absence of these factors. Growth factors are usually positive, *i.e.* they drive proliferation, although there are factors which inhibit proliferation. All act on cells via more-or-less specific receptors. Diffusible factors may be polypeptide (*e.g.* the classical growth factors such as epidermal growth factor, EGF) in which case the receptor (*e.g.* the EGF receptor, EGFR) must be on the cell surface. Alternatively they are steroids (*e.g.* the oestrogens) which, being lipid-based, can enter the cell in seeking their intracellular receptors.

The polypeptide growth factors, upon binding their receptors, dimerise them and trigger signalling pathways which result in the expression of genes whose

products drive cell division. One of the earliest described oncogenes, *ras*, which is mutated in about 40% of human cancers, plays a key role in signalling in response to polypeptide growth factors. It is a molecular switch which, when in the "on" position, transmits the signal down the pathway. The *ras* mutations which occur in cancers result in the switch being permanently on. The receptors for the polypeptide growth factors may also be altered: the main example of this is increased expression in breast cancer of *her-2* due to amplification (multiple copies) of the gene. Since there are then many copies of the HER-2 receptor in the breast cancer cell membrane, these dimerise in the absence of the growth factor, so activating the signalling pathway. The pathway itself comprises a number of protein kinases (*i.e.* enzymes that with ATP phosphorylate OH containing residues in proteins) and several of these may be activated in cancer. The best known example is the activation in chronic myeloid leukaemia of the ABL kinase through translocation generating the Philadelphia chromosome. Another is *braf,* activated in melanoma.

Steroids bind to their receptor in the cytoplasm which then migrates to the nucleus to activate genes for cell proliferation. Many steroid-dependent cancers will progress to steroid independence: the molecular basis for this is not well characterised.

One of the genes activated by the growth factor pathway, *myc*, is regarded as an oncogene and plays a major role as a transcription factor in the activation of a range of genes. However, its up-regulation seems to be always secondary (*e.g.* to growth factor signalling) with few exceptions, *e.g.* Burkitt's lymphoma where it is activated by translocation. One example of a negative growth factor is TGF-β whose receptor is often deleted in the MSI variant of bowel cancer mentioned previously (p3).

Cell proliferation is also controlled through a family of transmembrane proteins, the heterodimeric integrins. In normal epithelial cells these are organised into focal adhesion plaques on the basal aspect of the cell. They interact with the ECM largely through the tri-peptide motif Arg-Gly-Asp which is present in many proteins of the ECM. Inside the cell, integrins are linked to the cytoskeletal system and are thus involved in cell shape and cell motility. Additionally they are associated with signaling pathways which interact with growth factor pathways and so, in a complex fashion, control growth and death of the cell. Some integrins bind to receptors on other cells, *e.g.* leukocytes binding to activated endothelial

cells. Integrin expression, both quantitatively and in the organization of the adhesion plaque, is often disturbed in cancer.

Cell cycle check points There are two main call cycle check points, G1 before S and G2 before M. The importance of these is bound up with control of DNA damage: if there is significant unrepaired damage, the cell will stop cycling and die, so removing the risk of a mutated cell surviving and developing into a cancer. Failure of check points, by allowing proliferation of DNA damaged cells, contributes indirectly to genomic instability. Not surprisingly, mutations in genes whose products are involved with the cell cycle frequently occur in cancer.

Chief in the G1/S checkpoint is the RB system located within the nucleus. This consists of a protein RB encoded by *rb* (from retinoblastoma, the disease in which this suppressor was first characterised), and a range of other proteins whose role it is to modulate RB function. Very briefly, in early G1, RB is *under*phosphorylated and binds transcription factor E2F; during G1 it is phosphorylated by a protein kinase. It then releases E2F which activates genes whose products are responsible for DNA synthesis. If there is DNA damage, *p53* is activated which in turn induces the expression of *p21* which inhibits phosphorylation so DNA is not replicated. Another inhibitor of phosphorylation is P16. Loss of RB, P21, P53, and P16 all lead to failure of the G1 checkpoint, as frequently seen in cancer.

The G2/M checkpoint similarly involves control through phosphorylation of proteins involved in triggering mitosis. Again, P53 and P16 are important in this process.

Cell death

Apoptosis Apoptosis, or programmed cell death, is a physiological means for removing unwanted cells. It may originally have evolved as a means for re-modelling tissues during embryogenesis but is also important in normal tissue homeostasis to maintain a balance with cell proliferation. Perhaps more importantly, apoptosis deletes cells which are in some way damaged, for example infected with a virus or DNA damaged. There are two pathways triggering apoptosis, one cell surface receptor mediated (extrinsic: this is important, *e.g.* in killing virus-infected cells by cytotoxic T cells), the other developing in response to DNA damage (intrinsic). In the intrinsic pathway, P53 is again involved. It induces expression of pro-apoptotic members of the BCL-2 family of proteins and blocks

anti-apoptotic proteins (including BCL-2 itself). The pro-apoptotic BCL-2 family members, *e.g.* BAX, cause the mitochondrial membrane to break down. The consequent release of Cytochrome C results in the activation of cytoplasmic proteases known as caspases which degrade the cell in an ordered manner (hence "programmed") to generate membrane-bound apoptotic bodies which are phagocytosed by neighbouring cells. The protein BCL-2 itself blocks the process at the level of the mitochondrial membrane.

Senescence As we are mortal, so are our cells. It was noted many years ago by Hayflick that "normal" human fibroblasts divide a limited number of times *in vitro* before becoming senescent – ceasing division and showing marked changes of morphology – at the "Hayflick limit". It is now known this is due to the erosion of the ends of the (linear) DNA molecules. The DNA replication complex is unable to go to the end of linear DNA, and the ends are protected by structures comprised of tandem repeats of a short sequence of DNA at the ends of each chromosome, known as telomeres. When the telomere becomes too short, DNA replication stops. Germ line cells, when they divide, replace the missing telomere repeats by means of the enzyme telomerase but most somatic cells lack this enzyme, hence mortality. Cancer cells are immortal, or at least able to divide much more than normal cells. This is because, in nearly every cancer, the telomerase system is re-activated.

Angiogenesis
Without an independent blood supply, a tumour cannot grow beyond a few micrometres. The physiological stimulus for angiogenesis is ischaemia which stimulates the production of vascular endothelial growth factor (VEGF). This drives the growth of new capillaries. Cancers seem to take off when they undergo the "angiogenic switch", so acquiring the ability to produce VEGF constitutively. Other factors are involved but VEGF is the key. Similarly, lymphangiogenesis occurs. However, the formation of larger vessels; arterioles and venules, does not depend on VEGF and so is not a typical feature of angiogenesis. As a result, angiogenesis generates fragile capillaries, the blood supply remains poor and the tumour centre can become necrotic.

Metastasis

Metastasis is a complex process involving several steps: detachment from neighbouring cells; digestion of the ECM to allow migration, movement, entry into the circulatory system either via capillaries or lymphatics (intravasation), survival in the circulatory system, extravasation, and proliferation at the new site. Some normal cells do all these things, *e.g.* leukocytes move around the adult body and cellular migration is a key function in embryogenesis and wound healing. But in cancer, cells which would normally stay put acquire a pathological wanderlust.

Adhesion and detachment The basal aspect of epithelial cells are attached to the ECM by integrins and to each other by tight junctions and adherent junctions forming continuous belts on the lateral face (near the apex), joining the cells sideways. Tight junctions are what they say they are: they control diffusion between the cells of an epithelial sheet (*e.g.* in the bowel) and also prevent mixing of the apical and basal membranes, so maintaining the polarised nature of the cell. Adherent junctions are strong, providing the "glue" for holding the sheet of cells together.

Tight junctions are comprised of several membrane proteins amongst which the most prominent are the claudins. These form polymeric strands within the cell membrane which bind to those in adjacent cells, hence forming a tight junction. Claudin expression is often changed in metastatic cancer, most frequently increased. This may be an epiphenomenon as claudin expression is controlled by growth factor signalling. Likewise, adherent junctions are complex: however there is a clear-cut connection with metastasis and other disregulations in cancer cells. There are three important players: E-cadherin, APC, and β-catenin one of which is frequently involved in carcinogenesis. E-cadherin is a transmembrane protein whose extracellular domain binds tightly to E-cadherin on adjacent cells. Its intracellular domain binds β-catenin which, if it dissociates, binds to APC and is degraded. If E-cadherin or APC are defective, β-catenin is free to diffuse into the nucleus where it activates the expression of *myc*, cyclins and metalloproteinases. Hence disruption of this system allows both detachment of the cell and further activation of cancer-related cell functions.

Digestion of ECM The proteins of the ECM, of which collagen is the most prominent, provide a barrier to cell migration. They are digested by a family of proteases, the metalloproteinases (MMPs), so-called because they have a Zn ion

at the active site. There are over twenty MMPs, many of which are up-regulated in invasive cancers.

Movement Cells move by extending pseudopodia at the leading edge which bind the ECM via integrins. These are attached to the (actin) microfilament system; they signal shortening of the filaments and simultaneous release of the integrins at the trailing edge so the cell moves forward. Signals which stimulate migration include growth factors which are present in the connective tissue underlying epithelia. Hence, in cell motility, growth factor signalling and integrin functions are involved. As previously noted, both these components may be altered in cancer.

Intravasation, survival, extravasation The fragile nature in growing cancers of capillaries and lymphatics, together with poorly formed basement membranes, facilitates intravasation. The circulation is a hostile environment for epithelial cells: it is clear that the vast majority of cancer cells which enter the circulation die there. This is most likely due to the fact that epithelial cells require signals via integrins to prevent apoptosis and so detached cells frequently die. The minority that survive do so perhaps by chance or because alterations in integrin signalling permits survival. Extravasation resembles leukocyte extravasation with tumour cells binding loosely to selectins on the endothelial cells, followed by tighter binding via integrins, and then transendothelial migration. The "seed and soil" hypothesis, to account for the preferential sites of metastasis of some cancers, is perhaps explained by specific integrin-endothelial cell interactions.

Immunity

Until comparatively recently the idea that immunity played any role in resistance to cancer was controversial. But now it is clear there are immune responses to cancers, most obviously the virus-induced cancers such as cervical carcinoma but also others for which there is no virus involvement, *e.g.* melanoma. Paradoxically, cancers can flourish in the face of immune responses, for example in papilloma virus-induced cervical carcinoma T cell response to the viral gene products E6 and E7 can actually *increase* as the carcinoma progresses. There are many reasons for this evasion of immunity by cancers, but one likely explanation is loss of HLA (class 1) expression, a common phenomenon in many cancers. Without HLA, cytotoxic T cells cannot recognise their targets, hence the paradox of growing tumours in the face of a strong T cell response. We could therefore regard *hla* genes as tumour suppressors.

MOLECULAR BIOLOGY – SO WHAT?

Until recently it has been hard to point to effective therapies derived from the understanding of the molecular pathology of cancer, but this is changing. Two clear examples are Imatinib (Glivec) and Herceptin (Trastuzumab). The former is the archetype of a now large family of drugs which target protein kinases in signalling pathways: it was developed to inhibit the ABL kinase as a treatment for chronic myeloid leukaemia. Herceptin is a monoclonal antibody which targets the HER-2 protein in breast cancer and blocks its signalling. There is also the likelihood of better screening techniques (*e.g.* PCA-3 for prostate) and chemoprevention (specific oestrogen receptor modulators to prevent breast cancer) which stem from molecular biology. It is hoped these changes herald the beginning of a revolution in the management of cancer so that, one day, our understanding will lead to control of this disease.

Pre-Malignancy

Rebecca Fitzgerald
MA(Cantab) MD FRCP

The development of an epithelial malignancy is now recognized as a multistep process in which a hyperplastic or metaplastic epithelium gradually becomes dysplastic and finally invasive over a period of years. These pre-invasive lesions, sometimes referred to as intraepithelial neoplasia, gradually accumulate molecular abnormalities until they acquire the key cellular characteristics for invasion as defined by Hanahan and Weinberg. A recent study used high-throughput sequencing technology to analyse the mutations that benign colonic polyps, dysplastic polyps and invasive colon cancer have in common. This resulted in general conclusions about colorectal tumourigenesis which may be applicable to the pathogenesis of other cancers. The authors found it takes as long as seventeen years for a large benign tumour to evolve into an invasive adenocarcinoma but the time taken for that lesion to metastasise may be as rapid as two years.

Many of these pre-invasive lesions occur in the context of chronic injury and there is increasing interest in the role of inflammation in the pathogenesis of cancer. Examples of such pre-invasive lesions include pancreatic intra-epithelial neoplasia (PanIN), intestinal metaplasia of the gastric mucosa, cervical intra-epithelial neoplasia (CIN), and Barrett's oesophagus.

Barrett's oesophagus is a metaplastic lesion of the lower oesophagus in which the normal stratified squamous epithelium is replaced by columnar epithelium with intestinal differentiation. It predisposes to oesophageal adenocarcinoma which is a chemoresistant and frequently lethal cancer. Oesophageal cancer has been increasing rapidly in the western world to the extent that it has recently been highlighted by the Chief Medical Officer as a major public health concern. The stepwise metaplasia-dysplasia-adenocarcinoma sequence occurring in the context of Barrett's oesophagus, exhibits some of the most common genetic lesions in solid tumours. Barrett's oesophagus is an ideal tool for the study of cancer progression because it is visible endoscopically and highly accessible (unlike the pancreas), there is a field effect which can be spatially mapped, and

patients are monitored over time giving rise to longitudinal data (unlike colonic polyps, which are focal and excised). Furthermore, the key risk factor for this rapidly increasing disease is reflux exposure as manifested by heartburn symptoms and so it can be regarded as a response to chronic injury.

There are a number of key questions which arise in the area of Barrett's oesophagus which may be germane to our understanding of the pathogenesis and management of patients with pre-invasive lesions in general. The first of these is how we detect pre-invasive lesions and whether screening programmes are justified. Colon cancer screening is now being adopted in the UK and takes the form of faecal occult blood screening which can be performed at home and this is followed up by colonoscopy for positive cases. Mammography, cervical cancer and prostate screening have been carried out for many years now and there continues to be vigorous debate about the pros and cons. Barrett's oesophagus is largely undetected in the community and, due to the relatively low prevalence of oesophageal cancer compared with breast and prostate cancer, screening has not been recommended, particularly since endoscoping everyone with heartburn is not a feasible proposition. However, evidence from a number of non-randomised studies demonstrates an improvement in five year actuarial survival from 13-43% to 62-100% in patients with surveillance detected cancers. Since oesophageal adenocarcinoma is increasing rapidly, and with the advent of less invasive diagnostic tests such as ultrathin transnasal endoscopy and a capsule sponge device, this may need to be reconsidered. However, it is vital when considering any form of screening to carefully weigh up the merits of early cancer detection against the anxiety caused, potential side-effects of the test and, financial cost.

The second question surrounds understanding the relative contribution of inherited and environmental factors to the development and progression of pre-invasive disease. If we could understand this then we would be better able to predict which patients are at highest risk of progression to cancer and over what time frame. In the case of colonic polyps these are easily removed at the time of diagnosis and patients can then be monitored over time. In contrast, patients with Barrett's oesophagus or DCIS may be offered invasive surgical treatment with significant effects on quality of life (oesophagectomy or mastectomy respectively) when only a proportion of these patients would progress to cancer if not treated. Therefore, it is imperative that we understand which are the highest risk patients so that treatment can be targeted at these individuals using chemopreventive or less invasive, non-surgical methods. For example, anti-

inflammatory agents or small molecular inhibitors for signalling pathways which confer oncogenic dependence could be given. In the gastrointestinal tract, mucosal ablative therapies such as radiofrequency ablation are promising and do not have the risks associated with surgery.

The rapid development of laboratory tools in the –omic era coupled with the development of minimally invasive technologies for diagnosis and treatment mean there are real opportunities to make progress in research and patient management of pre-invasive lesions. Given the high incidence of cancer which is often diagnosed at a late and incurable stage early detection and intervention are key to reducing population mortality from cancer. However, early intervention will not be without psychological and pecuniary costs to society.

Screening

Stephen W. Duffy
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Many cancers are difficult to treat, having already disseminated at the time of presentation or recurring despite apparently successful treatment. For this reason, and because most cancers exhibit a gradient of poorer prognosis with advanced stage at presentation, screening for early disease and precursor lesions (p11) is of considerable interest. For screening to be worthwhile the disease has to be a sufficient health problem to justify the outlay, the procedure has to be acceptable in terms of the demand on health resources (both for the actual screening and the associated further diagnostic investigations) and of the impact on the subjects screened (anxiety, false positives, and investigations undergone). Finally, the prospect of early detection should confer a significant improvement in outcome.

This last criterion has traditionally been investigated by randomised screening trials in which healthy populations are randomly allocated to either invitation to screening or no invitation, and the criterion for success is a reduction in population mortality from the disease in the invited group. An exception occurs in the case of screening for a precursor lesion such as in cervical screening. Here, the aim is to diagnose precursor lesions and, by removing them, prevent the cancer from occurring at all. In such cases, the appropriate measure of the effect of screening may be the incidence of invasive carcinoma rather than disease mortality.

Cancers for which there are population screening programmes in the UK include:

Breast cancer Screening for breast cancer (p41) with mammography (x-ray of the breasts) has been shown by randomised trials to reduce mortality from the disease by around 20% in the invited population and by considerably more in those accepting the invitation. The aim of mammography is to detect breast cancer at a sufficiently early stage that treatment will be successful, thereby preventing future death from the disease. The UK has a programme of three-yearly screening in women aged 50-70, currently being extended to 47-73. The

programme screens 1.7 million women and is estimated to prevent approximately 1,400 breast cancer deaths per year.

Cervical cancer Cervical screening is usually achieved by cytology, *i.e.* microscopic examination of cells scraped from the cervix. As noted above, the aim is to detect cervical intraepithelial neoplasia, remove the abnormality and thus forestall the occurrence of cancer. Although there has been little randomised trial research into this intervention, the combined weight of available experimental and observational evidence indicates that cervical screening is effective. The UK programme offers cervical screening every three years to women aged 25-49 and every five years for women aged 50-64. Without this programme, the incidence of cervical cancer in this age range would be more than double its present level. Because the causal infectious factor, human papilloma viruses, accounts for almost all cases of the disease, there is interest in testing for the virus as a screening tool, combined with vaccination programmes aimed at reducing viral colonisation and transmission.

Colorectal cancer Screening for colorectal cancer (p97) by faecal occult blood testing (FOBT) reduces mortality from the disease by 15-20%. The UK screening programme offers 2-yearly screening to men and women aged 60-69. The programme has only run since 2006 and aims to detect colorectal cancer early while it is successfully treatable. There is ongoing research into endoscopic screening to identify and remove precursor lesions (adenomatous polyps), so preventing the onset of malignant change.

While the concept of early detection is appealing, its success is not guaranteed. Although lung cancer (p53) is characterised by late stage at presentation and poor survival, cases which *are* diagnosed at an early stage have much better outcomes. However, trials of chest x-ray screening for lung cancer found no reduction in either advanced disease or lung cancer mortality in association with screening. Computed tomography screening for lung cancer is under trial at the moment. This imaging modality is more sensitive than x-ray but it is not yet clear whether it has potential to reduce mortality from lung cancer.

Other cancer screening strategies for which there is evidence of benefit include prostate specific antigen testing for prostate cancer and ultrasound screening for liver cancer. The former has been shown to reduce mortality from prostate cancer in one randomised trial, but at a cost of many additional cases of prostate cancer diagnosed. It is likely that many men have prostate cancer which does not

progress to symptomatic disease in their lifetime. The use of ultrasound screening for liver cancer reduces mortality in subjects at high risk, *e.g.* hepatitis B infected individuals. The disease is relatively rare and so general population screening is not indicated. This raises the important issue of selecting an appropriate target population for screening. Existing screening programmes typically define their target populations by age and/or sex, although this is not inevitable. If, for example, the CT screening trials for lung cancer show a benefit, it might be appropriate to define the target population in terms of exposure to risk factors such as tobacco smoking (p55) or working with asbestos (p56). This is not simply a matter of health economics. There are human costs to screening, such as the anxiety associated with being tested for a serious illness, and the physical and psychological effects of false positive tests. It is therefore important that the target population is sufficiently at risk of disease that the potential harms of screening are outweighed by the potential benefits.

Barrett's Oesophagus

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As described previously (p11), Barrett's oesophagus is a condition in which the squamous epithelium of the oesophagus undergoes metaplastic change to become columnar (glandular) epithelium. This is usually in response to acid reflux, *e.g.* gastro-oesophageal reflux disease (GORD). Barrett's oesophagus is a pre-malignant condition and, as such, there has been widespread interest in the surveillance of patients by upper gastrointestinal endoscopy. It is hoped that, by offering appropriate treatment to high risk Barrett's patients, the incidence of oesophageal adenocarcinoma can be reduced.

First suspected to be a congenital abnormality, Barrett's oesophagus is now well-recognised as an acquired condition. Its development and progression in (typically) older middle-aged patients with a history of chronic gastro-oesophageal reflux disease is well-documented. The acquired nature of Barrett's oesophagus was acknowledged in 1970 when squamous-to-columnar metaplasia was demonstrated in a GORD dog model.

Barrett's oesophagus predominantly affects Caucasian men in the Western world. The condition is 14 times more common in Caucasian men than in African Americans, with even lower incidence rates amongst Asians. The condition has a strong male/female bias, with men three times more likely to be affected than women. The risk of developing Barrett's oesophagus increases with age, and the condition is usually diagnosed between ages 55 and 65. Obesity is also a risk factor. Barrett's oesophagus is most commonly detected in patients who suffer from chronic GORD, and prevalence is 25 times greater in patients with reflux symptoms than in those without. The severity of GORD required to precipitate Barrett's varies, but a minimum of five years of severe reflux disease is generally accepted as being the minimum requirement. Typically, patients have a history of GORD spanning back a couple of decades before Barrett's is detected. Infection with *Helicobacter pylori*, the bacterium implicated in peptic ulcer disease, is, perhaps counter-intuitively, protective against the development and progression of Barrett's oesophagus.

For the vast majority of patients with Barrett's, the primary concern is that the metaplasia will develop into carcinoma. Barrett's oesophagus is associated with an increased risk of developing oesophageal adenocarcinoma, measured at 30- to 125-fold greater than in patients without the condition.

In the decade from 1976 to 1986, the incidences of oesophageal and gastric cardia adenocarcinomas in men in the US increased more rapidly than any other types of cancer, whilst rates of oesophageal squamous cell carcinoma and more distal gastric carcinoma remained stable or declined. The increase in incidence of oesophageal adenocarcinoma means it now ranks as the ninth most commonly diagnosed cancer in the world. In some areas of the Western world the prevalence of oesophageal adenocarcinoma now equals or even outnumbers that of oesophageal squamous cell carcinoma which, just a few decades ago, was more prevalent. In addition to this, oesophageal adenocarcinoma has a very poor prognosis, with less than 25% of patients surviving five years. This is largely attributed to its typically advanced stage at diagnosis.

The reasons for this marked increase in incidence remains unclear. It has been postulated that the increase was due to previous misclassification of oesophageal adenocarcinoma as gastric cardia tumours, although a concomitant reduction in the incidence of gastric cardia carcinoma in parallel to the increase in oesophageal carcinoma has not been observed. A more plausible explanation for the rising incidence of oesophageal adenocarcinoma in the Western world is the rising levels of obesity, a well-known major risk factor for this cancer. However, the rise in obesity levels cannot sufficiently explain the rising incidence of this cancer. Oesophageal adenocarcinoma occurs 6-8 times more frequently in men than in women, yet the rise in obesity levels is similar between the sexes. Other potential explanations for the rising levels of oesophageal adenocarcinoma include the increase in rates of gastro-oesophageal reflux, the fall in *H. pylori* infection rates, and increased use of medications which relax the lower oesophageal sphincter.

It is not thought that an increasing prevalence of Barrett's oesophagus is responsible for the rise in the incidence of oesophageal adenocarcinoma. Whilst incidence levels of Barrett's oesophagus have increased over recent decades, this has been mirrored by the increasing use of upper gastrointestinal endoscopy. It therefore seems likely that the prevalence of Barrett's has remained unchanged. However, Barrett's oesophagus remains the only known precursor lesion of

oesophageal adenocarcinoma, leading to increasing interest in Barrett's and efforts to monitor its progression.

PATHOGENESIS

Barrett's oesophagus develops when the normal squamous epithelium of the distal oesophagus is replaced by columnar mucosa. The metaplastic epithelium develops following injury to the oesophagus, usually through destruction of the squamous cell mucosa by harmful gastric contents secondary to gastro-oesophageal reflux. Damage to the epithelium alone, however, is insufficient to result in the development of Barrett's oesophagus, as the normal healing process of the oesophagus usually permits regrowth of squamous cell mucosa. It is only when the environment of the oesophageal epithelium is abnormal during the repair process, that metaplasia occurs. In most cases of Barrett's it is the unusually acidic environment arising as a result of chronic gastro-oesophageal reflux that provokes the abnormal repair of the oesophageal epithelium with columnar cells. This theory is the reasoning behind high-dose acid suppression post-ablation therapy, which can encourage squamous epithelium to regenerate normally.

However, it is not only an acidic environment which induces development of a metaplastic oesophageal epithelium. Chronic irritation of the oesophagus by duodenal contents or chemotherapy has also been shown to result in the development of Barrett's oesophagus.

