LECTURE NOTES

Oncology

MARK BOWER
JONATHAN WAXMAN

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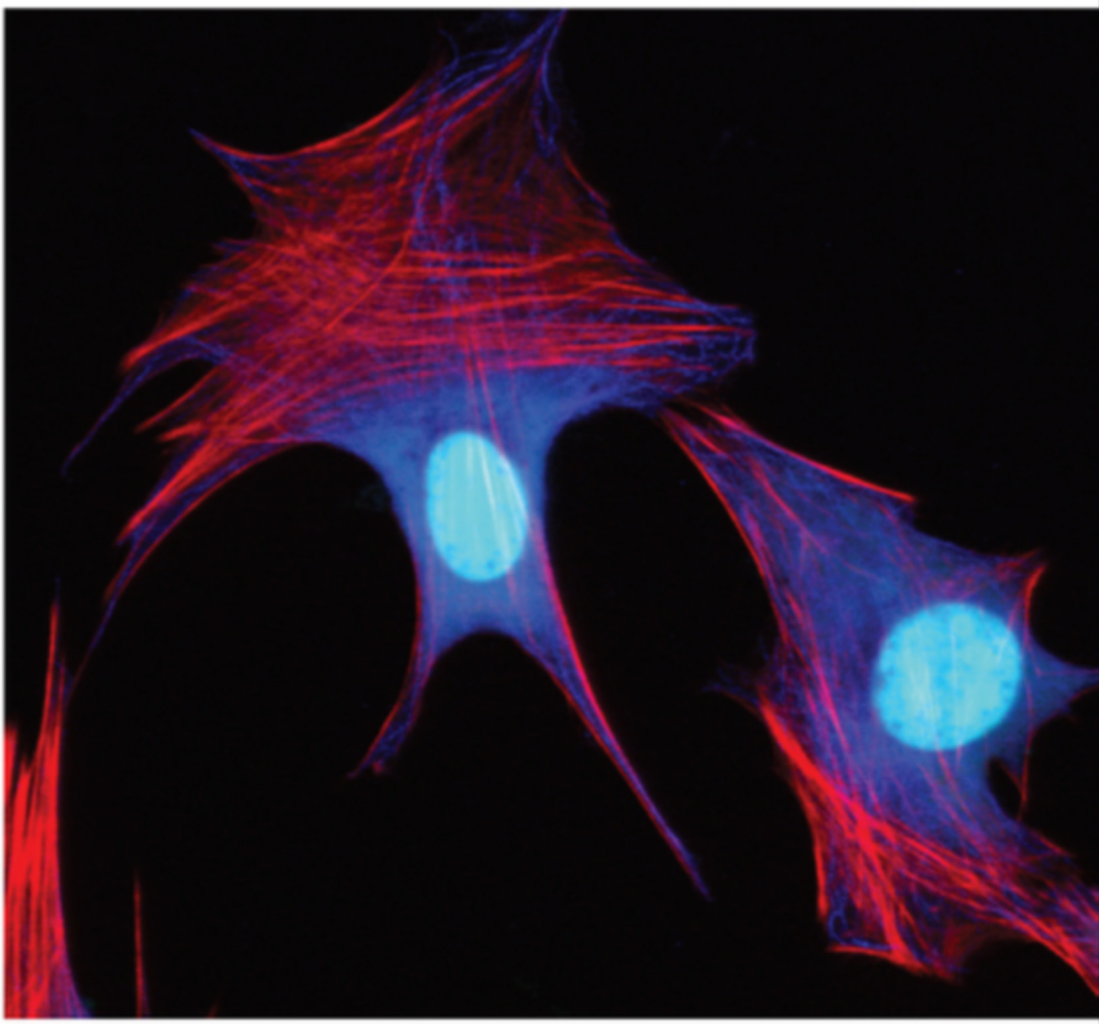
2nd edition



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Lecture Notes: Oncology

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Oncology

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Preface to the second edition

We are delighted that *Lecture Notes: Oncology* has progressed to a second edition, returning by popular demand with an updated format, enormous revisions and a few poor jokes.

The last decade has seen tremendous changes in oncology, with marvellous developments in targeted therapies, based on an understanding of the molecular biology of cancer. We are at a stage in oncology where death rates have fallen in many cancers, and where the survival for patients with metastatic disease has, in many instances, doubled. Cancer doctors used to proudly talk about curing a small minority of tumours such as lymphoma, leukaemia, choriocarcinoma and testicular cancer, but currently this shortlist of survivable cancers has increased, providing optimism in oncologists and delight in patients.