Complications of Barrett's include strictures, ulcers and adenocarcinoma. They arise secondary to duodenogastric reflux of bile acids and pancreatic enzymes, which expose the oesophageal mucosa to alkaline conditions. This effect is unsurprising, given that the co-carcinogenic effect of bile acids in the colon and other regions of the gastrointestinal tract is well-documented.

It is now widely accepted that there is a pathway of progression from Barrett's oesophagus to oesophageal adenocarcinoma. This involves metaplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD) and adenocarcinoma. There are two lines of evidence that support this hypothesis. Firstly, consecutive oesophageal biopsies taken in the monitoring of individual Barrett's patients are consistently seen to progress through these disease states (more or less) consecutively. Typically, patients who present with uncomplicated Barrett's later develop LGD, HGD and finally oesophageal adenocarcinoma. Secondly, areas of metaplastic and

dysplastic oesophageal epithelium are often found next to each other within tissue biopsies.

There is considerable uncertainty surrounding whether or not it is possible for Barrett's oesophagus to regress. Whilst many studies on individual patients claim to have documented regression of Barrett's, neither medical management nor anti-reflux surgery have been definitively proven to promote regression of metaplasia and conversion back to squamous mucosa in a randomised controlled trial. Monitoring apparent regression of Barrett's oesophagus in a few individual patient cases is not sufficient to demonstrate the plausibility of metaplasia regression. The number and site of biopsies taken may vary between consecutive endoscopies and the interpretation of findings of both endoscopy and biopsy may be biased by inter-observer variation. Furthermore, the anatomy of the distal oesophagus may be altered after anti-reflux surgery, meaning that consistent monitoring of any one particular region of epithelium becomes problematic.

One question commonly asked by patients with Barrett's oesophagus is whether there is a genetic component to the disease, and whether relatives should be alerted to an increased risk of developing Barrett's. As yet, no single mutation has been identified. Groups who have investigated the heritability of Barrett's have, however, shown that Barrett's oesophagus occurs more frequently within family groups than would be expected by chance. Nevertheless, if there is a genetic predisposition to Barrett's, the penetrance of the phenotype must be low, as the majority of first-degree relatives of patients do not develop Barrett's oesophagus themselves.

CLINICAL FEATURES

On the whole, patients with Barrett's oesophagus exhibit the same symptoms as those with uncomplicated GORD: epigastric and/or retrosternal pain, heartburn, and regurgitation. However, new research suggests that a diverse range of extra-oesophageal symptoms may result from reflux disease. In addition to the commoner symptoms, patients with GORD may also experience chest pain mimicking angina pectoris and a range of ear, nose and throat symptoms such as hoarseness, chronic cough, globus, pharyngitis and sinusitis. Less frequently, GORD patients may complain of dental erosion, asthma and other respiratory symptoms resulting from acid aspiration.

Often a diagnosis of GORD, and the resultant increased risk of developing Barrett's oesophagus, may be missed if heartburn is not present. In fact, it is estimated that heartburn is absent in 32% of GORD patients. For this reason, it is essential that the awareness of atypical symptoms of reflux disease is increased to ensure that all GORD and Barrett's oesophagus patients are identified and subsequently offered treatment to prevent disease progression.

Despite their similarities, the symptoms of Barrett's oesophagus differ from those of GORD in two respects. Firstly, in Barrett's oesophagus symptoms are usually reported as less severe than the symptoms of GORD. This has been attributed to the reduced sensitivity of the metaplastic columnar epithelium to harmful gastric contents, compared to the previously healthy squamous mucosa. Secondly, patients with Barrett's oesophagus are more likely to develop complications than those with non-metaplastic GORD. It is estimated that approximately half of patients with Barrett's oesophagus already have complications at the time of presentation. These include erosive oesophagitis, ulcers, strictures, dysplasia and adenocarcinoma.

Although not routinely conducted, more invasive procedures have elucidated some additional commonly occurring clinical differences between Barrett's oesophagus patients and those with uncomplicated GORD. Oesophageal pH monitoring shows that patients who have Barrett's show striking increases in both the frequency and duration of reflux episodes over a 24 hour period compared to those without metaplasia. This suggests the oesophageal epithelium is exposed to acidic conditions for a greater period of time in patients with Barrett's. Increased exposure to acidity probably follows reduced competence of the lower oesophageal sphincter. In fact, a mechanically defective sphincter is thought to occur in over 95% of Barrett's patients. In addition to this defect, patients frequently show ineffective oesophageal peristalsis, and hence delayed clearance of refluxed gastroduodenal contents compared to those patients who have uncomplicated GORD. Higher levels of gastric acid secretions are also noted in approximately 50% of Barrett's oesophagus patients.

These differences go some way to explaining why some patients who suffer from GORD develop Barrett's oesophagus, while others do not.

INVESTIGATIONS

Barrett's oesophagus can only be diagnosed through endoscopy with biopsy. On endoscopy, Barrett's is characterised by salmon-pink or red tongues of tissue (extending to the gastro-oesophageal junction) which protrude into areas of pearly white squamous epithelium. Alternatively, the brightly coloured abnormal mucosa can sometimes be seen to extend around the entire inner circumference of the oesophagus, again in continuity with the gastric mucosa. Biopsies taken from the affected region usually show intestinal metaplasia. This can be recognised by the presence of easily-visible goblet cells, the mucin-producing cells of the intestinal epithelium. If any nodular or ulcerated lesions are seen on endoscopy, they are biopsied to check for oesophageal adenocarcinoma.

Once a patient has been diagnosed with Barrett's oesophagus, they are enrolled in a surveillance programme. This involves undergoing regular endoscopies whilst receiving ongoing treatment for their reflux disease. Each endoscopy involves four quadrant biopsies at two centimetre intervals in all oesophageal tissue which appears abnormal. These biopsies aim to identify areas of the oesophagus exhibiting signs of metaplasia, as well as identifying if areas of previous metaplasia have progressed to dysplasia or carcinoma. Dysplasia refers to abnormal tissue in which there is increased cell growth and cells appear atypical, with both architectural and cytological changes, but these changes are confined by the basement membrane. Two types of dysplasia are recognised – low-grade dysplasia (LGD), with a lower rate of progression to adenocarcinoma, and high-grade dysplasia (HGD) which more frequently develops into carcinoma. LGD is treated conservatively, while HGD is often resected. Histology of resected areas of HGD shows existing adenocarcinoma in 30-50% of cases.

Early definitions of Barrett's oesophagus restricted the condition to cases in which columnar metaplasia was found three or more centimetres proximally of the gastro-oesophageal junction. This is now referred to as "long-segment Barrett's oesophagus". Modern definitions also include "short-segment Barrett's oesophagus", in which there is metaplasia contained within the area three centimetres proximal to the gastro-oesophageal junction. This amended classification system may have contributed to the rising incidence of Barrett's over recent years.

In the majority of cases the metaplasia is intestinal in nature, although both cardiac and gastric fundic mucosae replace the squamous epithelium in some cases. In fact, multiple types of metaplastic mucosa are seen to occur alongside

each other in a single patient. Intestinal epithelium is characterised by the presence of goblet cells and the arrangement of cells into villous projections; cardiac mucosa by the presence of simple mucous glands; and gastric fundic epithelium by the presence of both chief and parietal cells.

One common problem in the classification of dysplasia in Barrett's oesophagus is that there is significant intra- and inter-observer variation in the histological presentations considered dysplasia. This can be attributed to the fact that the differences seen between metaplastic and dysplastic epithelia are subtle and represent a continuing spectrum from those that are clearly metaplastic to those exhibiting high-grade dysplasia. The implication of this is that any classification of histological appearance of a patient's biopsy should not be interpreted too literally and, in cases where therapeutic decisions are made based on the classification of dysplasia, a second opinion should be sought. It also means that the sequential history of a patient may not be entirely accurate. For example, a single patient's presentation of Barrett's may be defined as low-grade dysplasia by one pathologist in one endoscopy, and then as non-dysplastic metaplasia by a second pathologist at a subsequent endoscopy. The disease state may, however, have remained stable and not actually improved.

In an attempt to overcome the problems presented by inter-observer variation in the diagnosis of dysplasia, a new five tier classification system has been developed, known as the "Vienna classification" system. It is hoped this system will be clearer to follow and thereby lead to less variation in the diagnosis of dysplasia.

MANAGEMENT

There are a number of therapeutic options available to patients with Barrett's oesophagus. The ultimate aim of each is to reduce the likelihood that oesophageal metaplasia will progress to carcinoma. The treatment of choice often depends on the results of histological examinations of biopsied tissue, in conjunction with patients' personal preferences and suitability.

The standard first-line treatment for a patient diagnosed with uncomplicated Barrett's oesophagus is medical therapy with a proton pump inhibitor (PPI). PPIs suppress production of acid from the parietal cells of the gastric mucosa. PPIs have also been shown to help in reducing reflux of bile, which may contribute significantly to oesophageal epithelial damage in conjunction with gastric acid. In

many patients, treatment with a PPI is sufficient to completely relieve symptoms associated with GORD.

24-hour pH monitoring of the oesophagus shows that even patients treated with high doses of proton pump inhibitors still experience periods of uncontrolled acid reflux. It is therefore unsurprising that medical therapy does not seem to cause regression or even halt progression of Barrett's oesophagus. Combined with concern over the effects of lifelong medical therapy, some patients have sought alternative treatments for their condition.

An alternative to medical management for Barrett's oesophagus is anti-reflux surgery. Reflux disease occurs due to poor functioning of the lower oesophageal sphincter, providing an environment in which Barrett's oesophagus can develop. The most common type of anti-reflux surgery is Nissen fundoplication, in which the fundus of the stomach is wrapped around the distal oesophagus, creating a new sphincter mechanism with a normal pressure profile. Fundoplication has been shown to effectively restore sphincter function and relieve reflux symptoms in over 90% of GORD patients for at least 10 years. When performed successfully, anti-reflux surgery is deemed superior to medical therapy as it physically prevents reflux rather than simply neutralising harmful gastric contents. This provides 24-hour protection and also prevents reflux of harmful substances other than gastric acid, such as bile acids. Anti-reflux surgery has been shown to slow or even stop progression of Barrett's oesophagus along the metaplasia-dysplasia-carcinoma pathway, making it an increasingly appealing option.

Although fundoplication as an open procedure carries associated risks of pulmonary, thromboembolic and wound complications, the operation can now be performed laparoscopically. This allows a faster recovery time as well as reducing post-operative pain and lowering the risk of complications. Minor post-operative complications of the operation are not uncommon, with dysphagia, inability to vomit, inability to belch, early satiety, gastric bloating and increased passage of flatus occurring most frequently. It is for these reasons, and owing to the complexity of the operation, that only surgeons with considerable experience of performing open anti-reflux procedures should attempt the operation laparoscopically.

In addition to medical therapy and anti-reflux surgery, three endoscopic ablation techniques are also used in the treatment of Barrett's oesophagus. These are photodynamic therapy, endoscopic mucosal resection and thermal ablative

therapy. Unlike medical therapy and anti-reflux surgery which tend to be used as first-line therapies only in cases of non-dysplastic metaplasia, the endoscopic therapies are more commonly used in cases of dysplasia or even superficial adenocarcinoma. Ablative procedures aim to destroy the dysplastic/malignant columnar epithelium and promote regrowth of healthy squamous mucosa.

Photodynamic therapy In photodynamic therapy (PDT), the patient is given an intravenous photosensitising agent. This agent is selectively taken up by the dysplastic/malignant tissue in the oesophagus. Once sufficient time has passed for the photosensitising agent to accumulate in the dysplastic/malignant cells, the patient receives endoscopic therapy, in which a red light is shone on affected parts of the oesophagus. This activates the photosensitising agent, leading to the production of free radicals which destroy the dysplastic/malignant tissue. The patient is then treated with strong acid inhibitors, in the hope of promoting regrowth of squamous rather than columnar epithelium.

Whilst PDT has the advantage of high response rates, in up to 40% of patients the new squamous mucosa is seen to overgrow areas of epithelium which still contain columnar cells, creating trapped pockets of metaplasia. It has also been reported that, although biopsies after PDT may show improvements in the histological appearance of the oesophagus with less dysplastic tissue present, genetic abnormalities associated with dysplasia persist after therapy. This raises the concern that PDT-treated patients remain at the same elevated risk of developing carcinoma as before the therapy when they still displayed histological signs of dysplasia. In addition to these problems, there is potential for complications of PDT, including severe skin phototoxicity, oesophageal strictures, chest pain, dysphagia and small pleural effusions.

Endoscopic mucosal resection In endoscopic mucosal resection (EMR) the sub-mucosal oesophagus is injected with a saline/epinephrine mixture, causing the area of dysplasia/malignancy to become elevated above areas of healthy epithelium. The raised area can then be resected and subjected to histological examination, ensuring that all of the dysplasia/malignancy has been removed and that the lesion did not penetrate deeper than suspected.

Whilst EMR is useful in the treatment of localised high-grade dysplasia or superficial carcinoma, it brings its own risks. These include dysphagia, bleeding and oesophageal perforation. Recent studies suggest that the use of EMR

followed by PDT is more effective in the treatment of dysplasia than when one therapy is used in isolation.

Thermal ablative therapy Thermal ablative therapy, another endoscopic treatment, is commonly used in cases of Barrett's metaplasia or low-grade dysplasia. Like PDT, ablation is used to destroy the metaplastic/dysplastic mucosa, and then followed by high-dose acid suppression to encourage regrowth of healthy squamous epithelium. Although thermal ablative therapy is successful in the majority of patients, it has risks comparable to PDT. These include the possibility of developing trapped pockets of metaplasia.

Cancers of the Nasopharynx and Oropharynx

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Cancers of the head and neck are the sixth commonest type of malignancy worldwide. The incidence of carcinomas of the upper air and food passages is rising with over 500,000 new cases annually.

The incidence of head and neck cancers appears to be rising, particularly in females. This is probably due to changes in smoking and alcohol consumption. American data suggests age-adjusted incidence rates of 17.3 per 100,000 in white males and 5.6 per 100,000 in white females. Approximately 40% of these tumours are fatal, although the mortality rate is slightly lower in the UK. Here, there are approximately 7,800 new cases of cancers of the head and neck each year – accounting for approximately 4% of all carcinomas – leading to over 2,000 deaths. Around 1,600 of these new cases are cancers of the pharynx.

Most cancers of the head and neck, including those of the oropharynx, occur from the fifth decade onwards. However, carcinoma of the nasopharynx has a bimodal age distribution. In high incidence areas, 20% of cases are diagnosed in patients less than 30 years of age. There is a strong male predisposition in neoplasms of the head and neck, with a male/female ratio of approximately three to one.

There are striking variations in incidence of head and neck cancers amongst different ethnic groups. Carcinoma of the nasopharynx is particularly common in China, the Philippines, Malaysia, North Africa, and Saudi Arabia. In Taiwanese males it is the commonest cause of death with an incidence three times that of any other neoplasm.

ANATOMY

Structural anatomy
The pharynx is the superior part of the alimentary system, posterior to the nasal and oral cavities, and extending past the larynx inferiorly. It extends from the base of the occiput to the level of the superior aspect of the clavicles, and its posterior wall lies anterior to the pre-vertebral fascia.

The pharynx has three concentric layers: an internal mucous membrane, a supporting fibrous tunica, and an outer muscular coat with defects permitting the entry of vessels and nerves. These defects are the principal sites through which malignant tumours of the pharynx spread to adjacent tissues, such as the lymph nodes of the neck. The main muscles wrapped around the pharynx are the superior, middle, and inferior constrictor muscles.

Anatomically, the pharynx can be divided into the nasopharynx, oropharynx and laryngopharynx (or hypopharynx). The nasopharynx lies behind the nasal cavity, and extends from the base of the skull above to the superior aspect of the soft palate below. Posteriorly, it is bounded by pre-vertebral fascia, and anteriorly by the junction of the hard and soft palate. The nose opens into the nasopharynx through two choanae. The third and sixth cranial nerves run in the cavernous sinus of the superior nasopharynx so that superior extension of a nasopharyngeal tumour may cause cranial nerve palsies.

The oropharynx lies behind the oral cavity. It includes the posterior third of the tongue, vallecula, soft palate, uvula, faucial pillars and tonsils, and extends to the superior border of the epiglottis.

Innervation
The vagus nerve provides motor and sensory nerve supply to the pharynx, whilst the glossopharyngeal nerve provides only sensory innervation.

Lymphatic drainage
Lymphoid tissue in the pharynx forms an incomplete tonsillar ring around the superior part of the pharynx, comprising the palatine, lingual, and pharyngeal tonsils. The pharyngeal tonsils (adenoids) are in the mucous membrane of the roof and posterior wall of the nasopharynx. The palatine tonsils are masses of

lymphoid tissue in each side of the oropharynx that lie in the tonsillar fossa, between the palatoglossal and palatopharyngeal arches.

The pharynx has a rich lymphatic drainage system and so early node involvement is common in malignancy. The inaccessible node of Rouvière lies in the lateral retropharyngeal area, directly anterior to the lateral processes of the atlas vertebra, and is an early site of invasion. The superficial and deep cervical lymphatic chains run parallel to the external and internal jugular veins respectively. Efferent lymphatic vessels from the deep cervical nodes join to form the jugular lymphatic trunks, which themselves coalesce to form the thoracic duct on the left side.

For the purposes of neck dissection, regions of the neck are subdivided into levels – the number of which differs according to the classification used. Generally, nodes in the sub-mandibular triangle are considered level I. Levels II, III, and IV are the upper, middle, and lower jugular lymph nodes, respectively. Level V includes the spinal accessory and posterior triangle lymph nodes. Level VI lymph nodes are in the tracheo-esophageal groove, and level VII lymph nodes are in the superior mediastinum.

Histology
The pharynx is lined with stratified squamous epithelium, although the portion of the nasopharynx adjacent to the nasal cavity is lined with ciliated squamous epithelium. Most oropharyngeal tumours (60%) are squamous in origin, but primary tumours of the nasopharynx are often poorly differentiated, undifferentiated, or anaplastic. Lymphomas are also relatively common in the nasopharynx and oropharynx (particularly the tonsil).

AETIOLOGY
Important aetiological factors in the development of these carcinomas include excessive intake of tobacco and alcohol, particularly spirits. 90% of patients with a neoplasm of the head or neck provide a history of smoking or chewing tobacco. The fact that many smokers drink significant amounts of alcohol makes it difficult to assess how much risk is contributed by either factor in isolation. However, the effects of alcohol and tobacco are clearly synergistic: use of both increases the risk of developing cancers of the oropharynx by as much as fifteen fold.

The impact of alcohol and tobacco consumption is less clear when considering nasopharyngeal carcinomas. These appear to be aetiologically distinct. Other environmental agents which have been implicated include dietary factors, such as salted fish and vegetables. Case-control studies in Chinese patients have suggested a link between the consumption of salted fish and nasopharyngeal carcinoma.

Patients with nasopharyngeal carcinoma often have evidence of Epstein-Barr virus genome in the epithelial tumour cells. In addition, although infection with high risk human papilloma virus is not necessary for development of head and neck cancer (unlike cancers of the cervix), a causal role has been proposed for some neoplasms, particularly those of tonsillar origin.

PRESENTATION

The pattern of symptoms in carcinoma of the pharynx varies with the site of the neoplasm. In nasopharyngeal carcinoma, common presenting signs and symptoms include symptoms of the nose (*e.g.* bleeding, obstruction or discharge), unilateral hearing loss (with or without tinnitus), cervical lymphadenopathy, headache, and cervical nerve palsies.

Other sites of tumour extension include the para-nasal sinuses, nasal cavity, the orbit and middle ear. Cancers of the nasopharynx often present late, frequently with nodal involvement.

The important sites for cancer of the oropharynx include the posterior third of the tongue (33%), the tonsil (22%), the pharyngeal wall (17%), the faucial pillars (16%), and the soft palate (12%). Common presenting symptoms of oropharyngeal carcinoma include dysphagia with pain, a sore throat or lump in the throat, and pain referred to the ear.

Oropharyngeal cancer may also present with cervical lymphadenopathy and no other symptoms. Oropharyngeal tumours of different sites tend to present at different stages; for example, lesions of the tonsillar fossa tend to present later than those of the faucial pillar.

Investigations

Nasendoscopy is the use of a thin flexible tube with a light for inspecting the pharynx for lesions. However, definitive diagnosis can only be made following histological examination of the neoplasm. This may be achieved by taking a biopsy, or by fine needle aspiration cytology (FNAC). FNAC is frequently used to assess enlarged lymph nodes when the primary site has not been identified.

Once a cancer has been diagnosed by biopsy, a number of other investigations may be undertaken to visualise and stage the neoplasm. Plain radiography, computed tomography (CT) and magnetic resonance image (MRI) scanning are all used frequently. Radiography is used to assess whether the cancer has invaded the bones, and a chest x-ray is often taken to look for lung metastases.

MRI and CT scanning have had a dramatic impact on the accuracy and detail with which lesions can be visualised, and is of particular value in assessing carcinomas of the nasopharynx due to their inaccessibility. They can also be used to visualise impalpable but enlarged lymph nodes.

Other tests which may be used include bone scans, barium swallows, ultrasound, and positron emission tomography (PET) scanning.

STAGING AND GRADING

Staging is essential in order to develop treatment strategies and determine prognosis. The most common method of staging cancers of the nasopharynx and oropharynx is the TMN system. The same staging notation for lymph node spread and metastasis has been adopted regardless of the primary head and neck site. However, there is variation in notation for T staging. The TMN system is based on:

- tumour size (T)
- regional lymph node status (N)
- metastases (M)

TNM staging can be grouped into stages I, II, III and IV for the purposes of deciding treatment and predicting outcomes. These groups are as follows:

- stage I = T1N0M0
- stage II = T2N0M0
- stage III = T3N0M0, T1-3N1M0

- stage IV = T4N0-1M0, T1-4N2M0, T1-4N2M0, T1-4N0-2M1

Pharyngeal carcinomas with different primary sites tend to present at different stages and therefore have varying degrees of nodal involvement. At presentation, 87% of nasopharyngeal carcinomas have nodal involvement (N1-N3), compared with 76% of neoplasms of the tonsillar fossa, and 59% of neoplasms of the oropharyngeal walls.

Limitations of staging include variation in individual interpretation, and advanced lesions in which it may be difficult to determine the exact site of origin, and whether other sub-sites are involved.

MANAGEMENT

The management of pharyngeal carcinomas depends on the stage at presentation. In stage I or II disease, patients may undergo surgery, radiotherapy, or combined surgery and radiotherapy. Chemo-radiotherapy is rapidly emerging as the preferred primary treatment. In stage III or IV disease, patients may undergo surgery, chemo-radiotherapy or biological therapy, or a combination of the above. Chemotherapy is the treatment of choice for metastatic disease.

Surgery

Surgery has an important role in treatment of cancers of the pharynx, particularly the oropharynx. Small tumours of the pharynx may be removed using laser surgery, which can be combined with a light sensitive drug in a treatment called photodynamic therapy.

In most cases, a radical neck dissection is performed during surgery, where the lymph glands on one or both sides of the neck are removed. This may be performed as a prophylactic measure. Over recent years, less radical procedures such as modified comprehensive dissection and selective dissection have emerged, reducing the debilitating effect of neck dissection on shoulder and neck function.

In other cases, part of the lining of the pharynx may need to be removed. This can be replaced using a skin flap, usually from the radial forearm, which is sufficiently pliable to maximise use of the remaining musculature. If the cancer has invaded the mandible, the affected portion may be removed and replaced with a bone

graft, most commonly from the iliac crest or fibula. In most cases, this has excellent functional and aesthetic results. Occasionally, other bones such as the palate may need to be removed, in which case a prosthesis may be indicated.

Potential advantages of surgery alone include fast local disease clearance, avoidance of radiotherapy toxicity, lack of effect on the treatment of metachronous tumours, and ability to facilitate complete pathological staging.

Radiotherapy

Cure rates for surgery or radiotherapy alone are equivalent in most head and neck cancers. In nasopharyngeal carcinoma, radiotherapy is the treatment of choice, and surgery is limited to staging and elective dissection of neck nodes which have not regressed following radiotherapy. There are considerable technical difficulties in irradiation of this area due to the necessity of avoiding the upper part of the spinal cord and the temporal lobes of the brain.

In oropharyngeal carcinoma, a combination of surgery and radiotherapy is routinely used, although there is increasing emphasis on radical radiotherapy (with or without chemotherapy), with surgery as a last resort. Treatment with radiotherapy is simpler than in nasopharyngeal carcinoma, as the field can simply be extended to cover any extension of the tumour, although problems arise where there is extension of the tumour into the hard palate, mandible, or tongue.

Ionising radiation causes damage both directly to cellular DNA and indirectly through toxic free radicals produced from the reaction of radiation with intracellular water. This leads to breaks in the DNA which, if not repaired, will accumulate and result in cell death. Cancer cells are more susceptible to radiation than normal cells due to their impaired ability to repair DNA.

There is a spectrum of sensitivity for both normal and tumour cell types. The presence of oxygen is critical to the capacity of radiation to cause DNA damage. Most pharyngeal tumours are acutely and chronically hypoxic, and are therefore relatively resistant to radiation. However, trials with hypoxic-cell radiation sensitisers such as misonidazole have generally failed to show an improvement in tumour control.

External beam radiotherapy is most commonly used in cancers of the pharynx, and may require a plastic head or face mould to ensure the correct position is

maintained. A typical radical radiotherapy regime is likely to comprise 60-70Gy administered in fractions over six to seven weeks. However, the dose delivered depends on the general health of the patient, the type of cancer being treated and other constituents of treatment.

Advantages of treatment with radiotherapy alone include its suitability where surgical clearance is difficult, avoidance of mortality associated with surgery in high risk patients, the option of radiotherapy of clinically occult lymphatic disease (instead of neck dissection), and the ability to treat multiple synchronous primaries. Surgery remains an option if radiotherapy fails, although subsequent surgery is associated with increased mortality.

Combined surgery and radiotherapy
Larger head and neck tumours are often treated by a combination of surgery and radiotherapy in order to reduce the risk of loco-regional disease recurrence. The most important indicators for post-operative radiotherapy include positive resection margins, a T3 or T4 primary tumour, lymph node spread, and a poorly differentiated tumour.

Chemo-radiotherapy
Chemotherapy agents act upon cell division and therefore have a greater effect on rapidly dividing (*e.g.* malignant) cells. They can be broadly classified, according to their mode of action, into anti-metabolites (*e.g.* methotrexate), alkylating agents (*e.g.* cyclophosphamide), intercalating agents (*e.g.* cisplatin), spindle poisons, and other agents whose precise mode of action is unclear. Cancers vary in their susceptibility to chemotherapy agents for numerous reasons including variable drug delivery into the cell and activation or deactivation of the drug within target cells. Chemotherapy agents are therefore frequently given in combination which can lead to increased toxicity to normal cells.

Two large multi-centre phase III studies demonstrated that post-operative chemo-radiotherapy is associated with fewer loco-regional relapses and prolonged disease free survival in high risk, fit patients with resected carcinomas of the head and neck (oral cavity, pharynx and larynx) versus radiotherapy alone.

An improvement in overall survival was demonstrated by only one of these two trials, although a non-significant improvement was noted in the other.

Furthermore, the incidence of significant toxicity was considerably higher in those receiving combined therapy than in those receiving radiotherapy alone. Post-operative chemo-radiotherapy in high risk patients with locally advanced disease is now standard treatment, although there are currently no randomised trials considering this treatment approach in patients without high risk features.

However, over the last decade, chemo-radiotherapy has emerged as a primary treatment option, and is thought to be comparable to surgical resection in operable patients. Chemo-radiotherapy offers far superior organ preservation, and has excellent reported local control and survival rates. For these reasons, it has emerged as the preferred treatment in many centres. The choice between upfront chemo-radiotherapy and surgery followed by adjuvant chemo-radiotherapy remains controversial. It depends on numerous factors including local expertise, treatment goals, respectability, and patient preference.

Many carcinomas of the pharynx are locally advanced. Over 60% of squamous cell head and neck cancers have advanced loco-regional disease unsuitable for surgery at presentation. Primary radiotherapy in stage III or IV head and neck cancer is associated with a five year survival rate of just 10-30% and meta-analyses of early trials suggested this can be increased modestly with concurrent chemotherapy (4-8% increase in five year survival).

Recent data suggest an absolute risk reduction of death at three years of 14-25% (NNT 4-7). The most extensively studied agent is cisplatin, although combination regimens may be associated with a further reduction in mortality.

Metastatic disease is best managed with chemotherapy. Nasopharnyngeal carcinomas are particularly chemo-sensitive with response rates of up to 70% in advanced metastatic disease. However, combined chemo-radiotherapy is associated with increased toxicity, particularly mucositis and, for this reason, is most frequently confined to patients without co-morbidities.

Biological therapies
Cetuximab is a human/mouse chimeric monoclonal antibody that binds the epidermal growth factor receptor which is expressed in a number of cancers and is associated with poor clinical outcome. A recent multi-centre randomised trial compared radiotherapy alone with radiotherapy and concurrent cetuximab in patients with locally advanced squamous cell carcinoma of the pharynx (75%) or

larynx (25%). The addition of cetuximab was associated with significant improvements in median survival (54 vs. 28 months) and two year survival (62% vs. 55%). There was no increase in mucositis, although skin toxicity was significantly more common in the group receiving combined therapy.

There are now trials underway investigating the potential value of adding monoclonal antibodies such as cetuximab to chemo-radiotherapy. The supporting data for the use of monoclonal antibodies is not yet sufficient to adopt this therapy for carcinomas of the pharynx, although it may be considered in patients who are not good candidates for surgery or chemo-radiotherapy.

An alternative approach to tumour immunology may be the development of vaccines to viral antigens (*e.g.* Epstein-Barr virus) for high risk groups. However, tumour-associated antigens are not yet sufficiently characterised for this to be feasible.

Side effects of treatment

Each therapy for cancer of the pharynx is associated with specific side effects. In many cases, these are more significant to the patient than symptoms of the cancer itself. These side effects are treated symptomatically, for example with anti-emetics and analgesics.

The side effects due to radiotherapy to the head and neck are local and usually resolve following the completion of treatment. They develop after two to three weeks of radiotherapy and may be more severe if the patient is also undergoing chemotherapy. Side effects include anorexia and changes in taste, fatigue, alopecia, erythema, mucositis, oral infections (*e.g. Candida spp.*), and a dry mouth. The latter may persist after treatment depending on the proportion of salivary tissue irradiated.

Dry mouth and mucositis make it uncomfortable for the patient to chew or swallow. Patients should avoid spicy, very hot and very cold foods, as well as hard foods (*e.g.* toast), all of which may irritate the mucosa. Alcohol and tobacco are also irritants and should be avoided where possible. Mouthwashes, lozenges, artificial saliva and analgesics may be prescribed, and dental hygiene is particularly important.

Patients may develop anorexia which is often compounded by loss or changes in taste. Some patients benefit from early referral to a dietician for specific advice on diet and appropriate food supplements. Where eating and drinking become too difficult for the patient, a nasogastric or percutaneous endoscopic gastrostomy (PEG) tube may be inserted to maintain adequate nutrition.

The side effects of chemotherapy are systemic and vary depending of the patient and on the agents used. They typically develop more quickly than side effects caused by radiotherapy, but resolve once therapy is completed. Common side effects include fatigue, reduced blood cell counts (leukopenia, anaemia, and thrombocytopenia), nausea and vomiting, anorexia, diarrhoea and constipation, and alopecia.

Chemotherapy can also result in infertility, and patients who have not completed their family may wish to bank sperm or eggs. Reliable contraception should be used during chemotherapy as treatment is highly teratogenic.

The agent most commonly used to treat cancers of the pharynx is cisplatin. Side effects commonly experienced include nausea and vomiting, peripheral neuropathy, tinnitus and hearing loss, changes in taste, and reduced kidney function. Renal function, fluid intake, and urine output are recorded throughout treatment. Anti-emetics are usually prescribed to relieve nausea and vomiting.

Less common side effects associated with cisplatin include allergic reactions, anorexia, diarrhoea, bruising or bleeding, anaemia, and reduced resistance to infection. Blood cell counts are monitored throughout treatment, and patients are asked to contact the hospital immediately if they develop pyrexia or feel unwell. Transfusions may be required if the patient becomes severely anaemic or has significantly reduced blood coagulation.

Breast Cancer

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Breast cancer is the commonest type of cancer in the United Kingdom, accounting for approximately 25% of new diagnoses. It has an annual incidence of 120/100,000. Although only rarely affecting men, 290 are diagnosed with breast cancer in the UK each year. In the last thirty years there has been an 80% increase in breast cancer diagnoses, likely due to the advent of screening programmes. Despite treatment advances, breast cancer remains the commonest cause of cancer death in women, with a rate of 29/100,000 in 2003.

Most breast malignancies are sporadic with hereditary breast cancers accounting for only a small fraction.

ANATOMY

Structural anatomy

The breasts are modified sudoiferous (sweat) glands and, although present in both sexes, only fully mature in women during puberty. In males, the glandular tissue remains under-developed and breasts appear to serve only a rudimentary function. The breast exists as a circular swelling of tissue, typically extending from the second to sixth rib anteriorly. Each breast possesses a central nipple surrounded by a pigmented areola. For the purposes of examination, the breast is divided into four anatomical quadrants transecting the areola. The superior lateral quadrant extends upwards into the axilla to form the tail of Spence.

Each breast contains a single complex mammary gland composed of between ten and twenty simple mammary glands. A simple mammary gland describes all glandular tissue terminating in one lactiferous duct. Milk originates from lobules, each of which is composed of multiple alveoli. The alveoli are hollow cavities lined with myoepithelial cells and milk-producing cuboidal epithelial cells. Myoepithelial cells contract when stimulated by oxytocin to facilitate movement of milk away from the lobule. Milk then passes along the lactiferous duct which

widens at its terminus to form a lactiferous sinus. The lobular epithelium also secretes substances with both local and systemic effects. These glandular cells are significant as high turnover rate increases their risk of malignant change.

The breast is otherwise composed of connective tissue and adipose. Connective tissue aggregates within the breast to form suspensory ligaments – known as Cooper´s ligaments. These run from the clavipectoral fascia to the skin overlying the breast. Their function is to provide support and retain normal breast shape.

Vasculature
The blood supply to the breast arises from a number of sources:

- internal thoracic artery
- lateral thoracic artery
- thoracoacromial artery
- posterior intercostal arteries

Venous drainage typically passes to the axillary vein, although a proportion drains to the internal thoracic vein and the intercostal veins.

Innervation
Innvervation of the breast occurs via the anterior and lateral cutaneous branch of the fourth, fifth, and sixth intercostal nerves. Sensation to the nipple is supplied from the level of T4.

Lymphatic drainage
The majority (75%) of lymphatic drainage from the breast is to the axillary lymph nodes, particularly from the lateral breast quadrants. This is consequently a frequent site of cancer metastasis. The remaining lymph drains to para-sternal nodes, the contra-lateral breast, or abdominal lymph nodes.

Hormonal change
Breasts in women develop throughout the lifespan. The most significant changes occur during puberty and pregnancy. As breasts are composed largely of adipose, they may increase in size with weight gain. Breasts may also increase in size, as

well as becoming firmer, during pregnancy. This is largely the result of mammary gland hypertrophy in response to increased circulating prolactin. Changes to the size and consistency of the breast may also occur in breastfeeding, throughout the menstrual cycle, and with the combined oral contraceptive pill. Changes may be age related. Breast atrophy can follow oestrogen depletion at menopause and sagging may follow ligament elongation.

PATHOGENESIS

Cellular mutations
Neoplastic change in breast tissue can arise spontaneously or following a hereditary predisposition. Although breast carcinogenesis is a multi-stage process, a number of single genes have been heavily implicated in hereditary breast cancer. However, even non-hereditary breast cancers can have a have a family association. Three key mutations have been identified to date: *brca1*, *brca2*, and *tp53*.

Brca1 and *brca2* are tumour suppressor genes. *Brca1* is found on the long arm of chromosome 17 whereas *brca2* is on the long arm of chromosome 14. Their products are involved in the cellular DNA damage response. Mutation in either gene confers increased risk of cancer. However, penetrance of *brca1* is much greater and such mutations may lead to earlier onset (<40 years) of malignant change. *Brca1* tumours are also more likely to be high grade and oestrogen/progesterone receptor negative.

Tp53 is also a tumour suppressor gene and commonly implicated in a number of malignancies. It can activate DNA repair, suspension of the cell cycle, and apoptosis in response to genomic damage. Once again, mutations in this gene can significantly increase the risk of breast cancer.

Types of breast malignancy
There are two key types of breast cancer. *In situ* carcinomas are considered an earlier stage whilst invasive carcinomas are more advanced.

In situ carcinomas are malignant epithelial cells that have not invaded the basement membrane. There are two main types of non-invasive carcinoma: ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS).

DCIS is a carcinoma found in the lactiferous ducts that is not yet invasive. It is often considered a pre-malignant state as, if untreated, it may progress to invasive carcinoma. DCIS is often asymptomatic and, instead, is identified on mammography as areas of micro-calcification. Since the introduction of mammography, DCIS has been identified more frequently and now accounts for 20% of all newly diagnosed breast cancers. DCIS can present with similar markers to invasive cancer and can be oestrogen/progesterone receptor positive. DCIS is treated by wide local excision (WLE) or mastectomy.

LCIS is rarer than DCIS, and involves malignant change within the lobules at the ends of the ducts. The natural history of LCIS remains unclear, however, like DCIS, it is non-invasive and tends to be multi-focal. LCIS may progress to invasive cancer and so increased surveillance and/or hormone therapy are indicated.

Invasive carcinomas
Invasive carcinomas may be histologically classified either as a specific type (*e.g.* invasive lobular cancer) or as a carcinoma not otherwise specified (NOS). The majority of invasive breast cancers are NOS and are graded using the Bloom Richardson scale. This system grades tumours from 1-3, with higher grades accompanied by poorer prognoses.

Of the invasive carcinomas, lobular carcinoma is most common, accounting for 10-15% of breast cancer diagnoses. It typically presents between ages 40 and 45, and is associated with increased risk of malignant change in the unaffected breast. It can be difficult to detect invasive lobular carcinoma since it often appears as a thickening of breast tissue rather than as a discrete lump. Furthermore, micro-calcification is unusual so imaging by mammography is often unsatisfactory. For these reasons it is possible for the lump to remain undetected until later stages. Surgery is the mainstay of treatment, typically a wide local excision (WLE) or mastectomy where there is evidence of local metastasis.

Paget's disease of the breast is often caused by cancerous cells from a deep carcinoma, such as DCIS, migrating along the ductal system to the nipple. It presents as a red, encrusted rash with a discrete edge. This rash is frequently mistaken for eczema. Surgery is often indicated, with adjuvant therapies as appropriate.

Inflammatory breast cancer is rare, affecting just 1-2% of women with breast cancer. Patients typically present with inflamed skin overlying the tumour. Inflammatory breast cancer often has a *peau d'orange* (orange peel skin) appearance. Inflammatory breast cancer is often aggressive so treatment should not be delayed. Both surgical and adjuvant therapies may be indicated.

Metastasis

Early spread occurs along the lymphatic drainage from the breast, most commonly to the axillary lymph nodes. Bone is the most common site of breast cancer metastasis. Other sites include lung, liver, and brain.

AETIOLOGY

A number of risk factors have been identified in the aetiology of breast cancer. Most are associated with female reproductive development and include:

- early onset of first menarche
- late onset of menopause
- nulliparity
- late pregnancy (>35 years)

These factors may increase breast cancer risk by increasing exposure to oestrogens. It is possible that each menstrual cycle advances the risk of acquiring breast cancer by a small degree. This possibility is supported by a number of other risk factors which increase oestrogen exposure:

- oral contraceptive pill
- hormone replacement therapy (HRT), particularly oestrogen-progesterone HRT
- not breastfeeding

There is a significant genetic element, with risk of developing breast cancer doubling in the presence of a first degree relative with the disease. Individuals with one of three genes (*brca1*, *brca2*, and *tp53*) have a greatly increased risk of developing breast cancer. Some ethnic groups – particularly Ashkenazi Jews – have an increased predominance of the *brca1* gene. The familial pattern of inherited breast cancer suggests an autosomal dominant mode of inheritance with limited penetrance.

Other known risk factors for breast cancer include:

- alcohol consumption
- increased body mass index (BMI)
- poor diet (*e.g.* high saturated fats)
- low levels of physical activity
- smoking
- high socioeconomic status

PRESENTATION

Patients may present with a high risk family history or after noticing a breast change. Family history is an important feature of any breast history. Clinicians should seek a full family history, including first and second degree relatives. This should also include any family history of ovarian cancer. Other important family features may include:

- age of diagnosis
- tumour sites
- multiple cancers (including bilateral disease)
- Jewish ancestry

When patients present with a breast change, the following information should also be elicited:

- time elapsed since the lump was first noticed
- lump changes during the menstrual cycle
- previous lumps
- pain
- nipple discharge
- previous mammography or participation in screening

A thorough history of all known risk factors (p45) must be elicited.

All patients presenting with suspicious breast lesions should undergo triple assessment. This includes clinical examination, imaging, and histology/cytology. Each part of the assessment is scored from 1-5 depending on whether the findings are normal, benign, probably benign, possibly malignant or malignant.

The score gives a better idea of the patient's condition and helps to plan further treatment.

Clinical examination

The physical examination may be sensitive, embarrassing, and/or uncomfortable. For this reason, a chaperone should be offered. The patient should be exposed to waist level and the bed angled at 45° to provide adequate support. Stages of the examination include:

Inspection Both breasts should be inspected and compared from the front. The following features should be noted:

- size – highly variable
- symmetry – minor variation is normal, but any significant difference is probably due to underlying pathology
- skin – key changes to identify include temperature, puckering, *peau d'orange*, nodules, discolouration, and ulceration
- nipples and areolae – compare size, shape and level of both nipples. Key changes to look for are inversion, discharge and nipple changes (*e.g.* discoloration, deviation, retraction, or destruction). There may also be duplication or accessory nipples and ectopic breast tissue

The patient should next be asked to raise and hold their arms stationary above their head. This position can accentuate skin tethering. They should then tense their pectoral muscles by pressing both hands against their hips.

This is followed by inspection of the axilla and arms for any changes. These may include lumps, prominent lymph nodes, distended veins, and lymphoedema. The supraclavicular fossae must also be inspected for visible lymph nodes.

Palpation Palpation is performed using a flattened hand. With the patient at 45°, the "normal" side is palpated through each quadrant feeling for any lumps or changes in texture, noting any discomfort. This process is complicated by the highly variable nature of breast tissue. The axillary tail must also be palpated.

In the presence of a lump, the following features must be noted:

- site
- size
- shape
- surface
- consistency
- edge

In some cases it may be appropriate to examine for signs of metastases. See p45 for common sites of breast cancer spread.

Although early breast cancer may provide few clinical signs, established lesions may present with:

- a hard, irregular lump
- tethering or fixation to skin or underlying chest wall
- palpable axillary lymph glands

Many of the presentations of breast cancer can overlap with other breast pathologies including:

- lumps – fibroadenoma, nodularity (*i.e.* normal variation)
- painful lumps – cyst, abcess or cellulitis
- nipple discharge – Paget's disease of the breast, hormone imbalance, local infection
- nipple inversions – duct ectasia or periductal mastitis

Imaging

Mammography Mammography uses x-rays to resolve an image of the ductal structure of the breast. It also highlights abnormalities such as microcalcification. It is primarily used in women aged over 35 as aging is accompanied by a decline in the proportion of glandular tissue.

Ultrasound Ultrasound is often used in conjunction with mammography to increase diagnostic accuracy. It is also the primary form of imaging modality in women aged under 35 owing to the high density of the breast. There are a

number of limitations to using ultrasound as it is operator dependant and often fails to detect micro-calcification.

MRI MRI investigation uses the magnetic properties of atoms to provide a series of cross-sectional images of the breast. Some research suggests that MRI provides a higher level of sensitivity although this may be at the expensive of specificity, resulting in false positive results. When considered alongside the expense of MRI, this reduced specificity has prevented the use of MRI as a population screening tool for breast cancer.

Histology/cytology

Fine needle aspiration cytology FNAC can ascertain the cytological status of a suspicious breast lesion. A 10ml syringe with a 21 gauge needle is inserted into the lump, often guided by ultrasound, CT, or MRI. In the case of a cyst, total aspiration is possible, and may eliminate the cyst volume. In denser lesions, such as fibroadenomas, the sample is smeared between two slides. The slide is later stained using eosin and haematoxylin prior to interpretation. Each sample is assigned a cytology code, as described below:

Code	Meaning
C1	Insufficient material to make diagnosis
C2	Definitively benign
C3	Probably benign
C4	Potentially malignant
C5	Definitively malignant

Core biopsy Core biopsy enables a histological assessment of the lump. The procedure includes the following stages:

- local anaesthetic injected into overlying skin
- second, deeper injection of anaesthetic
- small puncture is made using a scalpel
- core biopsy needle is inserted
- automatic firing mechanism removes a small core of tissue

Core biopsy is often used when FNAC results in a cytology score of C1 or C3. Alternatively, the whole lump can be excised for histological examination. Other tests may determine the progesterone or oestrogen receptor status of sampled cells.

STAGING AND GRADING

Breast cancer staging uses a TNM system which considers tumour size, lymphatic spread, and distant metastases. Staging is a measure of growth and spread whereas grade is a measure of malignant aggressiveness. Breast cancers are categorised as:

- grade 1 – low grade
- grade 2 – intermediate grade
- grade 3 – high grade

Both values are used to inform management strategies and to estimate prognosis.

MANAGEMENT

Operative management

Factors affecting management include the nature of the disease, as well as patient preference. Most patients are treated by WLE of the mass, so maximising the quantity of breast tissue preserved.

Wide local excision Once imaging has determined the location and extent of a tumour, the goal is to achieve a suitable margin to maximise the likelihood of total clearance. It is frequently used to remove small lumps for cosmetic and practical reasons.

Mastectomy Mastectomy involves complete removal of the affected breast. This procedure may be favoured for a number of reasons, *e.g.* in the presence of a large tumour. Although it may result in a less favourable cosmetic outcome, it is often possible to reconstruct the breast or offer a prosthesis. Mastectomy is the treatment of choice in the presence of nipple involvement or a multifocal cancer. In some instances, mastectomy can be performed solely at patient request.

Radiotherapy to the remaining breast following mastectomy is not routinely performed unless some doubt remains over clearance or possible local metastases.

In radical mastectomy, axillary lymph nodes are removed along with pectoralis major, and the breast tissue.

Sentinel lymph node biopsy Sentinel lymph node biopsy involves sampling axillary lymph nodes for histological examination. Biopsy or removal is usually carried out in women undergoing breast surgery to fully stage their disease. Recent studies show this technique can be of value in detecting lymphatic metastases in women scheduled for mastectomy.

The technique involves injection of radioactive material into the breast which tracks along the local lymphatic system. A dye is also injected. This helps identify the lymph nodes most likely to be affected which are removed and sent for pathological examination.

Radiotherapy Radiotherapy has a number of uses in managing breast cancer. It may be used to reduce tumour mass prior to surgery and afterwards in an attempt to eliminate remaining malignant cells. It can also be used in conjunction with chemotherapy to enhance treatment efficacy. The majority (80%) of surgical patients receive radiotherapy, usually post-operatively. This is particularly common following WLE. A typical regime consists of a five-week course for the affected breast, given for five days in a week. A dose of around 50Gy is given for this period, although an additional 10Gy may be administered in the sixth week.

Radiotherapy can reduce the risk of cancer recurrence from 30% to just 7% in the subsequent ten years.

Endocrine therapy Hormonal therapies may be indicated where a tumour is found to possess high levels of oestrogen and progesterone receptors. Oestrogen/progesterone receptor positive tumours are stimulated to grow when these receptors are stimulated. There are many selective oestrogen receptor modulators (SERMs) that act by blocking this pathway. The most commonly used SERM in breast cancer is tamoxifen which reduces epithelial cell proliferation. Tamoxifen is given for five years to prevent recurrence. Another hormonal therapy, anastrozole (Arimidex), is often given in conjunction or following

tamoxifen. It is an aromatase inhibitor and prevents conversion of androgens to oestrogen. Both drugs carry side effects similar to menopausal symptoms.

Chemotherapy Cytotoxic chemotherapy preferentially targets highly mitotic cells, such as those that are malignant. A number of different drugs may be given to target cells at different stages of division. The drugs can be administered orally or intravenously via a catheter. Six cycles of chemotherapy are usually given at 3-4 weekly intervals, however this can be tailored to suit the patient. Chemotherapeutic drugs also target non-malignant dividing cells leading to a number of systemic side effects. These include nausea, vomiting, hair loss, decreased libido, decreased fertility, fatigue, and suppression of bone marrow.

Biological therapy Trastuzumab (Herceptin) is a monoclonal antibody developed to block the HER-2 receptor. This is an effective treatment for HER-2 positive tumours, particularly in conjunction with chemotherapy. Other potential agents include bevacizumab (Avastin) and lapatinib (Tyverb).

Prostheses Prostheses are offered following mastectomy to help alleviate the psychological and cosmetic impact. They are available on the NHS and include shell or full prostheses, swimming prostheses, and artificial nipples.

Reconstruction Reconstructive surgery is an alternative to fitting a breast prosthesis. It should be offered to all women undergoing operative management for breast cancer. A period of six to twelve months is often left after the initial operation to permit maximum recovery. In cases where enough skin and tissue exists, a subcutaneous implant may be fitted. Alternatively, a skin flap can be taken from elsewhere on the body (often the back) and combined with an inflatable saline implant. Nipple reconstruction is also available.

Lung Cancer

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Lung cancer is the leading cause of cancer death worldwide. It can be divided into two sub-types based on histological examination of tumour biopsies. These are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the latter being the most prevalent. SCLC metastasises rapidly and aggressively and has a poorer prognosis. NSCLC is slower growing and often more amenable to treatment. This chapter limits itself to discussion of NSCLC as the most frequently encountered histological sub-type.

Worldwide, there are around 1.35 million new cases and 1.18 million lung cancer deaths per year. Approximately half of these cases arise in developing countries. Global incidence for males is 35.5 per 100,000 and 12.1 per 100,000 for females. There has been a change in the pattern of distribution between the sexes over the past twenty years. Despite an age standardised decrease in incidence rates of lung cancer for males in the United States and Europe, female incidence rates have increased by 22% over the same period. This is probably explained by changes in smoking habits. Five year survival for lung cancer is in the region of 15% in the United States, 10% in Europe and 8.9% in developing countries.

In the UK there were 33,400 deaths in 2005 from lung cancer, which accounts for 6% of all deaths and 22% of cancer mortality. Age standardised mortality rates are higher in men at 54 per 100,000 compared to 30 per 100,000 for women. Since 2001, the number of new cases has dropped below 50 per 100,000.