Oncology involves an understanding of the processes that lead to the development of malignant disease, and this understanding has led Medicine by its nose to the frontiers of science. These are exhilarating times to be an oncologist and we hope that the reader of this book enjoys our efforts to convey our excitement in oncology.

Mark Bower
Jonathan Waxman

Part 1

Introduction to Oncology

Chapter 1

What is cancer?

Cancer is not a single illness but a collection of many diseases that share common features. Cancer is widely viewed as a disease of genetic origin. It is caused by mutations of DNA and epigenetic changes that alter gene expression, which make a cell multiply uncontrollably. However, the description and definitions of cancer vary depending on the perspective as described below.

Epidemiological perspective

Cancer is a major cause of morbidity in the United Kingdom with around 289 000 new cases diagnosed in 2005. There are more than 200 different types of cancer, but four of them (breast, lung, colorectal and prostate) account for over half of all new cases. Overall it is estimated that one in three people will develop some form of cancer during their lifetime. In the 30-year period 1976–2005 the overall age-standardized incidence rates for cancer increased by 35% in men and 16% in women but have remained fairly constant over the last decade (1996–2005). The cancers whose incidence is rising fastest in men are malignant melanoma, mesothelioma, prostate cancer and hepatocellular cancer, while in women they are mesothelioma, melanoma, endometrial cancer and oral cancer.

Cancer incidence refers to the number of new cancer cases arising in a specified period of time. Prevalence refers to the number of people who have received a diagnosis of cancer who are alive at any given time, some of whom will be cured and others will not. Therefore prevalence reflects both the incidence of cancer and its associated survival pattern. In 2008 approximately 3% of the population of the UK (around two million people) are alive having received a diagnosis of cancer. The single cancer that contributes most to the prevalence is breast cancer, with an estimated 550 000 women alive who have had a diagnosis of breast cancer.

Sociological perspective

Patients with cancer adopt a medically sanctioned form of deviant behaviour described in the 1950s by Talcott Parsons as 'the sick role'. In order to be excused their usual duties and to not be considered responsible for their illness, patients are expected to seek professional advice and to adhere to treatments in order to get well. Medical practitioners are empowered to sanction their temporary absence from the workforce and family duties as well as to absolve them of blame. This behavioural model minimizes the impact of illness on society and reduces the secondary gain that the patient benefits from as a consequence of their illness. However, as Ivan Illich pointed out it also sets up physicians as agents of social control by

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Table 1.1 The top cancer books (in the authors' opinion).

	Title	Author
1	*Cancer Ward*	Alexander Solzhenitsyn
2	*A Very Easy Death*	Simone de Beauvoir
3	*Age of Iron*	J. M. Coetzee
4	*Cancer Vixen*	Marisa Acocella Marchetto
5	*One in Three*	Adam Wishart
6	*C: Because Cowards get Cancer, Too*	John Diamond
7	*Before I Say Goodbye*	Ruth Picardie
8	*Illness as Metaphor*	Susan Sontag
9	*The Black swan*	Thomas Mann
10	*Mom's Cancer*	Brian Fies
11	*Coda*	Simon Gray
12	*Cancer Tales*	Nell Dunn

medicalizing health and contributing to iatrogenic illness – 'a medical nemesis'. Of all the common medical diagnoses, cancer probably carries the greatest stigma and is associated with the most fear. The many different ways in which cancer affects people has been explored in literature (Table 1.1).

Experimental perspective

In the laboratory, a number of characteristics define a cancer cell growing in culture. The four features listed below are used by scientists experimentally to confirm the malignant phenotype of cancer cells:

1. Cancer cells are clonal, having all derived from a single parent cell.

2. Cancer cells grow on soft agar, in the absence of growth factors.

3. Cancer cells cross artificial membranes in culture systems.

4. Cancer cells form tumours if injected into immunodeficient strains of mice (Box 1.1).

Histopathological perspective

Cancer is usually defined by various histopathological features, most notably invasion and metastasis, that are observed by gross pathological and microscopic examinations. Laminin staining of the basement membrane may assist the histopathologist in identifying local invasion by tumours that breach the basement membrane. In addition a number of microscopic features point to the diagnosis of cancer:

- Cancer cells differ morphologically from normal cells
- Tumour architecture is less organized than that of the parent tissue
- Cancer cells have increased nuclear DNA and nuclear:cytoplasmic ratio
- Cancer cells have hyperchromatic nuclei with coarsening of chromatin and wrinkled nuclear edges