Survival rates in the UK are low. In an analysis that followed patients diagnosed between 1993 and 1995, only 21.4% of males and 21.8% of females were alive after one year, and five year survival was 5.5%. This is one of the poorest cancer prognoses, with only three exceptions: liver, pancreas, and pleura. One year survival has slightly improved in both sexes since 1971. However, this is likely to reflect improvements in palliative care rather than successful treatment, as the five year survival rate remains very poor.

The peak incidence of lung cancer in the UK is between 75 and 80 years of age. This is important as patients will have increasing numbers of co-morbidities which can affect their eligibility for treatment and response to treatments.

ANATOMY

The respiratory tract can be divided into two functional areas: the conducting portion which carries air to and from the lungs, and the respiratory portion which is responsible for gas exchange between air and blood.

The conducting portion includes the trachea, which divides into left and right primary bronchi. In each lung, the primary bronchus branches into secondary bronchi, and then into progressively smaller airways known as bronchioles. These further divide into terminal bronchioles, and finally into respiratory bronchioles and alveoli. There are approximately 25 divisions between the trachea and the alveoli.

The respiratory portion begins at the respiratory bronchioles which feed into the alveoli. There are around 300 million alveoli in the each lung, and they are the site of gaseous exchange. Blood is oxygenated from alveolar air, and carbon dioxide (the waste product of metabolism) is removed. Gas exchange occurs rapidly and efficiently as the distance between the blood in the alveolar capillary and air inside the alveolus is usually less than 1µm. To meet the metabolic demands of tissues, this exchange surface is vast (approximately $70m^2$ to $140m^2$).

There are different types of epithelium lining different portions of the respiratory tract. The trachea is lined with pseudo-stratified ciliated columnar epithelium, and the bronchioles with ciliated columnar epithelium which then become ciliated cubodial epithelium with scattered cilia. The alveoli are lined with simple squamous epithelial cells known as type I pneumocytes.

PATHOGENESIS

Lung cancer affects the epithelial cells that line the conducting passageways, mucous glands and alveoli. Normal cell turnover is controlled by many proteins and complex signalling pathways. Genetic mutations arise within a single affected cell and, over subsequent cell divisions, heterogenicity develops to build further abnormalities. The International Agency for Research on Cancer (IARC) has classified 81 compounds in cigarette smoke as carcinogens. Carcinogens are

mutagens – they cause genetic mutations by modifying DNA or by causing chromosomal damage. These compounds can act on many sites throughout the bronchial tree, resulting in the different histological features associated with NSCLC. Tumour suppressor and oncogenes particularly associated with lung cancer include:

p53
Identified as one of the most common genes to be affected in human cancer. Squamous cell carcinomas have the highest frequency of *p53* mutations – 50 to 70%. Adenocarcinoma and large cell neuroendocrine tumours also show mutations in *p53*, albeit at a lower incidence.

Rb
Affected in most types of lung cancer, especially large cell neuroendocrine tumours.

K-ras
Often affected in atypical adenomatous hyperplasia (AAH) and adenocarcinoma.

Metastasis
NSCLC metastasises through four main routes:

- local invasion (into surrounding structures)
- lymphatic spread (*e.g.* peri-bronchial and hilar lymph nodes)
- transcoelomic spread (*e.g.* pleural, pericardial and peritoneal cavities)
- vascular spread via capillaries and veins (*e.g.* to brain, liver, bone and adrenal glands)

AETIOLOGY

Tobacco smoke
Researchers first linked tobacco smoking to lung cancer in the early 1950s. Today, it is well established that cigarette smoking is the most important risk factor in the development of lung cancer. The increased incidence of lung cancer is strongly correlated with patterns of cigarette smoking. In 2002, a report published on global cancer statistics reported that 85% of lung cancer in men and 47% of the disease in women was the consequence of tobacco smoking. In the

UK it is estimated that 90% of all cases of lung cancer are caused by tobacco smoking with people who smoke twenty cigarettes or more a day being twenty times more likely to develop lung cancer than those who never smoked.

Environmental tobacco smoke

There is a strong link between environmental tobacco smoke (passive smoking) and lung cancer. A meta-analysis of 37 studies on lung cancer and environmental tobacco smoke found a 24% increased risk in lifelong non-smokers who lived with a smoker. The British Medical Association (BMA) estimates that 1000 people die each year in the UK as a result of passive smoking.

Occupational and other environmental factors

Whilst exposure to tobacco smoke is the clearest aetiological agent in the development of lung cancer, substances such as asbestos, nickel, chromium, iron oxides, sources of radiation, and emissions from coal gas plants are all implicated in the development of lung cancer. Radon, a naturally occurring radioactive gas, is estimated to be responsible for approximately 2000 lung cancer deaths every year in the UK.

PRESENTATION

In the early stages, NSCLC is asymptomatic, making detection and diagnosis challenging. Approximately 80% of patients with lung cancer present with stage III or IV of the disease, excluding them from potentially curative surgery.

The lung parenchyma has no sensory nerve fibres and therefore symptoms only occur in the latter stages when compression, invasion or metastasis into surrounding tissues or organs occurs. In addition, patients may overlook these symptoms or mistake them for other conditions. Patients often have co-morbidities such as chronic obstructive pulmonary disease (COPD), heart failure, hypertension and diabetes which make the recognition of new symptoms difficult.

The most common bronchopulmonary symptoms are brought about by compression or invasion of the primary tumour into the surrounding lung parenchyma and include:

- cough
- haemoptysis
- shortness of breath
- wheezing
- chest or shoulder pain or both
- fever

Many patients are smokers or ex-smokers and attribute their cough and breathlessness to a "smokers cough". A slogan used by the UK Lung Cancer Coalition ("there is no such thing as a smokers cough") highlights the importance of identifying the underlying cause behind any cough. Patients should be educated to be alert to any recent changes to a regular cough such as more productive, increased cough frequency, or sputum that is blood streaked.

Chest or shoulder pain suggests parietal pleural involvement or further extension beyond the lung. Superior sulcus tumours may produce shoulder pain, arm pain, brachical plexopathy, or Horner's syndrome.

Most patients with NSCLC report at least one bronchopulmonary symptom. These include cough (46%), shortness of breath (43.3%), and haemoptysis (15.4%). Mediastinal spread of left-sided tumours or nodes may cause left recurrent laryngeal nerve injury leading to hoarseness. Obstruction of the superior vena cava may occur due to right-sided tumours or associated lymphadenopathy.

Systemic features of malignancy include common, non-specific symptoms, such as weight loss, anorexia, malaise, weakness, and severe fatigue. Symptoms related to para-neoplastic syndrome are much less common, but patients can present with pain in the arm or leg from hypertrophic pulmonary osteoarthropathy, or with symptoms of hypercalcaemia.

Guidelines based on the most common symptoms seen in lung cancer are now used to identify potential malignancies. A patient presenting with unexplained or persistent cough, dyspnoea and weight loss should be referred to a specialist within two weeks.

Physical examination
Physical signs observed in patients with lung cancer include:

- clubbing
- lymphadenopathy
- pleural effusion
- lobar collapse
- unresolved pneumonia
- superior vena cava syndrome
- Horner's syndrome
- pericardial tamponade

Imaging

Chest x-ray The chest x-ray is an essential and compulsory first-line investigation for suspected lung cancer. It is a simple and cheap diagnostic tool, but is an insensitive method of diagnosis, requiring considerable interpretation and clinical judgment.

Computerised tomography CT is used to identify evidence of metastatic disease, assess local tumour invasion, and search for mediastinal and hilar lymphadenopathy. CT has a diagnostic accuracy of 88% in the mediastinum and 80% in the aortopulmonary (AP) window. The accuracy rises to 95% for adenocarcinoma, but is only 71% for squamous cell carcinoma. The presence of enlarged mediastinal nodes on CT does not exclude that patient from surgery because false positives can occur, *e.g.* post-obstructive infection can lead to inflammatory lymphadenopathy.

Positron emission tomography PET uses a glucose analogue labelled with positron emitting fluorine, 18F-deoxyglucose (FDG), to collect functional information about cells. Malignant cells have a higher rate of glucose metabolism than normal cells and therefore absorb more FDG. They are identified on the scan as high activity areas. It is a highly sensitive and specific method for mediastinal staging.

Histology/cytology

Bronchoscopy Before bronchoscopy is performed the patient must be assessed to determine whether they are medically stable and fit according to British Thoracic Society (BTS) guidelines. The National Institute for Clinical Excellence (NICE) consider bronchoscopy a "reasonably accurate" method for diagnosis of central disease (lesions >2cm) but it is not recommended for patients with peripheral lung disease.

Sputum cytology Sputum cytology is a useful alternative diagnostic method for patients unwilling to undergo, or medically unsuitable for, bronchoscopy. NICE guidance states that, whilst it is useful for detecting central masses, it has a low sensitivity in identification of peripheral mass malignancies.

Percutaneous transthoracic needle biopsy This procedure involves inserting a needle through the skin to remove tissue or fluid from the area of disease. The site for insertion of the needle is guided by fluoroscopy, CT, or ultrasound.

Additional investigations

A number of additional tests are available and include mediastinal node sampling, pleural aspiration, and assessment of lung function (spirometry).

STAGING AND GRADING

The International System for Staging Lung Cancer is currently used for NSCLC. It is based on the TNM descriptors which are used to classify malignant tumours according to the extent of the primary tumour (T), regional lymph node involvement (N) and distant metastasis (M), if present.

From this information the cancer is assigned a stage which is important in determining prognosis and subsequent treatment. Staging cancer enables the health care team to manage patients appropriately according to the extent of their disease and expected survival.

MANAGEMENT

Determining the extent of tumour spread (TNM stage) and histological subtype are essential in managing NSCLC. The specific treatment depends upon the disease at presentation: early, locally advanced, or advanced disease.

The majority of patients present with advanced disease and so receive palliative therapy. This does not aim to cure the disease, but to improve patients' symptoms and quality of life (p123).

In a study involving 40,909 patients with NSCLC, 67.7% presented with stage III or IV disease. This discussion therefore focuses on therapies for advanced disease (stage III and IV) as these are most commonly undertaken.

Patient eligibility

Performance status is used to assess patient eligibility for treatment. The most commonly used system is the World Health Organization (WHO) performance scale. Patients with a lower performance status respond better to chemotherapy and radiotherapy. The scale is as follows:

- asymptomatic - fully active, can carry out all functions without restriction
- symptomatic, but ambulatory – able to carry out light work
- in bed <50% of day – unable to work but able to live at home with some assistance
- in bed >50% of day
- confined to bed/chair

Surgical resection

For patients with early stage disease, surgical resection is the most successful treatment. However, only 15-25% of patients present with tumours that are potentially curable. Surgical resection is usually only recommended for *locally* advanced NSCLC-stage IIIa. Accurate staging and reliable assessment of clinical disease with CT and other investigations are vital. There are mortality and morbidity risks associated with surgery, and guidelines on appropriate patient selection for surgery are available from the British Thoracic Society. The pulmonary reserve of lung cancer patients is commonly diminished because of

tobacco use which may have implications for operative and anaesthetic management.

Surgery alone has a poor prognosis for stage IIIa (N2) disease, and these patients should be evaluated closely by the multidisciplinary team. Generally stage IIIb disease is inoperable, although carinal resections have been carried out for patients with T4N0M0 disease.

Radical radiotherapy

The goal of radical radiotherapy is to control the primary tumour and hilar or mediastinal lymph nodes. In a study from the United States involving over 40,000 patients, the most widely used therapy for NSCLC was radiotherapy with or without chemotherapy.

Radical radiotherapy involves external beam radiotherapy delivered at a high dose to the affected area. This is delivered daily in 2Gy fractions (treatments) five days per week to a total dose of 60Gy or more. Hyper-fractioned and accelerated regimes are also used. The former treatment consists of two or more fractions daily (<2Gy per fraction). Accelerated regimes are completed over a shorter time course than conventional therapy.

Patients must be accurately staged with a CT of the thorax/upper abdomen and mediastinoscopy to assess mediastinal nodes. PET scanning may also help to clarify the exact nature of the disease prior to radiotherapy.

Data comparing radiotherapy with best supportive care or other treatment regimes is limited and so overall effectiveness is difficult to assess. However, radiotherapy has shown increased survival compared to untreated NSCLC. Two year survival increased from 0-4% for untreated stage III patients to 12.5-24% for patients treated with radical radiotherapy.

Chemotherapy

Chemotherapy is the administration of intravenous cytotoxic drugs. These drugs directly damage cellular DNA (and RNA), promoting apoptosis and frank necrosis. Cytotoxic agents exploit the differences between normal and cancerous cells, but the drugs are not cancer specific and so can damage normal tissues. There is a narrow therapeutic window between the effective treatment of cancer and

normal tissue toxicity. This therapeutic window dictates the dose and schedule of chemotherapy.

Chemotherapy is used primarily in palliative care (p123) for alleviating symptoms and improving quality of life, but toxicity and associated side effects cause problems for many patients. First, second, and third line chemotherapy agents are available. However, due to performance status, most patients will only be eligible for first line therapy. There is no gold standard treatment. Single agent cytotoxic drugs commonly used in the management of NSCLC are listed below. They are reported to produce significant tumour shrinkage in at least 15% of patients.

Older drugs	New drugs
Cisplatin	Docetaxel
Carboplatin	Paclitaxel
Etoposide	Irinotecan
Vinblastine	Vinorelbine
Vindesine	Gemcitabine

Primary chemotherapy is usually given to patients unsuitable for surgery or radical radiotherapy. The aim of this treatment is to decrease tumour size so that they might progress to curative surgery or radical radiotherapy. Current regimes combine the new agents with cisplatin or carboplatin giving better side effect profiles, higher response rates, and improved survival.

Combination therapy

Improved survival for NSCLC patients may be gained by combining modes of treatment.

- adjuvant treatment (chemotherapy or radiotherapy) is given *after* curative-intent surgery or radiotherapy
- neo-adjuvant chemotherapy is given *before* planned curative-intent surgery or radiotherapy
- combined chemoradiotherapy is given to patients eligible for radical radiotherapy, either concurrently or sequentially

Sequential chemotherapy and radiotherapy for stage IIIa offers a survival advantage over radiotherapy alone and is the current gold standard of treatment.

Primary concurrent cisplatin-based chemoradiotherapy for inoperable stage III tumours shows increased survival compared with radiotherapy alone.

Side effects and contraindications
Contraindications to radical radiotherapy include pericardial effusion, cytologically positive pleural effusions and supraclavicular nodes. Contra-lateral mediastinal nodes are relative contraindications for stage III NSCLC. Severe weight loss and poor performance status are also contraindications for radiotherapy and chemotherapy.

Side effects of chemotherapy are very common and are usually dose related. The most commonly reported side effects are:

- nausea and vomiting
- hair loss
- myelosuppression
- mucositis
- fatigue

Radiotherapy side effects depend upon tissue sensitivity, fraction size, and treatment volume. They are usually self-limiting but toxicity can be enhanced by chemotherapy. The most common early side effects are:

- anorexia, nausea, malaise
- mucositis, oesophagitis, diarrhoea
- alopecia
- myelosuppresion

PALLIATIVE MANAGEMENT
The majority of patients with advanced stage NSCLC will die within the first year of diagnosis. Patients present with such extensive metastatic disease that management focuses on palliation of symptoms and treatments that improve quality of life. Palliative care is reviewed from pages p123 to p131.

Palliative chemotherapy

A meta-analysis of clinical trials for chemotherapy versus best supportive care for inoperable NSCLC found a significant survival advantage for cisplatin-based chemotherapy. However, this review focussed on patients less than 75 years old, with minimal weight loss and good performance status.

Chemotherapy improves symptoms of dyspnoea, haemoptysis and weight loss, and can reduce pain and cough. However, the use of palliative chemotherapy has been controversial for many years. Its use has only recently become accepted, as the side effects were deemed to outweigh survival benefits. Importantly, the minimum survival benefit required to accept the toxicity and side effects of chemotherapy varies from patient to patient. It is therefore vital that clinicians assess each case on an individual basis and that the ultimate treatment decision remains with patients and their families. The indications for palliative chemotherapy include:

- locally advanced or metastatic NSCLC not suitable for radical approach
- performance status 0-1
- adequate renal function (creatinine clearance >45ml/min)
- haemoglobin >9g/dl
- platelet count >100 x 10^9/L
- neutrophils >1.5 x 10^9/L
- liver function tests should be less than three times the upper normal limit, or less than five times the upper normal limit if known liver metastasis

Palliative radiotherapy

Radiotherapy is used to palliate the local symptoms of NSCLC, *e.g.* cough due to bronchial obstruction, haemoptysis, chest pain, dysphagia, and breathlessness. It is not beneficial when cough or dyspnoea are due to multiple lung metastases or pleural effusion.

A Cochrane review of fourteen trials focussed on the most effective and least toxic regime for palliative radiotherapy for NSCLC concluded that radiotherapy is effective in controlling symptoms from intra-thoracic tumours.

Symptom management

In the terminal phase of lung cancer up to 80% of patients present with symptoms of breathlessness, cough, anorexia, and asthenia (weakness or loss of strength).

Dyspnoea Dyspnoea is a subjective experience of difficult, uncomfortable and sometimes painful breathing. It is one of the most distressing symptoms of advanced lung cancer. Palliative radiotherapy can help improve symptoms with recommended doses of 10Gy in one fraction or 16-17Gy in two fractions. Other therapies for management of dyspnoea include physical de-bulking of the tumour via rigid bronchoscopy, laser treatment, photodynamic therapy, stents, and brachytherapy. Specialist breathlessness clinics are now available in most cancer centres and can significantly improve quality of life for patients with lung cancer. Pharmacological therapies for dyspnoea include bronchodilators (such as ß2-agonists), corticosteroids, and opioid analgesics.

Cough Cough is a recurrent and distressing symptom for patients with lung cancer. Cough and haemoptysis are improved by palliative radiotherapy, both external and endo-luminal. Cough can also be reduced by cough suppressants, bronchodilators, opioid and non-opioid analgesics.

Hoarseness Hoarseness may be due to recurrent laryngeal nerve involvement. NICE guidance states that this rarely responds to external beam radiotherapy and recommends referral to an ear, nose and throat specialist.

Superior vena cava obstruction (SVCO) SVCO is due to a tumour mass arising from either right middle or upper lobe bronchus or bulky mediastinal lymph nodes from right para-tracheal or pre-carinal stations. It leads to oedema of the face, neck and arms.   Common treatment methods include radiotherapy, systemic corticosteroids, and insertion of a superior vena cava stent.

Brain metastases Radiation therapy for brain metastases can produce good symptom relief and improved function. However, many patients feel worse after therapy and discontinue treatment. Corticosteroids such as dexamethasone are used to reduce symptoms caused by cerebral metastases by reducing cerebral oedema.

Other symptoms It is important to palliate other symptoms such as spinal cord compression, hypercalcaemia, and bone pain. The majority of patients also

develop fatigue, general malaise, anorexia and weight loss during or after therapy. In the majority of cases, symptoms are due to a combination of health status, tumour burden and nutritional status, and are not indictors of a particular systemic or organ specific problem.

Cervical Cancer

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Cervical cancer is the second most common malignant neoplasm affecting women worldwide. This disease accounts for nearly 10% of all cancers, excluding non-melanoma skin cancers. In 2002, there were around 493,000 new cases of invasive cervical cancer, the majority in developing countries. The areas with the highest incidence of cervical cancer are Southern and Eastern Africa, Melanesia, the Caribbean, and Central America. There is a 700% variation in the incidence of cervical cancer around the world, largely due to differences in health service provision. Historical incidence of cervical cancer in the UK exhibits a cohort effect. The increased risk in women born after the mid-1940s is consistent with changing sexual behaviour since the 1960s following introduction of the oral contraceptive pill.

Cervical cancer causes over 1,000 deaths each year in the UK. The mortality rate in 2005 was 2.6 per 100,000 females. This was 60% lower than in 1975. In the latter half of the twentieth century the death rate from cervical cancer for women aged 55-64 dropped by nearly 80% from 30 per 100,000 in 1950-52 to 6.2 per 100,000 in 1998-2000. Mortality rates from cervical cancer generally increase with age.

The fall in cervical cancer mortality is partly due to the success of the screening programme which was introduced in 1988. The decline seen in the UK has been mirrored by most western European countries.

ANATOMY

Structural anatomy
The cervix is comprised of an endocervical canal, and an opening at either end known as the internal and external os. The surface of the cervix facing into the vagina is known as the ectocervix. This is elliptical and convex in appearance. The opening which lies within the ectocervix is the external os and can vary in size and

shape. Factors affecting the shape and size include age, hormonal environment, and parity.

Between the external and internal os lies the endocervical canal which is also variable in size. At the end of the endocervical canal is the internal os which opens into the uterine cavity.

The squamous epithelium of the vagina and cervix is composed of four layers:

- basal cells (on the basement membrane)
- para-basal cells (oval shape, central nucleus)
- intermediate squamous cells (polygonal shape, arranged in clumps or singly that look flat or folded)
- superficial or mature squamous cells (pyknotic (shrinking) nucleus)

The squamo-columnar junction (SCJ) is the point at which the squamous epithelium lining the ectocervix and the columnar glandular epithelium of the endocervix meet. The position of the junction moves in relation to the anatomical external cervical os during female development. Changes in oestrogen such as those occurring during puberty, pregnancy or while on the combined oral contraceptive pill (COCP) move the SCJ outwards, thus exposing columnar epithelium to the lower pH of the vagina. It reacts by undergoing transformation back to squamous epithelium by a process known as squamous metaplasia. The area that lies between the original SCJ position and that reached as it moves outwards across the ectocervix is known as the transformation zone (TZ). The TZ is the location at which most pre-invasive lesions occur.

Vasculature
The arterial blood supply to the cervix arises from the:

- uterine artery (main supply)
- vaginal artery (cervical branch)

Innervation
The innervation of the cervix is from the Frankenhãuser plexus, originating from the terminal pre-sacral plexus.

PATHOGENESIS

Human papilloma virus (HPV) is the primary cause of cervical cancer. More than 90% of squamous cervical cancers contain HPV DNA. The virus is acquired mainly through sexual activity. HPV subtypes 16, 18, 45 and 31 are most commonly identified in cervical carcinomas.

Structure of HPV

Papilloma viruses have no envelope and consist of a capsid composed of 72 capsomeres. The absence of an envelope means that papilloma viruses are relatively stable and resistant to decay. They are able to survive extracellularly for more than a week. There are 130 different HPV types currently described.

Important proteins

There are a number of different key proteins implicated in the pathogenesis of HPV-induced cervical cancers. A number of these are outlined below.

E6 High risk (HR) E6 proteins inhibit P53 function. Upon binding of E6 to P53, ubiquitin-dependent degradation of P53 is increased. The half-life of P53 is shortened from three hours to 20 minutes. It is therefore degraded at a faster rate and its biological function is reduced.

E7 E7 is a HPV oncogene that induces cellular proliferation by binding proteins of the retinoblastoma (RB) family. The retinoblastoma gene is a transcriptional regulator that inhibits cell proliferation. *Rb* gene products control the transition of the cell cycle from the G1 to the S phase together with the E2F family of transcription factors (p5). Binding of E7 to the hypo-phosphorylated active form of RB, and its subsequent degradation, leads to E2F activation. This permits cellular progression into S phase of the cell cycle with subsequent cell replication and uncontrolled proliferation.

Transmission

Clinical, sub-clinical, and latent HPV infections are now the most common sexually transmitted infections. HPV can be detected in 5–40% of sexually active women. The majority of women who are sexually active will acquire HPV infection during their lifetime.

Disease progression

Cervical intraepithelial neoplasia (CIN) refers to the spectrum of neoplastic epithelial changes that take place in squamous epithelium. The severity of the lesion is assessed subjectively as grade (CIN) 1, 2 or 3, according to the level of neoplastic change. Grade 1 represents mild dysplasia; nuclear abnormalities throughout the epithelium and cytoplasmic differentiation in the upper two-thirds are present. Grade 2 represents moderate dysplasia, with differentiation in the upper third of the epithelium. Grade 3 represents severe dysplasia and carcinoma *in situ*.

CIN is potentially invasive at any stage, although the risk of invasion is proportional to the severity of the lesion. It is estimated that 11% of CIN 1 cases would progress to CIN 3 within 3 years. More than 12% of cases of CIN 3 progress to invasion if untreated, whereas about 30% spontaneously regress. The presence of abnormal mitotic cells is associated with progression. Due to inconsistencies in assessing lesion severity, cervical neoplasia is often classified as "low" (CIN 1) or "high" (CIN2 and 3) grade intra-epithelial neoplasia.

AETIOLOGY

Sexual intercourse

HPV is predominantly transmitted through sexual intercourse. Epidemiological studies on HPV infection have consistently shown the main risk factors for women are number of sexual partners, age of sexual debut, and the past sexual behavior of her partners. The strongest evidence that genital HPV is sexually transmitted comes from longitudinal studies of women who began sexual activity during the study period.

Smoking

Carcinogens from tobacco increase the risk of cervical cancer. It has been demonstrated that cigarette smoke induces malignant transformation in HPV16-immortalised human endocervical cells. Both nicotine and tobacco-specific carcinogens have been detected in the cervical mucus of smokers. Another hypothesis is that exposure to tobacco may affect the ability of the host to express an effective local immune response against viral infections. This could be because smoking reduces the number of Langerhans cells and other markers of immune function. A recent prospective study showed that smokers maintain

cervical HPV infections for longer and have a lower probability of clearing oncogenic infections than women who never smoked.

Parity
In women persistently exposed to HPV infection, parity above five full term pregnancies increases risk of neoplastic progression.

Contraceptive pill
The use of oral contraceptives for five or more years increases the risk of cervical cancer, possibly by encouraging unprotected sexual intercourse.

Dietary factors
Studies have shown that fruit and vegetables have a protective effect in reducing HPV-DNA persistence. In particular, lycopene and vitamin E both have protective effects.

HIV
HPV and HIV share specific behavioural traits. Compared with an HIV-negative population, HIV-positive individuals show increased progression from HPV infection to CIN lesions and cancer in the absence of screening. Progression of HPV infection is probably related to the severity of immunosuppression, as indicated by CD4+ cell counts.

PRESENTATION
Patients with CIN or micro-invasive carcinoma will likely be asymptomatic, although these early changes can be detected using cytological screening (*e.g.* Papanicolaou or "Pap" smear test).

Patients with invasive cervical carcinoma may present with post-coital bleeding, inter-menstrual bleeding or post-menopausal bleeding. They may also present with a foul-smelling discharge, which may be thin, watery and, occasionally, blood-stained. The patient may develop anaemia from vaginal bleeding. Other presenting symptoms include haematuria, urinary frequency, and dysuria.

Pelvic and/or leg pain is uncommon in early tumours, but often occurs later in the disease process. Metastatic disease affects the nerves and bone leading to severe and persistent pain. Rectal metastases may lead to a feeling of incomplete

defecation (tenesmus), diarrhoea or rectal bleeding. Patients may also present with a vesico-vaginal or recto-vaginal fistula but this is extremely rare.

Physical examination
Bimanual examination may reveal a hard, friable, enlarged cervix which may bleed on contact. In more advanced disease the cervix becomes fixed or replaced by a rough mass.

The supraclavicular and inguinal lymph nodes should be examined for signs of lymphatic spread, and the abdomen palpated for hepatomegaly or evidence of renal metastases.

Investigations

Colposcopy Colposcopy involves inspection of the cervix through a binocular microscope at ten times normal magnification using a light source. The patient attends as an outpatient, with the procedure performed using a speculum to expose the cervix. Squamous neoplasia is most commonly found in the areas adjacent to the junction of the columnar (velvety red) and squamous (smooth pink) epithelium, i.e. the SCJ.

Colposcopy is indicated if cytology shows dyskaryosis (nuclear abnormalities in the epithelial cells) or malignant change. CIN appears as a white area with a well-defined edge following the application of 5% acetic acid solution. In early cervical carcinoma a raised or ulcerated area may be visible with small blood vessels beneath the epithelium. These vessels may appear as a mosaic pattern or as punctuations ("dots").

Suspicious features on colposcopy include:

- intense acetowhite – pale on iodine staining
- mosaicism and punctuation due to atypical vessel formation
- raised or ulcerated surface

Biochemical investigations Squamous cell carcinomas (SCC) are associated with elevated levels of SCC antigen as well as cytokeratin fragments. SCC antigen and

CA125 will give prognostic information in patients with cervical carcinoma and may be valuable in indicating relapse prior to imaging.

Histology/cytology The term "dyskaryosis" is used to describe cells that exhibit general changes which do not fully suggest malignancy, but with suspicious nuclear changes. Cells showing abnormalities that cannot be classified as dyskaryosis are described as borderline. Malignant cells can be identified since they show nuclear enlargement with reduced cytoplasmic mass. The nuclei may also have a lobulated outline. There is increased intensity of staining of the nucleus and an increase in the number of mitotic bodies.

Correlation between cytological/histological changes in the cervix and severity of disease is poor, with more extensive lesions not necessarily exhibiting the greatest degree of dyskaryosis. The presence of dyskaryosis or malignant cells on cytology indicates that examination by colposcopy is necessary.

Neoplastic cells possess increased nuclear material in relation to cytoplasm and less surface glycogen than normal squamous epithelium. They are associated with a degree of hypertrophy of the underlying vasculature. These features are exploited in colposcopic examination. When exposed to 5% acetic acid the nuclear protein coagulates, giving the neoplastic cells a characteristic white appearance.

CIN can also be identified by applying Schiller's iodine solution which stains normal cervical epithelium dark brown. In CIN, the nuclear protein does not react with the iodine, and so the specimen remains pink. The increased capillary vascularity may be visible through the epithelium as red dots (punctuation) or a mosaic pattern.

The diagnosis of cervical cancer is established histologically by taking a biopsy of the lesion, which should be greater than 5 mm in depth to distinguish between micro-invasive and invasive disease. A biopsy sample must be taken from any suspicious lesion, because many smears are non-diagnostic or falsely-negative in the presence of invasive cancer. If a biopsy sample suggests micro-invasion, and if the patient does not have a grossly apparent invasive cancer, a cone biopsy should be performed. For accurate staging of clinically occult lesions, sufficient underlying stroma must be obtained to allow for adequate assessment of the depth and width of invasion below the basement membrane.

SCREENING

The NHS National Screening Programme was introduced in England and Wales in 1988. Three years later, 80% of all women between the ages of 20-65 were being tested on a 5-yearly basis. Today, the screening programme targets women aged between 25 and 64. Since the introduction of the programme, mortality from cervical cancer has fallen by 7% per year. It has been estimated that the risk of dying from cervical cancer falls by 75% when a patient attends regular screening appointments.

There has been a gradual decline over the past ten years in the percentage of eligible women who have attended screening at least once in five years. In 1996, 82% of eligible women were screened, compared with 79.5% in 2006.

Papanicolaou smear test

This technique involves taking a sample of cervical cells which are then assessed for signs of abnormality. The preparation is stained using the Papanicolaou technique, resulting in the nuclei staining blue, the superficial cytoplasm pink, and the intermediate para-basal cell cytoplasm blue/green.

The cervical screening programme uses this technique to detect CIN by screening the asymptomatic population. The programme aims to reduce mortality from cervical carcinoma through earlier detection of the disease.

Despite the success of the smear programme, Papanicolaou cytology has important limitations. Meta-analysis has indicated that the average sensitivity of cervical smear cytology in detecting CIN or invasive cancer is 51% and its average specificity is 98%. The test's high false negative rate is therefore its most critical limitation. About one-third of false-negative diagnoses can be attributed to slide interpretation errors and two-thirds to poor sample collection and slide preparation.

Although pre-invasive lesions developing from the endocervical epithelium can be identified by this process, the method is mainly for identifying squamous lesions and cannot reliably exclude endocervical disease.

STAGING AND GRADING

There are two types of invasive carcinoma of the cervix. Approximately 70-80% of lesions are squamous cell carcinoma and 20-30% adenocarcinomas. The degree of invasion histologically may be either:

- early stromal (invasion is less than 3mm below the basement membrane)
- micro-invasive (invasion is less than 5mm below the basement membrane)
- invasive (invasion is more than 5mm below the basement membrane)

Once a patient is diagnosed with invasive carcinoma, the cancer is staged. Stage is determined at the time of primary diagnosis and should never be changed, even after recurrence or upon later discovery of more extensive disease during surgery. Stage is determined clinically and on the basis of the size of the tumour in the cervix or its extension into the pelvis. Although the results of CT, MRI, or PET cannot be used for staging, the information obtained can be used to assess more accurately the extent of pelvic disease and lymph node metastasis, which may affect treatment recommendations.

Cervical cancer is staged using the International Federation of Gynecology and Obstetrics (FIGO) staging system. This is based on clinical examination, as opposed to surgical findings, and allows only the use of the following procedures in staging of cervical cancer:

- palpation
- inspection
- colposcopy
- endocervical curettage
- hysteroscopy
- cystoscopy
- proctoscopy
- intravenous urography
- x-ray examination of the lungs and skeleton
- cervical conization

The TNM staging procedure for cervical cancer produces an equivalent stage to the FIGO system. The TNM system for cervical cancer describes a stage 0 cancer (or CIN) as being full-thickness involvement of the epithelium without stromal involvment, stage I as limited to the cervix (there are various sub-classifications), stage II as invading beyond the cervix, stage III as far as the pelvic wall or lower

third of the vagina, and stage IV as invasion of the bladder or rectal mucosa and/or extension beyond the true pelvis (IVa), or distant metastases (IVb). Stages II and III also have a number of sub-classifications.

MANAGEMENT

Management of cervical intraepithelial neoplasia

Low-grade CIN (CIN 1) is managed by recurrent smear testing and colposcopy every 6 months, as evidence has suggested that this is a safe timescale. Alternatively, it can be treated in the same way as higher grade lesions. For patients with higher grade lesions (CIN 2 and 3 and dyskaryotic glandular cells), immediate treatment either by excision or destruction of the affected area (usually the whole of the transformation zone) is required.

The main therapies used for destruction are laser ablation or large loop excision of the transformation zone, LLETZ (using a diathermy loop wire). These can both be carried out under local anaesthetic. Lesions on the ectocervix can be adequately treated by removing tissue to a depth of 8mm. However, if the SCJ cannot be seen or a lesion of the glandular epithelium is suspected, then a deeper "cone" biopsy must be taken to ensure that all the endocervix is sampled. Following a cone biopsy, patients are advised to abstain from intercourse and not to use tampons for four weeks in order to reduce the chance of infection.

Complications of cone biopsy The commonest complication of cone biopsy is haemorrhage which may occur within twelve hours of the operation (primary), or between the fifth and twelfth day following the operation (secondary). Haemorrhage is best controlled by compression with vaginal packing or by re-suturing the cervix if more severe. Haemorrhage that occurs later is commonly due to infection, and the management includes blood transfusion and antibiotic therapy.

Later complications include cervical stenosis with dysmenorrhoea and haematometra (accumulation of blood in the uterus). Cone biopsy may also result in cervical incompetence and subsequent mid-trimester miscarriage.

Management of cervical carcinoma

Surgery and/or radiotherapy are the main treatments; a combination of the two may sometimes be employed. Cone biopsy is an option for patients with stage IA lesions who wish to remain fertile. Extended hysterectomy or radiotherapy can be used to treat stage IB-IIA.

Both surgery and radiotherapy have similar five year survival rates but surgery is usually associated with fewer long-term problems from vaginal stenosis. Stage II-IV is normally treated with intracavity and external beam radiotherapy.

Operative management A radical hysterectomy (also known as Wertheim's hysterectomy) is the recommended treatment for patients with stage I disease. The procedure involves removal of the uterus, the upper third of the vagina and internal iliac, external iliac and obturator lymph nodes. The ovaries may be conserved. Complications associated with the procedure include haemorrhage, infection, pelvic haematomas, and damage to the uterus or bladder which may result in fistula formation. The likelihood of developing vaginal stenosis is much less than following radiotherapy, meaning that coital function is better preserved. For these reasons, this is the preferred treatment in younger women.

Radiotherapy This is used to treat other stages of cervical cancer (apart from stage I), patients with bulky stage IB disease or those who are unfit for surgery for any reason. Patients with lymph node involvement at the time of surgery will also be given post-operative adjuvant radiotherapy. The standard radiation treatment of stage IB1/IIA is external pelvic irradiation plus intracavitary brachytherapy (ICT). This requires local insertion of a source of radium, caesium or cobolt-60, into the uterine cavity and vaginal vault.

Complications are the result of excessive radiation on normal tissues, and include radiation cystitis or proctitis as well as fistula formation and vaginal stenosis, dryness, bleeding, stricture formation, and ulceration. Radiotherapy also sterilizes pre-menopausal patients and so, in younger women, the ovaries may be preserved and suspended outside of the pelvis if post-operative radiation is planned.

The advantages of radical hysterectomy over radiotherapy (in suitable patients) include a shorter duration of treatment, preservation of ovarian function in younger patients, avoidance of vaginal stenosis, and no further recurrence of disease in the uterus or cervix.

Chemotherapy There have been numerous studies exploring the role of chemotherapy in the radical treatment of cervical cancer, but a clear beneficial role has yet to be demonstrated. Patients with recurrent pelvic or systemic metastatic disease may benefit from palliative chemotherapy (*e.g.* cisplatin).

Follow-up Continuous follow-up of patients is extremely important to evaluate results, provide reassurance and offer symptomatic relief to women whose treatment has not been curative. One recommendation is that there should be follow-up every three months for three years, every six months for two years, and annual follow-up thereafter.

Counselling should be provided to support the patient throughout her treatment and help her cope with all aspects of readjustment. In particular, this should focus on preventing sexual problems that may arise within relationships. Pre-menopausal patients who have had their ovaries removed may be treated with HRT if they are troubled by menopausal symptoms. Younger patients with a good prognosis should be advised to take HRT to reduce the risk of osteoporosis and cardiovascular disease. Progestins should be included in hormone therapy if the patient has been treated by radiotherapy and the uterus is still present. Endometrial carcinoma may develop if unopposed oestrogens are given.

Vaginal stenosis may result from radiotherapy so dilators can be used to help maintain vaginal size and shape. It is important to encourage patients who were sexually active prior to treatment to try and resume activity within a couple of months of treatment completion. Patients also need to be reassured that coitus will not cause the tumour to become active and that the cancer cannot be passed on to their partner.

Skin Cancers

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There are many types of primary cutaneous cancer, each differing in appearance and behaviour. Three types are responsible for more than 95% of all skin cancers. These are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM), the latter of which is the focus of this chapter.

The various types of primary skin cancer are classified on the basis of their cell of origin. The most common are keratinocytes (*e.g.* SCC) and melanocytes (*e.g.* MM), which are both components of the epidermis. The most common form of skin malignancy, BCC, is of controversial origin. BCC is generally considered to arise from keratinocytes, however this has been challenged with the suggestion that it may arise from the (i) basal cells of the epidermis (ii) basal cells of the epidermis and occasionally those of the infundibular and outer root sheath of the hair follicle (iii) dormant primordial epithelial germ cells (iv) pluripotential epithelial cells in the basal layer that persist throughout life, (v) cells of the pilosebaceous unit and (vi) cells of other appendageal structures.

Skin cancer, collectively, is the most common type of cancer, with in excess of 70,000 new cases registered each year in the UK. Skin cancer is often subdivided into malignant melanoma (MM) and non-melanoma skin cancer (NMSC), in part due to the disparity in associated mortality between these two broad subtypes. The majority of skin cancers fall within the NMSC category, encompassing both BCC and SCC. In 2002, over 65,000 NMSCs were registered in the UK, but this is likely to underestimate the full prevalence as registration is often inconsistent.

Malignant melanoma is the least common subset, comprising only 10% of skin cancer diagnoses. Nevertheless, its significance should not be underestimated as it is the major cause of death from skin cancer. In 2001, there were 6432 new cases of MM registered in England and Wales. The number of deaths from MM in the UK in 2004 was 1777. The incidence of MM in the UK has soared over the last 25 years, with increases in excess of any other major cancer.

Unlike most malignancies, MM is more common in women than men with a male/female ratio of 2:3. Although more females are diagnosed with MM, the five year survival rate is significantly greater for females than males. This reflects the fact that males tend to present with thicker lesions and the thickness of the lesion is a poor prognostic factor. The pattern of distribution also varies with gender, the majority of cases occurring on the lower limb of females and on the trunk in males.

The incidence of MM increases with age in both males and females from age fifteen years onwards. The median age of diagnosis in males is 62 and, in females, 60 years. MM also has a profound effect upon young adults – it is the most common malignancy in women aged 25-29 years and second only to breast cancer in women aged 30-35 years. Melanoma incidence rates are inversely related to geographic latitude, with higher rates found closer to the equator. Australia and New Zealand have the highest age-standardised rates of between 30-40 per 100,000 population. Within the UK, the highest rates of MM for men and women are found in the South West.

There are more NMSCs diagnosed in the UK than any other type of cancer. BCCs are the most common type, and outnumber SCCs by approximately 4:1. Both BCCs and SCCs are highly treatable with survival rates in excess of 95%. SCCs do have the potential to metastasise and, in 2003, there were 514 deaths in the UK from SCC. It is very rare for BCCs to metastasise although, untreated, they can cause significant local destruction and disfigurement.

Unlike MM, NMSCs are more common in men than women. They are most frequently found on areas of skin that received chronic sun exposure – face, neck, ears, forearms and hands – and occur less commonly on the trunk. The incidence of NMSCs increases with age from 25 years onwards, with a median age at diagnosis of 73 years. The mortality from NMSC is greatest in the age group ≥85 years for both men and women. As with MM, NMSCs have a higher prevalence in equatorial latitudes.

ANATOMY
The skin is the largest organ of the body, with a surface area of around $1.8m^2$. In adults, it comprises approximately 16% of body weight. The skin is a highly specialised, intricate organ with multiple functions: homeostasis (maintenance of body temperature), sensation (touch, temperature, pressure, pain), defence

(protection against microorganisms, mechanical injury, noxious chemicals and UVR), metabolism (involved in vitamin D production), immunity (antigen presentation by Langerhans' cells) and psychological (self-image and sexual attraction).

The skin is composed of two main layers, the epidermis and dermis, and a variable third layer, the subcutis. The epidermis, the outermost layer, is a stratified epithelium of ectodermal origin. It can be further subdivided into four layers based on the degree of maturation of the most abundant cell in the epidermis, the keratinocyte. These are – from deep to superficial – the basal layer (stratum basale), prickle layer (stratum spinosum), granular layer (stratum granulosum), and stratum corneum.

The basal layer contains the germinative cells responsible for constant production of keratinocytes. Mitoses are frequently seen in the basal layer. The basal cells are anchored to the basement membrane, which separates the epidermis from the dermis, by hemi-desmosomes, and to adjacent cells by true desmosomes. BCCs probably originate from the basal cells. Also located within the basal layer are melanocytes, Langerhans' cells and Merkel cells.

Melanocytes are derived from neural crest cells and function to produce the pigment melanin which protects neighbouring keratinocytes from damage by ultraviolet radiation. Melanocytes synthesise and secrete melanin-containing organelles, melanosomes, which are transferred to basal and prickle layer keratinocytes via the dendritic processes of the melanocytes. Under high power microscopy the melanosome granules are situated directly above the nuclei of the protected keratinocytes in an "umbrella-like" fashion, providing photoprotection for both epidermal nuclear DNA and the dermis. Melanocytes are found in contact with the basement membrane of the epidermis as well as hair follicles, the retina, uveal tract and leptomeninges. Melanocytes are the cells of origin of MM.

The dermis, of mesodermal origin, contains collagen, elastic fibers, blood vessels, sensory structures, skin appendages, fibroblasts and small numbers of macrophages, mast cells, and lymphocytes. The dermis functions to support the epidermis. There are two distinctive zones: a superficial, narrower papillary dermis and a thicker reticular dermis, situated between the papillary dermis and the subcutis.

PATHOGENESIS

The tumour suppressor genes *p53* and *p16* have been implicated in UV-induced mutagenesis. Loss of *p16* expression has been reported to occur in approximately 50% of primary melanomas. The occurrence of UV-specific CC-TT mutations in the *p16* gene raises the possibility of it being a target for UV-induced mutation. Normal senescence of human melanocytes is *p16*-dependent and, unlike human fibroblasts, does not involve *p53* or *p21*. The estimated prevalence of *p53* mutations in primary melanomas range from 5% to 66%, thus suggesting that it is not the initiating event in melanoma. The involvement of *p53* in NMSC is, however, well established.

AETIOLOGY

There are multiple, interrelated aetiological factors that underlie the development of skin cancer. Both endogenous and exogenous factors are involved. A variety of exogenous substances have been implicated, the most important of these is ultraviolet radiation. They include:

Endogenous
• genes (*e.g.* xeroderma pigmentosum, Gorlin's syndrome, familial melanoma)
Exogenous
• ultraviolet radiation (UVB and UVA)
• ionising radiation (*e.g.* x-rays)
• viruses (*e.g.* human papilloma virus)
• chemicals (*e.g.* industrial oils and hydrocarbons, dyes, solvents, arsenic, pesticides, tobacco)
• chronic irritation (*e.g.* at the site of burn scars)

Ultraviolet radiation

Ultraviolet radiation (UVR) is part of the electromagnetic spectrum. The sun emits ultraviolet radiation across a broad spectrum, from the high-energy UVC (200-290 nm) and UVB bands (290-320 nm), to the UVA band (320-400 nm) which borders visible light (400-800 nm). Ultraviolet C radiation does not reach the earth's surface as it is absorbed by the ozone layer. It is therefore not an important cause of skin cancer.

UVR has two key roles in the development of skin malignancy: DNA damage and immunomodulatory effects. UVA and UVB cause DNA damage via different mechanisms. UVB directly damages DNA and produces a characteristic CT (cytosine to thiamine) transition mutation. UVA, on the other hand, causes DNA damage indirectly through an oxidative stress mechanism. UVA, although 10,000 times less mutagenic than UVB, accounts for around 90-95% of total UVR.

An Australian statistician, Oliver Lancaster, provided the first convincing evidence of a link between exposure to sunlight and development of melanoma. Since then, a considerable amount of research has focused on the role of ultraviolet radiation in the aetiology of skin malignancy. Although ultraviolet radiation has been implicated in BCC, SCC and MM, the pattern of exposure linked with the various types of skin malignancy varies.

The link between sun exposure and development of SCC follows a typical dose-response relationship whereby a steady, chronic accumulation of UVR leads to development of the disease. This is highlighted by the fact that SCC lesions occur most commonly on regularly exposed skin (face, neck and back of hands) and the majority of diagnoses are made in elderly patients with life-long exposure.

The nature of UVR exposure responsible for increased risk of BCC remains unclear. Unlike SCC, there does not appear to be a clear relationship between cumulative UVR exposure and development of BCCs. Two case-control studies, one in Canada and the other in Western Australia, reported UVR exposure prior to the age of 20, especially in non-tanners, was important in predicting adult risk of BCC. BCC was associated with frequent severe sunburns and freckling in childhood. Adult UVR exposure did not significantly elevate the risk of BCC in either study.

Solar UVR exposure has been estimated to account for over 90% of melanomas in Australia and North America, with similar figures in Northern Europe. The risk of developing MM is linked to specific patterns of UVR exposure at particular times during the human life course. In a recent meta-analysis of 57 studies, it was shown that intermittent sun exposure and sunburn history are significant risk factors for MM. Interestingly, high occupational sun exposure was inversely associated with MM. Thus, the risk of MM seems to be increased amongst people who are intermittently exposed to high levels of UVR exposure (*e.g.* during holidays abroad) as opposed to a chronic long-term exposure. The timing

of UVR exposure is also of importance when assessing the risk of MM. It has been suggested that the early years are when the risk is greatest. In a study looking at melanoma risk of migrants arriving in Australia, it was found those arriving after age fifteen years from low sunlight areas had significantly lower mortality from MM than those arriving at a younger age.

Skin factors

Complexion Natural skin pigmentation and susceptibility to sunburn are both implicated in the risk of skin cancer. Those with types I and II skin are most at risk of skin cancer.

Melanocytic naevi One of the strongest predictors of MM is higher than average numbers of melanocytic naevi.

Atypical/dysplastic nevi syndrome This syndrome is often familial and characterised by the presence of a large number of melanocytic nevi in childhood. Their macroscopic appearance includes irregular borders and pigmentation, and histologically they show cytological and architectural atypia, albeit without frank malignant change. Individuals with this syndrome are at increased risk of MM, and require close monitoring.

Actinic (solar) keratoses Actinic keratoses are common, persistent, keratotic lesions with malignant potential. They are markers of sun damage. If left untreated, many lesions progress to SCC. Their presence is also an independent risk factor for MM.

Immunosuppression

Transplant patients require immunosuppression and, as a consequence, are at increased risk of developing a number of malignancies. Skin cancers are the most common malignancies found in transplant patients and there is reversal of the BCC to SCC incidence ratio. The SCC to BCC ratio in transplant patients is 3:1 and tumours are often multiple and highly aggressive.

Other factors

There are a number of additional important associations with developing skin malignancy. These should individually be explored when taking a history and/or assessing patient risk. They include:

- exposure to ionizing radiation. This is primarily associated with SCC development
- family history of skin cancer. Individuals who have a first degree relative that has been diagnosed with MM are at increased risk of developing MM
- previous skin cancer. Once a person has developed NMSC, they are at a significantly increased risk of developing subsequent NMSCs

PRESENTATION

The presenting symptoms of MM, SCC and BCC, although specific and distinctive, share some common characteristics. The development of any primary skin cancer involves a change in appearance, including size, that is persistent, even if there are periods of apparent regression. All skin cancers may ulcerate and give rise to bleeding although they can also exist in the absence of ulceration. The development of a new or changing pigmented lesion is the classic initial presentation of MM. BCC often presents as a slow-growing nodule or papule which, over time, may start to ulcerate. SCC lesions are often rapidly growing and have an ill-defined, keratotic nodular appearance.

Patients may wait some time before seeking medical advice about a skin lesion. In many instances a spouse or partner is the first to notice the lesion, especially those arising on the back or shoulders.

Physical examination

When a patient presents with a skin lesion it is important to examine the entire cutaneous surface in addition to the lesion in question.

The tools required for examination of the skin are simple: a source of bright light, a magnifying lens and/or dermatoscope. Concealing cosmetics should be removed prior to examination. Patients should be asked to undress to their underwear; it is possible to conduct the examination in such a way that areas can remain covered whilst examining another part of the skin, thus putting the patient at ease.

The order in which the examination is performed is not crucial, so long as the entire anterior and posterior surfaces of the skin are examined, along with the scalp and soles of the feet. Attention should also be paid to the nail beds since acral lentiginous melanoma can occur there. Photography of cutaneous lesions allows accurate documentation of their precise clinical appearance and location. This can be helpful for follow-up of suspicious lesions and prior to surgical removal. Any patient with a lesion clinically suspicious of MM should be examined for lymphadenopathy and hepatomegaly.

All lesions found on examination should be described in terms of the following features:

- type of lesion
- surface features
- colour
- size
- border regularity / symmetry
- distribution

Findings on examination vary between subsets of skin malignancy.

Malignant melanoma
Malignant melanomas can arise in pre-existing melanocytic nevi or *de novo*. They vary considerably in their macroscopic appearance making diagnosis based on assessment by the naked eye alone very difficult; there is no single colour or change that is diagnostic.

The ABCDE acronym for melanoma screening was devised to provide the layperson and healthcare professionals with a useful and memorable mnemonic to aid in the detection of early, potentially curable, MM. The features screened for include:

- **a**symmetry
- **b**order irregularity
- **c**olour variegation (>2 colours)
- **d**iameter (>6mm)
- **e**levation/**e**volution

Not all melanomas have five features; it is the combination that suggests a skin lesion might be suspicious. Lesions possessing some or all of these features require careful evaluation by a specialist. The final feature ("E") is important as nodular melanomas frequently lack other features of the ABCD criteria, potentially leading to a failure to recognise this subset. However, lesion change and evolution is a common feature and may increase the sensitivity of this screening tool.

There are four main clinical subtypes of MM which are defined by their clinical appearance, progression, anatomical site, and histological appearance.

Superficial spreading melanoma The most common form, accounting for 70-80% of all melanomas. Macroscopically it appears as a slowly enlarging black or brown lesion that may have both a macular and papular component. It grows laterally before vertical invasion develops.

Nodular melanoma The most aggressive form of melanoma accounts for approximately 10-15%. It presents as a rapidly growing, pigmented papule which may bleed or ulcerate.

Lentigo maligna melanoma Arising from lentigo maligna – variously described by pathologists as either a pre-malignant condition or melanoma *in situ*. Progression to lentigo maligna melanoma occurs on average in 5% of patients with lentigo maligna. It appears as an irregularly shaped, flat, pigmented lesion and some areas may have a mottled appearance. Nodules and ulceration can signify local invasion.

Acral lentiginous melanoma Arises as a pigmented lesion on the palm of the hand, sole of the foot or nail bed and usually presents late. It is the most common form of melanoma in blacks, Asians and Hispanics and the least common in Caucasians.

Squamous cell carcinoma SCCs may arise *de novo* or develop from precursor actinic keratoses. Clinically the lesions may resemble BCC, actinic keratoses or warts; the common initial appearance is an ill-defined, red lesion with a rough surface. SCC is more likely than BCC to possess an overlying crust and the scale may project above the skin surface to form a keratotic horn. Removal of the crust reveals a central cavity filled with necrotic keratin debris, often with a foul odour.

Basal cell carcinoma BCCs have three key presentations which reflect underlying histological differences.

Nodular basal cell carcinoma
The most common variant appears as pearly white papules with overlying dilated blood vessels, or "telangiectasia". Lesions frequently ulcerate forming nodulo-ulcerative BCC. A subset of nodular BCC is pigmented BCC which is equivalent except for the additional presence of melanin. These lesions can be mistaken on clinical examination for MM.

Superficial basal cell carcinoma
Presents as erythematous plaques which may demonstrate areas of healing with scarring. They are most commonly found on the trunk and can resemble eczema, psoriasis, or Bowen's disease (SCC *in situ*).

Morpheaform and sclerosing basal cell carcinoma
The least common variant of BCC, and the most difficult to diagnose clinically. Lesions resemble scar tissue or normal skin with a pale-white to yellow colour and a waxy texture on palpation. With an innocuous appearance, these lesions are frequently missed, resulting in delayed biopsy and diagnosis. They have an infiltrative growth pattern thus their extent is often significantly greater than expected based upon clinical appearance.

INVESTIGATION AND MANAGEMENT

Dermatoscopy
A dermatoscope is a hand-held magnifying device. Dermatoscopy is an *in vivo* technique of magnification, enabling the epidermis, dermo-epidermal junction and papillary dermis to be visualised. Dermatoscopy is a bridge between the gross appearance of the skin with the unaided eye and the histological appearance. The device has been found to improve clinical diagnostic accuracy, particularly in distinguishing MM from its benign non-melanocytic simulants.

Surgical excision/biopsy
One difference between management of primary skin cancer and some other cancers is that initial excision sometimes constitutes its entire treatment. Thus

the aim of surgical excision and biopsy can be two-fold: to establish a histological diagnosis and to remove, thereby treating, the malignancy.

Guidelines produced by the British Association of Dermatologists (BAD) state that excision of a lesion suspected of being a MM should be performed as a full-thickness skin biopsy to include the whole tumour with a 2-5mm clinical margin of normal skin laterally and with a cuff of subdermal fat. This type of excision is optimum for histological analysis, such that subsequent definitive treatment and prognosis can be based upon Breslow thickness.

Surgical excision is the treatment of choice for the majority of SCCs. It allows full characterization of the tumour and histological examination of the margins to determine the adequacy of the treatment. BAD guidelines suggest that low-risk tumours less than 2cm in diameter and with clinically well-defined margins should be excised with a surgical margin of 4mm. Excision with such margins is expected to completely remove the SCC in 95% of cases.

When managing BCC, the primary objective of excision is to remove the tumour entirely. Lesions should be removed deep to the subcutaneous fat. For well-defined, small (<20 mm) lesions a 3mm surgical margin will clear the tumour in 85% of cases, rising to 95% clearance with a surgical margin of 4-5mm. Morphoeic and larger BCCs require more extensive surgical resection. In order to be 95% confident of complete surgical resection of a primary morphoeic BCC, a surgical margin of 13-15 mm is required.

Histological analysis of a lesion can begin after excision/biopsy. Once again, findings differ by type of skin malignancy.

Malignant melanoma In melanoma *in situ*, the melanocytes are located within the epidermis. Initially there is focal proliferation of solitary melanocytes within the basal layer at the dermo-epidermal junction. These solitary melanocytes extend horizontally and can appear hyperchromatic, surrounded by a halo. In the later stages of melanoma *in situ*, nests of atypical melanocytes form in the basal layer and some cells ascend to the stratum spinosum. The lesion can further progress to involve the whole epidermis, up to the granular and cornified layers, giving the so-called "buckshot scatter" feature. In the micro-invasive stage that follows, a few atypical melanocytes descend to the papillary dermis. This stage is known as the radial growth phase (RGP), and it is generally believed that MM is unable to metastasise at this stage. If lesions are not recognised and removed,

they will progress to involve deeper structures such as the reticular dermis and subcutaneous fat. This is known as the vertical growth phase (VGP). Finally metastasis occurs, often detected initially by the presence of local satellite lesions. It may also be possible to observe local lymphatic or blood vessel involvement in a histological specimen.
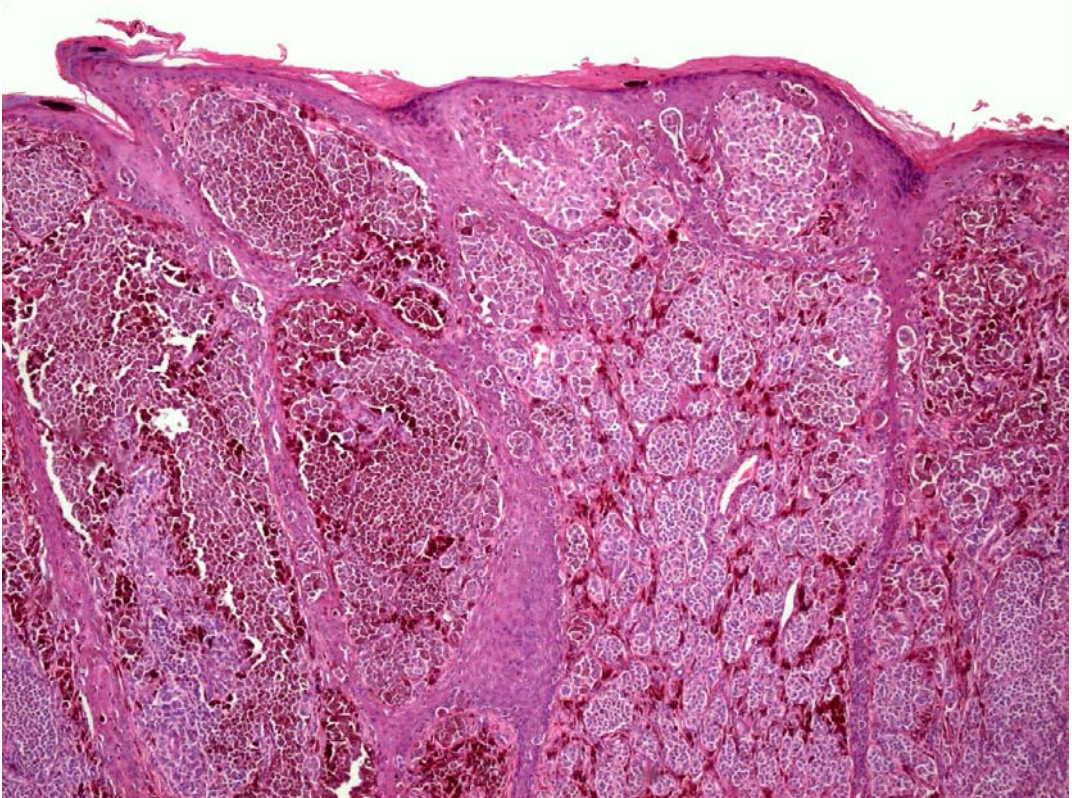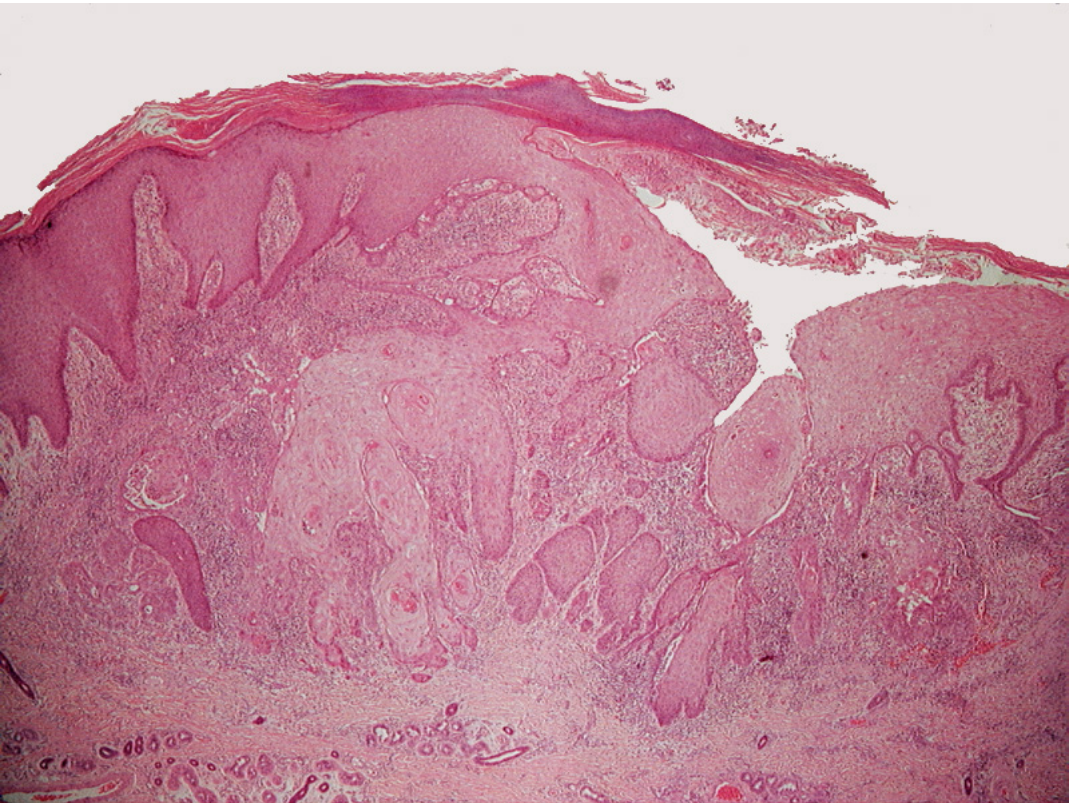

A histological specimen showing a superficial spreading MM in vertical growth phase. It invades the reticular dermis (Clark's 4) and there is an intra-epidermal component including pagetoid suprabasal migration. The deep part of the tumour is not shown.

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For poorly differentiated, or amelanotic, melanomas a silver stain (Fontana-Masson stain for melanin) may be useful in conjunction with a specialized immunohistochemical stain. Immunohistochemical stains include S-100, HMB-45, MART-1 and Tyrosinase. The most commonly used stain, S-100, is a polyclonal protein found in melanocytes, Langerhan's cells, and neural tumours.

Squamous cell carcinoma Histological features common to many malignancies also apply to SCCs, namely increased nuclear/cytoplasmic ratios, hyperchromatism, prominent and increased nuclei, disorganised architecture, and atypical mitoses. The high keratin content of SCCs results in a characteristic pink appearance on microscopy. Keratinisation can occur intracellularly and/or extracellularly, giving rise to horn pearls. Epidermal hyperplasia is apparent superficially and occasionally ulceration is present. SCC *in situ* is entirely intra-epidermal whereas deeper, invasive SCC transgresses the basement membrane and may give the appearance of nests, or islands, with surrounding desmoplastic stroma.

*A histological specimen showing a well-to-moderately differentiated squamous cell carcinoma invading the reticular dermis.*

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Basal cell carcinoma BCCs have a variety of histological presentations. The two major factors which influence the histological appearance of a BCC are the potential of cells to differentiate and the stromal response evoked by the

epitheloid component. The neoplastic cells have potential to differentiate towards follicular, sebaceous, eccrine, or apocrine structures. BCCs do infiltrate through the basement membrane into the dermis; however they appear to produce their own basement membrane-like material that the malignant cells reside upon. As with other malignancies, neoplastic cells in BCC have a high nuclear to cytoplasmic ratio and lots of mitotic figures.
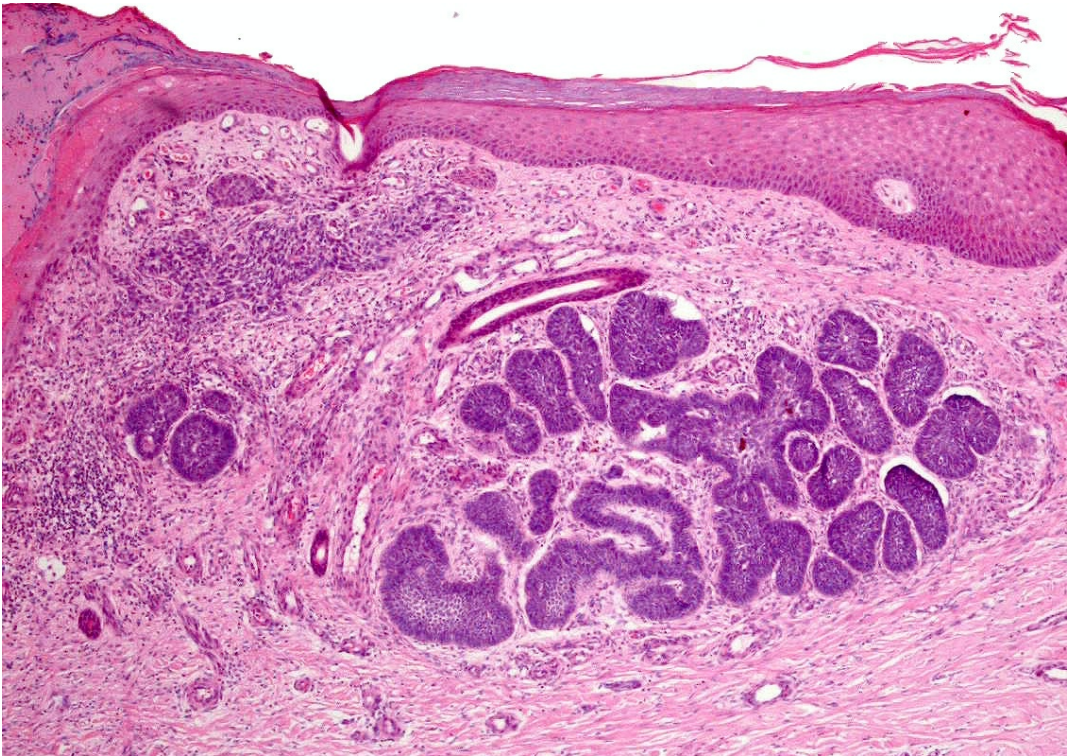
A histological specimen of a nodular BCC demonstrating involvement of reticular dermis with typical palisaded islands of basaloid cells and myxofibrocellular stroma plus clefting between epithelial and stromal elements.

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HISTOLOGICAL GRADING

Malignant melanoma
There are a number of histological features used to aid in the prognosis of MM. In 1969, Clark *et al* proposed a schema for describing melanoma invasion based upon anatomical depth of involvement (see table below).

Clark's Level	Description
I	Tumour cells confined to the epidermis (*in situ*)
II	Tumour cells extend to, but do not fill, the papillary dermis
III	Tumour cells fill and papillary dermis and extend to the junction of the papillary and reticular dermis
IV	Tumour cells extend into the reticular dermis
V	Tumour cells extend into the subcutaneous fat

A more precise assessment of the level of invasion is provided by Breslow thickness. Breslow thickness, described by Alexander Breslow in 1970, is defined as the depth from the granular cell layer to the deepest level of the neoplasm. Measured in millimetres, it is the most important prognostic indicator for survival in primary cutaneous melanoma. There is a direct correlation between primary tumour thickness and survival rates in cutaneous melanoma. The table below shows the correlation between histologically derived indicators of tumour thickness and disease prognosis.

Breslow Depth		Clark's Level	
Depth (mm)	Five year survival rate	Level	Five year survival rate
<0.75	95-99%	II	99%
0.76-1.49	90-95%	III	95%
1.50-4.00	60-75%	IV	75%
>4.00	<50%	V	39%

Squamous cell carcinoma
SCCs are graded according to their degree of differentiation. In the Broder's classification, tumours are graded from one to four according to their degree of differentiation, which is dependent on the level of keratinisation. Those which are grade four are most likely to metastasise.

MANAGEMENT

Non-melanoma skin cancer
As previously discussed (p88), the standard treatment for NMSC is surgical excision. There are, however, other techniques, surgical (*e.g.* Moh's micrographic surgery) and non-surgical, available. When a non-surgical technique (*e.g.* cryotherapy or topical imiquimoid treatment), which precludes histological analysis is utilised, an incisional biopsy to confirm diagnosis should be performed beforehand.

For the majority of patients with NMSC, no formal staging beyond examination for lymphadenopathy is required. Once full excision has been achieved, NMSC patients with a low risk of recurrence do not need long term surveillance and should be discharged from formal follow-up. The suggested time-frame for follow-up for patients with high risk SCC is five years which permits enough time to detect 95% of local recurrences and metastases. Patients with high risk SCC and those with clinical signs of lymph node involvement should be managed within a multi-professional setting and alongside an oncologist to consider non-surgical treatment options.

Malignant melanoma
The definitive treatment for patients diagnosed with MM is wide local excision (WLE). This involves removal of skin surrounding the original excision site to the depth of the muscle fascia. The recommended margin of skin to be removed is determined by the Breslow thickness, provided by primary histology. MM lesions which extend deep into the dermis require a greater margin. Recommended surgical excision margins for malignant melanoma are summarised below.

Breslow Depth (mm)	Excision Margin
In situ	2-5mm
<1mm	1cm
1-2mm	1-2cm
2.1-4mm	2-3cm
>4mm	2-3cm

Deviation from recommended surgical excision margins may be indicated when lesions are located on anatomical sites where complete closure is not achievable with such a wide margin. Such sites include the eye and distant peripheries.

In addition to WLE, further investigations are required for patients with intermediate or high risk disease. The aim of subsequent investigations is to accurately stage the patient according to the conventional American Joint Committee on Cancer (AJCC) staging system.

Patients with stage I and IIA disease should not be staged by imaging as the specificity and sensitivity is low. The BAD recommends that patients who are found to have stage IIB should, after initial excision, have the following staging investigations: chest x-ray, liver ultrasound or computed tomographical (CT) scan with contrast of chest, abdomen, and pelvis; liver function tests/lactate dehydrogenase, and a full blood count. Bone scans are only indicated if the patient has symptoms of bone metastases. Any patient found to have stage IIB or more advanced disease should be managed by a skin cancer multi-disciplinary team within a specialised cancer centre.

Adjuvant therapy
To date there are no adjuvant therapies of demonstrable benefit for melanoma. For this reason, it is recommended that management of patients at intermediate or high risk of relapse should be considered for inclusion in a clinical trial wherever possible. Clinicians should remain abreast of current trials available for their patients.

At present, elective lymph node biopsy is not recommended for clinically node negative patients. In the presence of clinically or radiologically suspicious lymph nodes, a fine needle aspiration cytology (FNAC) can be performed. The management of patients with confirmed positive lymph node involvement should begin with staging investigations and, if distant metastases are not detected, a block dissection of the lymph nodes should follow. The degree of lymph node removal is dependent upon the clinical and radiological presentation.

In stage IV disease there is a role for surgery in the removal of solitary lesions (including brain, lung, and liver) or for the treatment of symptomatic metastases. Those patients found to have unresectable metastatic disease should be referred to a specialist oncologist for medical and psychological management. Single-

agent dacarbazine (DTIC) is the standard chemotherapy used outside the context of a clinical trial. DTIC, an alkylating agent, shows response rates ranging from 10-20% and only small increases in median survival.

Colorectal Cancer

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Colorectal cancer (CRC) is a malignant neoplasm of the colon or rectum. Worldwide, it is the fourth most common cancer, whilst in the UK it is the third most common after lung and breast cancer. It results in an estimated 529,000 deaths per year, largely in developed countries. Although there is a higher incidence in the developed world, this association appears to be environmental. This is supported by the case of Japanese Americans who acquire risk comparable to Caucasian Americans within a single generation.

In 2003, the UK prevalence of CRC was 54.7 for men and 34.4 for women per 100,000. The sex difference may be because women present earlier with pre-malignant conditions, such as polyps. Since 1975, the mortality rate for CRC has reduced, despite an increasing number of cases. This may be due to earlier CRC detection or advances in management strategies. CRC preferentially affects older individuals, with 70 being the mean age of onset.

ANATOMY

Structural anatomy
The large intestine consists of the caecum, appendix, colon, rectum and anal canal. The colon has four parts: ascending, transverse, descending and sigmoid, which succeed one another in a continuous arch. It is distinguished macroscopically from the small intestine by the presence of taenia coli (thickened bands of longitudinal muscle fibers), haustra (sacculations of the colon between teniae), and omental appendices (fatty appendices of the colon). Furthermore, the colon has a larger diameter than the small intestine.

The caecum represents the beginning of the large intestine and is continuous with the ascending colon. It is a blind intestinal pouch, located in the right lower quadrant of the abdomen. The terminal ileum enters the caecum to form the ileocecal valve, which is located in the posterior-medial surface of the caecum.

The appendix is a blind intestinal diverticulum, also arising from the posterior-medial surface, approximately 3cm below the ileocecal valve. Its function is largely redundant. The ascending colon extends from the ileocecal valve to the right lobe of the liver where it angulates medially, downward and anteriorly to the hepatic flexure. The transverse colon is the longest and most mobile part of the large intestine, crossing the abdomen to the splenic flexure.

Continuing from the splenic flexure, the descending colon passes over the lateral border of the left kidney and descends retroperitoneally into the left iliac fossa, where it continues as the sigmoid colon. The sigmoid colon length varies from 15-50cm and has a characteristic S-shape. It extends to the third sacral segment, where it joins the rectum. The rectosigmoid junction is marked by the termination of the taenia coli. The rectum is 12-15cm long and is divided into an upper third, middle third and lower third. It follows the curvature of the sacrum and coccyx, and ends as it passes through the levator ani muscle to form the anal canal.

Functionally, the colon absorbs water and transports both urea and electrolytes. It absorbs over 90% of the water from contents in transit to produce a semi-solid faecal matter which is stored in the sigmoid colon and rectum in preparation for defaecation.

Vasculature
Embryologically, the large intestine develops from the midgut and hindgut. The midgut comprises the caecum, appendix, ascending colon, and most of the transverse colon. These are supplied by branches of the superior mesenteric artery (SMA). The hindgut consists of the distal part of the transverse colon, the descending colon, the sigmoid colon, and the upper third of the rectum. They are supplied by branches of the inferior mesenteric artery (IMA). The middle and lower rectum and the anus are supplied by the middle and inferior rectal arteries, which branch from the internal iliac artery and pudendal artery respectively.

Venous drainage follows a similar pattern. The midgut derivatives drain to the superior mesenteric vein, whilst the hindgut derivatives drain to the inferior mesenteric vein. Both veins drain to the liver via the portal venous system. This is significant for distribution of CRC metastases which frequently spread to the liver. Detectable liver metastases are found in up to 37% of patients at the point of surgery, and approximately 50% develop liver metastases during their illness. The

lower two thirds of the rectum drain to the systemic circulation via the internal iliac vein and internal pudendal vein. Systemic drainage by the rectum via the inferior vena cava explains why rectal cancers are more likely to produce isolated metastases to the lungs than are colon cancers.

Lymphatic drainage
The lymphatic system runs alongside the regional arteries. There are four types of lymph nodes:

- epicolic – most proximal nodes to the bowel wall
- paracolic – found at the mesenteric border of the colon alongside the marginal vessels
- intermediate – lie around the main colic arteries and drain to the main nodes
- main – at the origin of the superior mesenteric and inferior mesenteric arteries

The main nodes in turn drain to the para-aortic lymph nodes. The proximal two thirds of the rectum drain to the inferior lymph nodes, whilst the lower third drains to the inferior lymph nodes and internal iliac nodes. In general terms, the lymphatic spread of CRC progresses from the paracolic nodes along the main colonic vessels to the nodes associated with the cephalad or caudal vessels. Lymph node involvement is an important prognostic factor in staging CRC.

Colorectal cancer can arise in any part of the large intestine but some sites show a greater frequency of occurrence. 50% of colon cancers arise in the left side, with 25% occurring in the right. The greatest proportion of cancerous lesions are seen in the rectum (37%), followed by the sigmoid colon (27%), and the caecum (14%).

PATHOGENESIS

Architecture of the colorectal muscosa
The normal colorectal mucosa is made up of three main parts; the epithelium, lamina propria, and muscularis mucosae. The epithelium is lined with a single layer of columnar cells which acts as a protective barrier against the luminal environment. The epithelium itself is made up of columnar absorptive cells which are important for ion and water absorption and goblet cells which synthesize,

store, and secrete mucin. The surface epithelium is anchored and supported by a thin basement membrane composed of collagen and other proteins. Colorectal crypts are formed by the absorptive and goblet cells as well as undifferentiated precursor cells, specialised endocrine cells, and Paneth cells.

The lamina propria extends between the crypts and includes a range of cells involved in local defence against luminal agents. These are arranged amongst collagen which helps support the epithelial layer along with the muscularis mucosae. The muscularis mucosae is a thin smooth muscle that can alter the shape of the mucosa by contracting and relaxing. The submucosa possesses similar cells to the lamina propria but includes two neural plexuses – Meissner's plexus and Auerbach's plexus – as well as blood vessels and gut-associated lymphoid tissue (GALT). On the outside of the submucosa is the muscularis externa. This consists of an inner circular muscular layer and an outer longitudinal muscular layer that forms the taenia coli. Coordinated contractions of the taenia coli are important for peristalsis. The outermost layer is formed by several epithelial layers and a connective tissue layer to form the serosa.

Mucosa in the upper part of the anal canal is composed of columnar epithelium. The middle part contains stratified columnar epithelium which gives way, in the lower part, to stratified squamous epithelium.

Colorectal polyps
Colonic epithelium actively proliferates and regenerates. Normally, the proliferative zone is confined to the lower three quarters of the crypts and cells migrate upwards before extrusion from the mucosal surface. This process takes four to six days. In the early stages of colorectal carcinogenesis, epithelial cells are unable to repress DNA synthesis during migration in the crypt. This results in an enhanced proliferative capacity and expansion of the proliferative zone. There is a generalised disorder of cell replication and differentiation that continues and facilitates tumour growth.

A polyp is defined as a protuberant growth. In the large intestine, the most important type is the adenomatous polyp, which is derived from secretory epithelium. A small number of these may become malignant and form colorectal carcinomas. The incidence of adenomas increases with age so that, by the age of 60, they are found in approximately 20% of the population. Adenomas are well-demarcated growths of epithelial dysplasia, classified histologically as either

tubular or villous. These account for 75% and 10% of adenomas, respectively. The remaining 15% are intermediate in nature and classified as tubulo-villous.

Tubular adenomas are typically <10mm in diameter. Microscopically, they possess numerous cross-sectioned crypts lined by mucous-secreting epithelium. The majority possess a stalk (pedunculated), with a minority arising from a broad base (sessile).

Villous adenomas are often >20mm in diameter, usually sessile, and can extend over a wide area of epithelium. Microscopically, they possess elongated villi in a papillary growth pattern and are lined with columnar epithelium.

The adenoma-carcinoma sequence
Several lines of evidence indicate that adenomas are the precursors of CRCs. For example, epidemiological studies show a strong association between adenomas and CRC incidence. Furthermore, adenomatous change is frequently observed in bowel resected for CRC. In the genetic condition familial adenomatous polyposis coli (FAP), multiple adenomas arise in the large intestine during the second and third decades. A large proportion of these undergo malignant change, typically by age 35.

Molecular pathology of the adenoma-carcinoma pathway
The genetic events underlying development of colorectal carcinoma normally progress from healthy mucosa through aberrant crypt formation, adenoma, and carcinoma. These are each associated with further mutational DNA changes.

The most likely genetic event initiating this sequence is somatic inactivation (*i.e.* through mutation) of the tumour-suppressor gene *apc*. This induces aberrant crypts and polyp formation. Normally, *apc* controls epithelial replication and is inactivated during this process. It also regulates cell-to-cell adhesion through E-cadherin, and influences cellular migration. *Apc* inactivation therefore leads to impairment of these processes. *Apc* mutations have been reported in up to 80% of adenomas and 80% of carcinomas. Inactivation of *apc* results in an increase in β-catenin/TCF-mediated transcription that has been shown to up-regulate the oncogene, *c-myc*, a powerful growth promoter required for DNA synthesis. Another important oncogene that may become over-expressed due to mutation is *bcl-2*, normally a key inhibitor of apoptosis. Over-expression therefore prevents

apoptosis so that cell damage continues unchecked. These mutations together facilitate hyper-proliferation of the mucosa to form a small adenoma.

The transition from a small adenoma to a large, dysplastic adenoma involves the accumulation of several genetic changes. Mutation of *K-ras* results in continual signalling of cell division and is observed in 40-50% of adenomas and carcinomas. The *DCC* gene encodes a cellular adhesion molecule. Mutations in *DCC* occur in approximately 70% of colorectal carcinomas and become more frequent at each stage of carcinogenesis. Nearly 100% of hepatic metastases arising from colorectal primaries possess this mutation, suggesting loss of DCC heterozygosity may contribute to CRC progression.

Finally, malignant change in a dysplastic adenoma involves mutation of the tumour suppressor gene *tp53*. The P53 protein is a transcription factor that regulates the G_1-phase of the cell cycle. Mutations in *tp53* are present in up to 75% of CRCs and 30% of adenomas.

Loss of heterozygosity at any of these loci results in increased tumour growth due to loss of regulatory control. This pathway accounts for the large majority of colorectal carcinomas. Those remaining either involve different pathways, such as the microsatellite instability pathway seen in hereditary non-polyposis colorectal cancer (HNPCC), or other oncogenes/tumour suppressor genes.

GENETIC SYNDROMES AND CRC
All cancers have a genetic origin in that carcinogenesis requires gene mutation. Mutations can arise in somatic cells secondary to environmental insult or be inherited as a germline defect. The two main inherited syndromes that have a predisposition to CRC are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC).

Individuals with a first-degree relative with colorectal cancer have an increased lifetime risk of developing cancer. The likelihood that a cancer is inherited is increased if there are two or more affected individuals within a family. Furthermore, the relative risk increases where the affected individuals were younger at diagnosis and with the number of affected relatives. Therefore, it is important to assess the family history when assessing CRC risk.

Familial adenomatous polyposis

FAP is an autosomal dominant inherited syndrome with a penetrance approaching 100%. It accounts for about 1% of all CRCs. FAP is caused by germline mutations in the *apc* gene, leading to development of multiple adenomatous polyps. Almost all affected individuals develop between hundreds and thousands of adenomatous polyps throughout the large bowel. These begin in the recto-sigmoid region and, if left untreated, develop into CRC. The median age of adenoma diagnosis is fifteen years. For polyps that are left untreated, the mean age of CRC diagnosis is 35 with mortality occurring a few years later. Multiple adenomatous polyps develop in the second decade of life and are histologically identical to those seen in the adenoma-carcinoma sequence. Although the risk of each polyp undergoing malignant change is small, the high number results in a lifetime risk of malignant change to be almost 100% by age 40.

Hereditary non-polyposis colorectal cancer

HNPCC is an autosomal dominant syndrome. It is characterised by early age onset of colorectal cancer, localised predominantly to the right side (caecum to splenic flexure), excess synchronous and metachronous colorectal neoplasms, and is frequently associated with tumours of other organs such as endometrial, renal, ureteric, small bowel, and skin cancers. HNPCC patients also suffer from an increased frequency of poorly differentiated mucinous tumours with a high propensity for invasion.

It is thought to account for up to 6% of CRC cases, with a median age of onset of 45 years. Unlike FAP, HNPCC lacks excess polyposis but, once adenomas occur, they progress to carcinoma more rapidly than in sporadic CRC patients. HNPCC is classified into two Lynch syndromes and has a defined set of diagnostic criteria, the Amsterdam criteria. Patients diagnosed with colon cancer arising from HNPCC have a better prognosis than those with sporadic colon cancer.

HNPCC cancers do not follow the adenoma-carcinoma pathway but develop through the mutator genes/microsatellite instability pathway. HNPCC sufferers inherit a mutation in one of several genes responsible for repair of mismatch DNA. Four genes have been identified: *hmsh2* (60% of cases), *hmlh1* (30%), *hpms1* (5%), and *hpms2* (5%). If any one is defective, mismatched bases go unrepaired and the affected cell accumulates mutations at a higher rate.

Inactivation of these DNA mismatch repair genes (mutator genes) leads to genomic instability, often observed at microsatellite loci.

Other autosomal dominant conditions predisposing to CRC
Less frequent polyposis conditions include the autosomal dominant Peutz-Jeghers syndrome, juvenile polyposis, hereditary flat adenoma syndrome, and Cowdens disease.

Association with inflammatory bowel disease
Patients with ulcerative colitis have a 2-8.2 relative risk of CRC when compared with the normal population. A meta-analysis of 116 studies found the prevalence of CRC in ulcerative colitis was 3.7%, rising to 5.4% in pancolitis. The study estimated the cumulative risk of CRC for an ulcerative colitis patient to be 2% at ten years, 8% at twenty years, and 18% at 30 years. As a result, ulcerative colitis accounts for around 2% of CRCs. The extent of the disease is important as individuals with involvement of the ascending and transverse colon are more likely to develop CRC. Ulcerative colitis probably evolves from microscopic dysplasia, with or without a mass lesion, rather than from adenomas.

Crohn's disease has a comparable association with CRC to ulcerative colitis. It has a prevalence of 0.1% and a peak age of onset of between fifteen and 25 years.

SIGNS AND SYMPTOMS
CRC can present insidiously or acutely. In the UK, between 20 and 40% of CRC patients are diagnosed with incurable disease and 20% are admitted with emergency complications such as obstruction and/or perforation of the large bowel. Bowel symptoms are commonly found in the general population. It is therefore necessary to consider CRC only in patients developing new symptoms. Patients should be referred for rapid investigation if they have persistent, progressive, or sinister symptoms. Patients may delay presentation due to reluctance to discuss bowel function.

The type of clinical presentation may be influenced by the site of the colorectal tumour.

Abdominal pain

The most common presenting symptom is vague abdominal pain, although this is reported by 25-30% of the general population in any one year. It is characterised by its severity, timing, and association with eating. Patients with right-sided cancers may have obstruction of the ileocecal valve and experience intestinal colic an hour or so after eating. Pain may also be associated with diarrhoea or constipation. If a lesion causes partial obstruction, colicky pain may be reported. If there is constant localised pain, a localised perforation should be considered. Constant generalised pain may be due to peritonitis associated with a perforation.

Tenesmus

Tenesmus is the feeling of incomplete evacuation after defecation. Alternatively, it may be expressed as a feeling of needing to defaecate without actually passing a bowel movement. This symptom typically results from a growth located in the rectum or upper anal canal.

Rectal bleeding

A significant proportion of the population experience rectal bleeding each year. This isolated symptom therefore has a poor predictive value for CRC. The colour of blood in relation to stool is important since it can give an indication of the site of the bleeding. Bright-red blood is often associated with an anal cause, *e.g.* rectal varices but also occurs in rectal carcinomas. Left sided tumours are more likely to present with dark blood.

Alteration of bowel habit

Bowel habit varies between individuals. It is therefore important to determine "normal" variation before proceeding to investigate bowel habit. It is also important to ascertain whether alteration in bowel habit refers to constipation, diarrhoea, or a change in frequency. A change in bowel habit persisting for six weeks leads to a high suspicion of cancer. In the elderly, change in bowel habit is common and may be due to prescribed drugs and/or dietary factors.

Iron-deficiency anaemia

Occult gastrointestinal blood loss is an important cause of iron-deficiency and is associated predominantly with right-sided colonic neoplasms.

Abdominal mass

Generally, right-sided tumours present with fewer symptoms than left-sided or rectal tumours due to the large diameter and fluid contents. Thus, right-sided tumours grow to a larger size and so are more likely to present with a palpable abdominal mass.

STAGING CRC

Staging conveys the anatomical extent and severity of disease as well as its prognosis. Dukes' classification, based on histological analysis, is typically used to stage colorectal carcinoma. Another staging system used for CRC is the TNM system. There has been a move towards the using the TNM system since it offers an accurate independent description of the primary tumour and its spread.

Tumour grading

Histological examination of resected specimens also permits assignment of a differentiation grade. Colorectal carcinoma can be assigned the following grades:

- grade 1 – well differentiated
- grade 2 – moderately differentiated
- grade 3 – poorly differentiated

Grading tumours has little benefit for guiding the management of CRC. This is due to the subjective nature of grading and the fact that pathological staging at diagnosis is a more powerful determinant of clinical outcome.

DIAGNOSIS AND INVESTIGATIONS

Patients experiencing abdominal symptoms typically present to their general practitioner (GP) unless they have symptoms requiring emergency admission. The receiving doctor should take a complete history, including presenting symptoms, past medical history, drug history, and family history before the physical examination. On examination, the abdomen is palpated for any masses and their

site recorded. An important component is the digital rectal examination since it can assess for abnormal masses of the rectum, pelvic floor, and anal canal. The withdrawn finger is inspected for stool, blood, mucus or pus. Rectal examination is important since 40-80% of patients with rectal cancer will have a palpable mass.

Blood tests should include a full blood count, liver function tests and carcino-embryonic antigen (CEA). CEA is released into the bloodstream from both cancer cells and normal cells. Although elevated levels of CEA may indicate CRC, it has little diagnostic value as there are many conditions in which this component is raised.

Sigmoidoscopy

Sigmoidoscopy – whether rigid (25cm) or flexible (35 or 60cm) – requires minimum preparation. Visualisation is achieved through a fiberscope or videoscope. Rigid sigmoidoscopy can be used to measure distances from the anal verge which may be important for surgical decisions. Flexible sigmoidoscopy is, however, preferable as it causes less patient discomfort, allows greater visualisation of the mucosa, and has a longer reach. Biopsies and polypectomies can also be performed using this technique.   One important limitation is that it is restricted to the left-side of the colon.

Colonoscopy

If the patient has right-sided colon symptoms, or significant clinical doubt remains after sigmoidoscopy, visualisation of the entire colon is facilitated by colonoscopy. This reaches the caecum in 80-95% of procedures and can both detect and remove clinically significant adenomas throughout the colon and rectum. When colonoscopy is incomplete, the examination may be repeated, or a total colon assessment achieved with double-contrast barium enema. Colonoscopes are flexible to allow manoeuvrability through the bowel and are capable of air insufflation, irrigation, suction, and passage of biopsy forceps and polypectomy snares. Colonoscopy has a higher risk of complications than sigmoidoscopy such as perforation, haemorrhage and nosocomial infection.

Barium enema

Double-contrast barium enema is used more frequently than single-contrast since it has a greater sensitivity and specificity (>80%) in diagnosing CRC. Barium is introduced into the bowel via a catheter and insufflation of air or CO_2 delineates the mucosa outlines. This procedure requires excellent preparation of the bowel. It has the advantage of being safe, widely available, and does not require sedation. Whilst it may detect lesions, it is limited by its inability to facilitate therapeutic or advanced diagnostic procedures, such as biopsy.

Virtual colonoscopy

If colonoscopy or barium enema provide unsatisfactory results, a virtual colonoscopy can be used to visualise the colon in three dimensions. A spiral CT is performed which can detect polypoid lesions as small as to 6mm. This technique uses less radiation than conventional CT, is inexpensive and readily available.

Ultrasonograpy

Ultrasonography can be used to detect liver metastases and investigate any masses in the abdomen. It is economical and widely available.

Computerised tomography

A CT scan is more sensitive to liver metastases than ultrasonography, detecting metastases >1.5cm in diameter. A series of radiographs are created and analysed by computer. It can detect enlarged lymph nodes but cannot determine whether these are due to inflammation or malignancy.

Magnetic resonance imaging

MRI scans have limitations similar to CT in evaluating liver metastasis and depth of tumour invasion. Although it does not expose patients to radiation, it is more expensive and takes longer than CT scanning.

Future developments

Other tests under development include intra-operative ultrasonography (liver metastases), radio-immunodetection (anti-CEA antibody to identify tumours), and PET scanning.

MANAGEMENT

Management of CRC depends on the stage of disease and involve one or more of surgery, chemotherapy, and radiotherapy.

Surgery

Provided the patient is fit for surgery and does not have advanced disseminated disease, resection of the cancer is the primary management strategy. The type of surgery performed depends on the location, stage, size and presence of metastases.

Colonoscopy may suffice to remove small polyps in the bowel. Surgery should achieve "curative resection" – complete excision with no residual tumour – in 40% of cases. Where disease is at an advanced stage, resection will aim to overcome obstructing lesions and to alleviate pelvic symptoms. The classical resection principles aim to prevent any local recurrence of cancer. Advantages of laparoscopic surgery over open surgery are reduced blood loss, less postoperative pain, and less scarring. Patients may also benefit from a reduced period of post-operative ileus and a shorter in-patient stay.

After resection, the remaining bowel ends are anastamosed, provided they are close together. This ensures patency of the colon and negates the need for a permanent colostomy. When the bowel cannot be rejoined, the proximal end is brought out onto the skin of the abdominal wall to form a stoma so thatbowel motions pass into a colostomy bag. These may be permanent or temporary whilst the bowel heals.

Resected samples are analysed by histopathology to ensure the margins are clear. Adequate lymph node resection is imperative for staging and selection of patients for adjuvant treatment. A minimum of twelve negative lymph nodes should be examined to accurately define "node negative disease". Involvement of the apical node is an important diagnostic marker, since a positive node suggests there may still be positive nodes left in the patient. This predicts a poorer prognosis.

In advanced disease, surgery may remove the obstructing primary tumour or, where this is not feasible, bypass the obstruction. In some patients with left-side colon obstruction, stenting via a flexible sigmoidoscopy may provide important symptom control.

Approximately a third of colorectal cancer patients have liver metastases at initial presentation. Without liver surgery, the mean survival is around a year. Liver resection may be possible if there is no extra-hepatic or bi-lobar disease. It can yield survival rates of 25-35% at five years. If the primary tumour is large neo-adjuvant chemotherapy or radiotherapy may be used to reduce its size and improve surgical outcome.

Chemotherapy

Chemotherapy drugs are cytotoxic, with the majority inhibiting cellular proliferation by inhibiting DNA/RNA synthesis. This affects both normal and cancer cells. Chemotherapy can be used as adjuvant therapy to reduce the risk of cancer returning (stage II and III) or as palliative treatment to reduce symptoms (stage IV). The drugs typically used are 5-flurouracil (5-FU) and leucovorin (folinic acid). 5-flurouracil is a thymidylate synthetase (TS) inhibitor that prevents formation of thymine, so inhibiting DNA and RNA synthesis. Addition of leucovorin stabilises the 5-FU-TS complex, promoting maximum TS inhibition. Adjuvant chemotherapy improves patient five year survival by 5-10%. In advanced disease, chemotherapy can add four to six months to the life of each patient. Side effects of fluorouracil treatment are common with three out of ten people requiring further medical assistance to ameliorate symptoms. These include fatigue, nausea, vomiting, plantar-palmar erythema, diarrhoea, oral mucositis, and, rarely, angina and neurological toxic effects.

Radiotherapy

Radiotherapy is rarely used for advanced colorectal cancer. However, it may be used as an adjunct pre-operatively to shrink cancer and improve surgical outcome. Post-operatively it is used to remove any remaining cancer cells and/or shrink any persisting tumour. Radiotherapy uses radiation to eliminate growing and dividing cells by apoptosis. It is used in rectal cancer at stage II/III where tumours have spread through the rectal wall but not reached the lymph nodes. Radiotherapy is not typically used in colon cancer as there is a risk of significant damage to other abdominal structures. It aims to prevent local recurrence, thus reducing morbidity and mortality. Side effects from radiotherapy include wound infections, reduced wound healing, diarrhoea, bowel blockages, and post-operative pain.

Pre-operative radiotherapy has been shown in increase five year survival rates by 16%. Around 10% of patients that have pre-operative radiotherapy develop colorectal cancer recurrence compared with 25% of those undergoing surgery alone.

Chronic Myeloid Leukaemia

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Leukaemias are a broad range of haematological malignancies of the myeloid or lymphoid systems. They are relatively rare conditions with an annual incidence of approximately ten per 100,000 of the population. They are classified as acute (short natural history) or chronic (long natural history), and on their lymphoid or myeloid stem cell origin.

Chronic myeloid leukaemia (CML) belongs to a group of disorders collectively known as the chronic myeloproliferative disorders, which result from over-production of one or more myeloid cell lineages. Other disorders belonging to this group include myelofibrosis, essential thrombocythaemia, and polycythaemia rubra vera. CML involves the clonal expansion of transformed, primitive, haematopoietic progenitor cells of myeloid, monocytic, erythroid, megakaryocytic, B-lymphoid, or T-lymphoid lineages. Throughout most stages of the disease, leukaemic cells found in the blood and bone marrow are primarily myeloid. In approximately 90% of cases, these express an aberrant fusion protein as a result of a chromosomal translocation, known as the "Philadelphia chromosome". This is an acquired abnormality that involves the reciprocal exchange of portions of chromosomes nine and 22. CML displaying this translocation is referred to as typical/classical CML or Ph-positive, which has important implications for diagnosis, treatment strategy, and disease monitoring.

CML accounts for 15% of the total number of cases of adult leukaemias in the UK. The median age of patients at presentation is 45-55 years, with approximately 20% over sixty years of age. The annual incidence of CML 1.5 per 100,000 of the population in the UK, representing approximately 700 new cases per year. Around 2700 people in England and Wales currently have CML. The condition is very rare in children. 95% of patients with CML are in the chronic phase of the condition at the time of diagnosis.

The chronic phase of the condition typically lasts from between four and six years. Progression during this phase is usually slow. This is followed in two thirds

of patients by progression to an accelerated phase lasting between three and nine months in which there is rapid progression and increasing number of blast cells, thrombocyctosis, or anaemia.   Finally, this progresses to a blast or final phase. The one third of patients who do not enter the accelerated phase progress directly to this phase, often called a "blast crisis".   During the blast phase the disease may resemble acute myeloid leukaemia (AML) or, in some cases, acute lymphoid leukaemia (ALL).   The latter ("lymphoid blast crisis") is associated with a poor prognosis.   At present, it is believed that the only curative treatment of CML is via stem cell transplant from a suitably matched donor.   However, in recent years treatment has been revolutionised by the use of an agent known as imatinib (*e.g.* Gleevec or Glivec), which targets the underlying molecular defect associated with CML. This has been associated with significantly improved patient outcomes.

PATHOPHYSIOLOGY

Molecular basis

When compared to many other malignancies, the underlying defect associated with Ph-positive CML is relatively well-characterised at the molecular level. The Philadelphia chromosome (Ph) is a shortened chromosome 22 that results from reciprocal translocation between the long arms of chromosomes nine and 22. This defect is also found in up to 30% of cases of ALL and in 2% of cases of acute myeloblastic leukaemia. The translocation adds a 3' segment of the *abl* gene from chromosome 9q34 to the 5' part of the *bcr* gene on chromosome 22q11 resulting in a hybrid *bcr-abl* gene. *Abl* encodes a non-receptor tyrosine kinase of 230 kilobases, and consists of eleven exons. The breakpoint in this gene is 5' of exon two, so that exons two to eleven (known as a2 to a11) are transposed into the major breakpoint cluster region of the *bcr* gene on chromosome 22 between exons twelve to sixteen (known as b1 to b5). The resulting fusion gene is translated into a 210kd chimeric protein called P210$^{BCR-ABL}$. In certain cases, alternative splicing can result in the expression of variant fusion proteins, and this has been associated with the development of sub-types of CML in which there is pronounced monocytosis, thrombocytosis, or neutrophilia.

Non-receptor tyrosine kinases are important in signal transduction and regulation of cell growth. ABL contains two N-terminal SRC homology domains (SH2 and SH3) which regulate its activity, and a C-terminal nuclear localization sequence necessary for correct cellular localisation. The creation of the P210$^{BCR-ABL}$ fusion

protein results in a number of structural changes that are thought to be responsible for the leukaemogenic transformation. The N-terminal domain of the fusion protein has increased tyrosine kinase activity due in part to reduced activity of the SH3 domain which, under normal circumstances, has a negative regulatory role. As a result, the ABL portion of the fusion protein becomes constitutively active, allowing multiple new protein-protein interactions, and the activation of several different signalling pathways. Interaction occurs with growth factor receptor-like proteins (GRB2) and an oncogene-like protein (CRKL), with the former important in the activation of RAS-related signalling pathways. RAS is a small guanine nucleotide binding protein and an important mediator in signalling pathways controlling cell proliferation and differentiation.

The Ph chromosome results from the transfer of 3' DNA sequences derived from the *abl* gene on chromosome 9 with 5' sequences of the *bcr* gene on chromosome 22, forming a fusion gene, *bcr-abl*. The length of the BCR-ABL protein varies, and is determined by the breakpoint within the *bcr* gene. Chronic-phase CML is driven by the constitutively active BCR-ABL tyrosine kinase, which activates multiple pathways, leading to the malignant expansion of myeloid cells. iImatinib mesylate inhibits the tyrosine kinase activity of the BCR-ABL fusion protein by blocking the ATP-binding pocket, thus preventing the leukaemogenic effects of the Ph chromosome.

A major difference between the normal ABL protein, and the BCR-ABL fusion protein is altered cellular localisation. Under normal circumstances, ABL is found in both the nucleus and cytoplasm, and can move between as it possesses both nuclear localisation and nuclear export sequences. By contrast, BCR-ABL remains in the cytoplasm due to its constitutively activated tyrosine kinase domain. This is the primary mechanism by which apoptosis in CML cells is inhibited, as translocation of ABL to the nucleus is required for this process to occur. This contributes to the increased, uncontrolled proliferation of CML cells.

It is highly likely that a number of different signalling pathways are activated by P210$^{BCR-ABL}$ and the mechanism by which this results in uncontrolled cell proliferation remains to be fully elucidated. Similarly, the basis for the occurrence of the initial chromosomal translocation is largely unknown. As with other cancers, development of CML probably reflects a multi-step process in which several consecutive events are required for development of the disease. Multiple regions of BCR-ABL serve as important control elements for RAS, which is central to most prominent signalling pathways in CML.   Activation of RAS is

mediated through a series of adapter proteins, such as GRB2, CBL, SHC, and CRKL. Adapter proteins also connect BCR-ABL to focal adhesion complexes, PI-3 kinase, and other messenger systems such as JAK-STAT kinases. Signalling events downstream of RAS are less well characterised. They are thought to involve mitogen-activated protein kinases (MAPKs).

Pathogenesis

CML occurs when a single pluripotential haemopoeitic stem cell acquires the Philadelphia (Ph) chromosome carrying the *bcr-abl* fusion gene. Its progeny therefore possess a proliferative advantage over normal haematopoietic cells. This results in the aberrant clone, known as a Ph-positive clone, slowly replacing normal haematopoietic elements. Despite the almost complete abolition of normal blood cell production in favour of leukaemic cells, these cells function almost normally. However, in addition to their proliferative advantage, CML cells possess the ability to survive longer than normal cells due to reduced sensitivity to apoptosis. A subset of these cells also remain quiescent making them difficult to eliminate and resistant to standard chemotherapy regimens.

Although the mechanism of formation of the Ph chromosome remains largely unknown, a number of stimulating factors have been implicated. These include exposure to high doses of radiation, which is an acknowledged risk factor in the development of a number of leukaemias. Experimental procedures have demonstrated that exposure of myeloid cells lines to high dose ionising radiation induces expression of the BCR-ABL fusion protein. Another important factor in development of CML may be related to the proximity of the *bcr* and *abl* genes during specific points of the cell cycle. During interphase, these genes come into close proximity, and this may facilitate mutual translocations.

Following the molecular changes underlying development of the disease, myeloid progenitor cells undergo expansion, and are released into peripheral blood prematurely. This is partly a result of insensitivity to apoptosis, and reflects a shift in balance in favour of increased differentiation. Furthermore, these cells are resistant to the effects of growth regulatory molecules such as inhibitory cytokines. Their adherence ability is also compromised when compared to normal cells which adhere to bone marrow stromal elements to ensure controlled release into the bloodstream. CML progenitor cells have defects in this mechanism mediated by cell-surface glycoproteins called integrins, and are released into the bloodstream earlier than their normal counterparts.

AETIOLOGY

The majority of cases occur sporadically, with the only known predisposing factor being exposure to high doses of radiation. This was demonstrated by increased incidence of CML amongst survivors of the nuclear explosions in Japan, and amongst patients who received radiotherapy for treatment of ankylosing spondylitis. It has been estimated that as many as one third of atomic bomb survivors went on to develop CML.

PRESENTATION

Common features in patients with CML at the time of diagnosis include:

- fatigue
- anaemia
- weight loss
- sweating
- haemorrhage/increased tendency to bruising
- splenomegaly.

Less common features include:

- splenic infarction
- leucostasis
- gout
- retinal haemorrhage
- fever

At presentation, patients commonly complain of fatigue, shortness of breath (related to anaemia), and abdominal discomfort with the sensation of a mass in the left upper quadrant due to splenomegaly. Indeed, splenomegaly is the commonest physical sign at diagnosis, and may vary from being just palpable at the left costal margin, to filling the whole abdomen and extending towards the right iliac fossa. There may also be hepatomegaly, with palpation revealing a soft, ill-defined lower liver edge. It is also common for patients to experience spontaneous or excessive bruising in response to minor trauma.

Up to a quarter of patients are asymptomatic at the time of diagnosis when the disease is detected as a result of routine blood tests carried out other reasons. A number of less common symptoms may also be present including non-specific

fever and sweats unrelated to infection. Visual disturbances have also been reported due to leucostasis, a condition of blood hyperviscosity caused by a very high leukocyte count. In very rare cases there may also be retinal haemorrhage, splenic pain due to infarction or gout.

INVESTIGATIONS

The diagnosis of CML is made by peripheral blood analysis together with a bone marrow aspirate to confirm the diagnosis. The latter includes cytogenetic studies to demonstrate the presence of the Philadelphia chromosome. Fluorescence *in situ* hybridisation (FISH) studies may also be carried out on these cells using a fluorescent probe specific to the BCR-ABL fusion protein. This produces a very rapid result. The routine investigations to confirm suspected CML are a full blood count including blood film, bone marrow aspirate to assess cellularity and for chromosome analysis, urea and electrolytes, and serum lactate dehydrogenase. Additional investigations may also be carried out and these include a bone marrow trephine biopsy to examine the extent of fibrosis, vitamin B12 levels, and HLA typing of patient and family members with a view to future bone marrow transplantation. Cryopreservation of the patient's cells should be performed if autologous stem cell transplantation may be considered at a later stage. Males should be offered cryo-preservation of semen, as infertility is a risk. Cytogenetic analysis combined with polymerase chain reaction (RT-PCR) studies are commonly used to monitor response to treatment and disease progression.

The usual findings upon investigation are as follows:

- raised white blood cell count usually >30 x 10^9/ litre
- increased granulocytes, particularly neutrophils and eosinophils, at all stages of development
- primitive blast cells
- reduced haemoglobin concentration. Presence of immature nucleated red cells
- raised platelet count (300-600 x10^9/litre)
- Philadelphia chromosome in both bone marrow and peripheral blood
- hyper-cellular bone marrow with prominent granulocytic hyperplasia
- raised serum vitamin B12

Diagnosis of advanced disease depends on specific criteria. These include:

- progressive splenomegaly and increasing white cell count despite administration of cytotoxic therapy
- anaemia or thrombocytopenia that responds poorly to cytotoxic therapy.
- rapid white cell doubling
- 10% blasts in the blood or marrow
- thrombocytosis >$1000x10^9$/litre
- development of chromosomal changes in addition to the Philadelphia chromosome
- myelofibrosis

Blast crisis is defined as greater than 20% blasts in the blood or bone marrow.

MANAGEMENT

Imatinib mesylate
A number of drugs are available for the treatment of CML, however the only definitively curative method requires allogeneic bone marrow transplantation. Despite this, since 2003 in the UK a specific tyrosine kinase inhibitor known as imatinib mesylate (*e.g.* Glivec, Gleevec) has been the first line treatment of patients in the chronic phase of the disease. Its mechanism of action involves blockade of the ATP-binding pocket of the BCR-ABL fusion protein, thus rendering it inactive. It is administered orally, is generally well-tolerated, and has significantly improved patient outcome. It is estimated that up to 80% of patients have a significant lasting response to the drug, with overall and event free survival significantly better than with any existing drugs. It is also utilised in accelerated and blast phases of the condition. In recent years a series of further drugs with similar mechanism of action to imatinib, referred to as second-generation tyrosine kinase inhibitors, have also become available. These agents include dasatinib and nilotinib, and may be used where resistance to imatinib occurs, often as part of clinical trial

Several other drugs were used prior to the tyrosine kinase inhibitors, and may continue to be used in cases where imatinib is inappropriate, or where resistence occurs. Treatment regimes may be tailored to individuals depending on their age. In older patients (>50 years) emphasis is placed on palliative treatment, whereas younger patients are usually encouraged to consider aggressive therapy such as allogeneic bone marrow transplantation.

Interferon alpha

Recombinant interferon alpha produces a good haematologic response in 60% of patients in the chronic phase of CML. In addition, 20% lose the Philadelphia chromosome. Interferons are glycoproteins produced in response to antigenic stimuli, including viruses and malignancies. They have several effects including modulation of the immune response, inhibition of proliferation and angiogenesis, and they have anti-viral activities. They have been used in the treatment of patients with both solid tumours and haematological malignancies. The mechanism of action of interferon alpha in CML is not understood, but it is known to have anti-proliferative effects on CML progenitor cells. It may also inhibit survival of leukaemic cells by acting on cytoadhesion mechanisms. Interferon alpha was commonly employed as first line treatment in CML prior to the widespread use of imatinib. Administration is *via* daily subcutaneous injections, and the main side effect is an influenza-like illness which usually abates quickly. Other more serious side effects include anorexia, weight loss, rashes, alopecia, and thrombocytopenia. This results in discontinuance of treatment with interferon alpha in up to one fifth of patients.

Hydroxyurea

Hydroxyurea was commonly used to reduce the white cell count in newly diagnosed patients prior to introduction of interferon alpha. It acts specifically on myeloid cells by inhibiting the enzyme ribonucleotide reductase. It is usually given orally, but does not eradicate Ph-positive cells. Side effects include mouth ulceration, rashes, gastrointestinal upset, and bone marrow changes, although it is usually well tolerated.

Bone marrow transplantation

This involves the intravenous infusion of haematopoietic progenitor cells to re-establish marrow function in a patient with damaged or defective bone marrow, and is an effective therapy for various types of leukaemia. The bone marrow is usually harvested from the posterior iliac crest by repeated aspirations. There are two main types that may be used. Autologous bone marrow transplantation involves the use of the patient's own marrow to restore haematopoietic function. The main advantages of autologous transplantation are that it may be used in older patients, and the risk of graft versus host disease (GVHD) is eliminated. It is also useful when a closely matched allogeneic donor cannot be found. The re-infused haemopoietic stem cells can be obtained from bone marrow or from

peripheral blood that is collected following chemotherapy, or the use of growth factors such as granulocyte colony stimulating factor. Harvested bone marrow is stored in liquid nitrogen. The patient then undergoes intensive chemotherapy and/or radiotherapy before the marrow is re-infused. The marrow may be treated *in vitro* with monoclonal antibodies to remove malignant cells prior to re-infusion. The main side effects associated with this method are pneumonitis in the first month following transplantation, increased risk of haemorrhage, and hepatic venular occlusion. In recent years, the use of peripheral blood stem cells has become a more frequently used strategy.

An alternative is allogeneic bone marrow transplantation from a suitably HLA-matched donor. This may be a sibling, other relative, or unrelated individual sharing a similar HLA profile. Approximately 30% of patients have a sibling who is a suitable donor. Donation involves the aspiration of approximately a litre of bone marrow. The recipient is given high-dose ablative chemotherapy and, commonly, total body irradiation. It is necessary to provide adequate immunosuppression to avoid destruction of the allograft by residual host immune cells, eliminate residual leukaemic cells, and provide space for the transplanted bone marrow to grow. The donor bone marrow cells are infused intravenously and localise in the marrow, with the peripheral blood count rising within a month. The results of allogeneic transplant undertaken in first complete remission are far superior to those in relapse situations. Age is an important factor, with 55 years being the upper age limit normally considered for transplantation. This is because there is a higher frequency of GVHD with increasing age. This is a serious condition in which lymphocytes from the graft attack specific tissues in the host, most commonly the skin, liver, and gastrointestinal tract.

Allogeneic bone marrow transplantation is the only known cure for CML, which may be achieved in up to 70% of patients. However, the procedure is associated with a substantial risk of serious complications such as GVHD within the first two years. Despite this, the procedure is potentially curative and, even though later relapse may occur, it is often pursued in younger patients, especially where a HLA-matched donor is available.

Palliative Aspects of Cancer Care

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Palliative medicine established itself as a full medical specialty in 1987. However, dying patients have not always enjoyed the benefits of a modern holistic approach towards their care. Cancer patients have long needed specialist support towards the end of their lives, but little research existed in this area before the 1960s. When treatment was not curative, the patient was:

> "*At best, overlooked and, at worst, abandoned by physicians who told their patients to go home, as there was nothing more they could do*".
> *Lancet Oncol.* 2007 May;8(5):430-438.

This is in stark contrast to modern attitudes towards palliative care. The World Health Organization defines this type of care as:

> "*An approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*".
> http://www.who.int/cancer/palliative/definition/en/ (25/08/07)

Embedded within this are the key principles of multidisciplinary teamwork and effective communication which contribute towards better care and quality of life for patients and families.

This palliative care model has evolved from the work of a few prominent figures in the field, such as Elizabeth Kubler-Ross, whose research into the psychological and social impacts of terminal diagnosis helped to change attitudes towards dying patients and death in the Western world. A second grandee of palliative care was Dame Cecily Saunders who believed that:

"You matter to the last moment of your life and we will do all we can not only to help you die peacefully but to live until you die".
Oxford Handbook of Palliative Care, 1ˢᵗ ed. 2005. OUP.

This influential philosophy was the basis for development of the Modern Hospice Movement in the 1960s, and sparked changes in practice which revolutionised care for dying cancer patients.

CANCER AND PALLIATIVE CARE

At least one in three people in England will develop cancer during their lives. 200,000 people are diagnosed and 120,000 die annually in the United Kingdom.

Palliative care for cancer patients is a major priority. It becomes even more important when other life-limiting co-morbidities such as heart failure, neurological disorders, genetic disorders, and HIV/AIDS are taken into account. This presents a huge challenge to the NHS, since healthcare successes elsewhere mean people are tending to live longer in poorer health:

> *"There is broad agreement based on local and national epidemiological surveys, government reports and WHO data that the currently available palliative services from a range of providers are inadequate to meet some existing, and the rapidly growing, health and social care needs of the world's citizens with advanced disease"*.
> *BMJ* 2005;330:327.

In addition, the British population is continually diversifying and care must meet the cultural needs of ethnic minority communities as well as other marginalised groups such as refugees, prison inmates, and patients with learning difficulties. As a result staff require better education and training to help develop services which provide a greater level of understanding, and more flexibility within the physical, spiritual, psychological and social domains encapsulated by modern holistic palliative care.

SYMPTOMS IN CANCER

Patients receiving palliative care for cancer may present with a number of important symptoms including oedema, cachexia, dyspnoea and cough. Gastrointestinal symptoms include diarrhoea, constipation, oral complaints such as mouth ulcers, and weight loss. Nausea and vomiting may result from

treatment (*e.g.* radiotherapy or chemotherapy), hypercalcaemia, raised intracranial pressure, or bowel obstruction.

Pain

Pain is a common symptom, with approximately 3.5 million people worldwide suffering cancer pain every day. Pain is influenced by many factors such as site, intensity of stimulus, subjective capacity to deal with pain, and levels of psycho-social wellbeing. Indeed, pain is traditionally classified into four inter-related modalities: physical, psychosocial, emotional, and spiritual. It may take much longer to relieve pain in a patient who is angry, anxious, or showing signs of withdrawal. It is therefore important that pain management is considered as part of a holistic assessment of the patient which aims to improve all aspects of quality of life.

Physical pain in patients with cancer occurs for a number of reasons. Bone pain is the most frequent cause, although nerve compression and infiltration of soft tissue are also common. Pain falls into a number of categories: being caused by the tumour itself or by treatment, being related to cancer and debility, or an unrelated entity. Often it will change according to variables such as time and site of onset, associated symptoms such as sensory change, or activities such as movement, eating, or micturition. These features may be used to identify the precise cause. In patients with advanced cancer, pain may arise from pathological fractures, liver capsule pain, neuropathy, metastases, and inflammation or distension due to tumour bulk.

Tumour effects

In addition to pain, the presence of the tumour itself may cause a number of other symptoms which, if addressed, can help improve patient comfort and dignity. For example, gastrointestinal cancers may bleed leading to anaemia, fatigue, and breathlessness. Oesophageal tumours may result in dysphagia and/or odynophagia which may be partially relieved by insertion of a stent. Liver cancer – or a distant primary with liver metastases – can lead to liver failure and stigmata of liver disease. Such symptoms – *e.g.* massive ascites – are easily treated once recognised.

Psychological symptoms

Physical pain is inherently linked to other clinically important features of the disease process such as state of mental health. Persistent pain can cause depression and anxiety, both of which are common symptoms in patients nearing the end of life.

Another common psychological symptom is confusion, especially when patients undergo long stays in hospital. It is estimated that the prevalence of delirium among hospitalized terminal patients is as high as 85%. Insomnia can also cause problems as patients may be irritated by disease symptoms or side-effects from medication. Patients also suffer disruption to normal routines and may experience unwelcome changes to sleep patterns. This may be partly because they are rested during the day and disturbed at night by the hospital environment. Sleeplessness may be complicated by psychological distress and anxiety.

Palliative emergencies

Palliation is often viewed as a passive process, but emergencies do occur and patients should be monitored closely for worrying symptoms. Emergencies include spinal cord compression (*e.g.* due to spinal metastases), and pulmonary embolism as cancer is a thrombogenic process. Patients with impaired mobility may also be at risk of developing pressure sores and acquiring infection from indwelling catheters. Other emergencies include bowel obstruction, superior vena cava obstruction, hypercalcaemia, intractable breathlessness, uncontrolled pain, and terminal restlessness.

Terminal symptoms

The terminal phase of life is a period of daily deterioration, *e.g.* of strength, appetite, and awareness. Patients may also experience "terminal restlessness" caused by factors such as cerebral irritability (particularly if they have a cerebral tumour or metastases), pain, fear, and side-effects of medication. In their last few hours, patients may also develop the characteristic "death rattle"; noisy moist breathing resulting from an inability to remove secretions from the airways.

PALLIATIVE MANAGEMENT OF CANCER PATIENTS

Comprehensive palliative care is provided in hospital, hospice, and community settings. It incorporates in-patient care, day therapy, community support, education, and bereavement services. Modern hospice care is championed as best practice, largely because the system is designed to deliver specialist care in a patient-centred environment. Patient services include symptom management, post-treatment rehabilitation, respite, and terminal care.

Although the general medical model also advocates such care, some believe the delivery of palliative care in other settings is compromised by factors such as time, resources, and conflicting interests.

The Liverpool Care Pathway has been developed specifically with the aim of transferring the hospice model of care to other settings. It includes a number of goals which should be achievable regardless of location. These include discontinuing inappropriate interventions, setting up appropriate and timely pain relief, and assessing the spiritual needs of the family and how they will be informed of impending death.

However, it should not be assumed that all patients wish to spend their final days in a hospice. Many patients wish to stay at home as long as possible. Furthermore, hospices are limited in some areas of care such as out-of-hours admissions and carrying out certain clinical procedures. The Gold Standards Framework (GSF) has been developed specifically with the aim of improving and standardising palliative care in the community:

> *"GSF is a tried and tested framework of strategies, tasks and enabling tools to help primary care teams deliver the best possible care for people nearing the end of their lives"*
> National Gold Standards Framework Centre. 2007.

The GSF recognises the importance of communication and co-ordination of services in working towards key priorities for each individual patient such as control of symptoms, carer support, continuity of care (including-out-of hours), and care in the dying phase. Underpinning this is the need to identify patients early, assess their needs, and plan ahead.

Other recent initiatives have included Preferred Place of Care (PPC) which addresses the need for increased patient choice and awareness of services. This is

particularly important as PPC acknowledges that patients' preference and needs may change as their disease progresses.

General management
The palliative care model advocates holistic management in order to maximise patient dignity and quality of life (QOL). However, this is a subjective concept which varies from person to person on a daily basis. Tools exist to measure QOL, such as the European Organization for Research and Treatment of Cancer's international, cancer-related core QOL questionnaire (the EORTC QLQ-C30). Although useful in clinical trials, such indicators are less effective in assessing individual patients' satisfaction with care.

This re-emphasises the importance of communication and shared decision-making in achieving patient satisfaction. Similarly, a multi-disciplinary approach is vital to ensure the best possible patient outcomes. To achieve this, palliative care teams incorporate a range of professionals including doctors, nurses, physiotherapists, occupational therapists, dieticians, chaplains, clinical psychologists, and volunteers.

Pain management
Pain management for patients with advanced stage cancer can be complex. The WHOs Analgesic Ladder is used as a guide for administering appropriate pain relief. It covers non-opioids (*e.g.* NSAIDs) for mild pain, weak opioids such as codeine for moderate pain, and strong opioids (*e.g.* morphine, diamorphine, and fentanyl) for severe pain. In all cases analgesics should be given regularly and with appropriate drugs (*e.g.* laxatives) to counteract known side effects such as constipation. The gold standard treatment for cancer pain is morphine which is commonly given orally. A recent systematic review found no difference between the efficacy of sustained release morphine (MSR) and immediate release morphine (MIR). Morphine is particularly useful in helping to control severe and breakthrough pain.

There are several issues surrounding administration of opioids which may compromise their effective use. These include perceived lack of experience and training of staff, and a concern that opioids hasten death by causing respiratory depression. This creates an ethical dilemma which is often resolved using the doctrine of double effect. In summary, this states that a harmful effect of a

treatment is justifiable if it is simply the side effect of a positive act. However, one retrospective study suggested there is no significant difference in the lifespan of those whose opioid dose was increased in the last week of life, and those whose dose was maintained.

Some types of pain may be unresponsive to opioids. One example is mesothelioma chest wall pain which can be difficult to control and responds more frequently to inter-costal and para-vertebral nerve blocks. Neuropathic pain may be responsive to opioids, but can also respond to other drugs such as tricyclic antidepressants (*e.g.* amitriptyline), anti-convulsants (*e.g.* gabapentin), and corticosteroids (*e.g.* dexamethasone). The latter is thought to reduce oedema (relieving pressure on nerves), as well as reduce inflammatory sensitization of nerves. NSAIDs are effective in neuropathic cancer pain for the same reasons.

Other types of pain may require more aggressive management. For example, palliative radiotherapy for bone pain is common. Similarly muscle pain can be managed with drugs such as diazepam but alternative treatments such as physiotherapy and aromatherapy may also be effective. One systematic review found three studies that reported reduced pain following aromatherapy and massage.

Management of other physical symptoms
Patients frequently receive palliative radiotherapy and/or chemotherapy to treat or delay symptom progression. Radiotherapy is, for example, often indicated in cases of spinal cord compression.

Other symptoms such as nausea and vomiting, fatigue, weight loss, and oedema are managed with appropriate drugs or interventions. Anything which improves the patient's QOL will be considered. For example an anaemic patient may be offered a blood transfusion to increase energy levels. It is hugely important that the correct cause of a problem be identified so that appropriate treatments can be given.

Alternative strategies for managing cancer and associated symptoms are being explored. An unexpected result of one study which treated mesothelioma patients with thalidomide was a significant improvement in symptoms –

specifically pain control and appetite – although the drug had no effect on tumour size

Management of psychological symptoms

The National Council for Hospice and Specialist Palliative Care Services (NCHSPCS) defines psychosocial care as:

> "*The psychological and emotional well-being of the patient and their family/carers, including issues of self-esteem, insight into an adaptation to the illness and its consequences, communication, social functioning and relationships*"

Psychosocial Issues in Palliative Care, 1st ed. 2003. OUP. p1.

Psychological symptoms are managed in various ways including through cognitive behavioural therapy (CBT) and psychotherapy. These symptoms can also be improved by good patient-staff communication and ensuring continuity of care.

Depression among terminally ill patients can be as high as 69%. It is therefore helpful to use clinical screening tools to assess psychological morbidity, even if there is difficulty in distinguishing between clinical depression and "appropriate" levels of sadness. One such tool is the Edinburgh Depression Scale – adapted from a scale used to measure post-natal depression. Drug treatments for psychological symptoms vary but benzodiazepines, anti-psychotics, and anti-depressants such as amitriptyline are frequently used to manage anxiety. Depression may be treated with many classes of drugs including monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs).

Managing spiritual needs and bereavement

Spiritual needs are not confined to religious beliefs, although these are frequently important to patients nearing the end of life. In hospitals and hospices, multi-faith spiritual support is usually offered by a chaplaincy team. Emphasis is placed on good communication with the patient to ascertain their individual beliefs and expectations. This is important as certain faiths will have preferences relating to diet, privacy, cross-gender care, and preparation of their body after death.

Palliative care extends to the relatives of patients during the illness and after death. Bereaved families are often invited to remembrance services held in

hospices, which provide an opportunity to talk to professionals and share grief. In addition, many settings provide bereavement counselling for both adults and children.

Managing social and lifestyle preferences

Considering individual social and lifestyle preferences is crucial in helping patients maintain quality of life. Particular routines or aspects of a patient's life may be important to them, for example being able to drive a car, or being able to go out with family. It is important to facilitate these activities where possible and this is achieved with the help of interventions such as occupational therapy, physiotherapy, counselling, and patient education.