Box 1.1: Onco-mice

Mice have been used as a laboratory model in cancer research for a century. In the 1930s, Sir Ernest Kennaway showed that polycyclic aromatic hydrocarbons were carcinogenic by inducing skin cancers in mice. In 1969 the first inbred mice were developed that were essentially genetically identical except for gender. These strains allowed the transfer of cells and tissues between mice without rejection as they are syngeneic (genetically identical). This has allowed the effects of experimental treatments on murine cancers to be evaluated in laboratory mice. Some inbred strains also spontaneously develop cancers (e.g. BALB/c mice frequently develop lung tumours) so that the effects of cancer prevention strategies can be studied. The development of immunodeficient mice allowed the transfer and study of human cancer cells in mice without the mice rejecting the xenograft (graft between different species). The first immunodeficient mice were 'nude mice', an inbred strain that lacks a thymus gland and T lymphocytes; they are hairless because of a mutation in a linked genetic locus. Subsequently, in 1983, even more immunodeficient SCID (severe combined immunodeficiency) mice were developed that lack both T and B cells. Genetically modified transgenic mice have been manufactured by knocking out specific genes ('knockout mice') or adding extra trans-genes, usually from different species ('transgenic mice'), to embryonic stem cells. These mice are used to elucidate the influence of individual genes on the phenotype. Finally, mice were the original source of monoclonal antibodies produced by immunizing inbred mice with the desired antigen and fusing spleen cells from the mouse with myeloma cells to yield hybridoma cells that produce monoclonal antibodies.

- Cancer cells may be multinucleated or have macronucleoli
- Cancer cells may have numerous and bizarre mitotic figures

Cancers may be heterogenous with cells of varying sizes and orientation with respect to one another despite their clonal origin.

Molecular perspective

The molecular features that identify a cancer are described in 'Six steps to becoming a cancer' in Chapter 2. These six properties are:

1. Grow without a trigger (self-sufficiency in growth stimuli).
2. Don't stop growing (insensitivity to inhibitory stimuli).
3. Don't die (evasion of apoptosis).
4. Don't age (immortalization).
5. Feed themselves (neoangiogenesis).
6. Spread (invasion and metastasis).

How to read a histology report

The diagnosis of cancer is most commonly established following a histopathological report of a biopsy or tumour resection. A histopathological report should include both gross pathological features (tumour size and number and size of lymph nodes examined) and microscopic findings (tumour grade, architecture, mitotic rate, margin involvement and lymphovascular invasion). The grade and stage of a cancer are important prognostic factors that may influence therapy options (Box 1.2).

Box 1.2: Histopathology definitions

Quantitative changes: too small

Atrophy
Acquired shrinkage due to a decrease in the *size or number* of cells of a tissue, e.g. decrease in size of the ovaries after the menopause.

Quantitative changes: too big

Hypertrophy
Increase in the size of an organ or tissue due to an increase in the *size* of individual cells, e.g. pregnant uterus.

Hyperplasia
Increase in the *size* of an organ due to an increase in the *number* of cells, e.g. lactating breast.

Qualitative changes

Metaplasia
Replacement of one cell type in an organ by another. This implies changes in the differentiation programme and is usually a response to persistent injury. It is reversible so that removal of the source of injury results in reversion to the original cell type, e.g. sqamous metaplasia of laryngeal respiratory epithelium in a smoker. Chronic irritation from smoking causes the normal columnar respiratory epithelium to be replaced by the more resilient squamous epithelium.

Dysplasia
Dysplastic changes are changes in cell type, as for metaplasia, that do not revert to normal once the injury is removed, e.g. cervical dysplasia initiated by human papillomavirus infection persists after eradication of the virus. Dysplasia is usually considered to be part of the spectrum of changes leading to neoplasia.

Invasion
The capacity to infiltrate the surrounding tissues and organs is a characteristic of cancer.

Metastasis
The ability to proliferate in distant parts of the body after tumour cells have been transported by lymph or blood or along body spaces.

Table 1.2 Histological features of benign and malignant tumours.

Features of malignancy	Features of benign tumours
Macroscopic features	
Invade and metastasize	Do not invade or metastasize
Rapid growth	Slow growing
Not clearly demarcated	Clearly demarcated from surrounding tissue
Surface often ulcerated and necrotic	Surface smooth
Cut surface heterogenous	Cut surface homogenous
Microscopic features	
Often high mitotic rate	Low mitotic rate
Nuclei pleomorphic and hyperchromatic	Nuclear morphology often normal
Abnormal mitoses	Mitotic figures normal

A histopathological definition of cancer: is it malignant or benign?

Malignancy is usually characterized by various behavioural features, most notably invasion and metastasis. However, the histopathologist may have to identify a cancer without this information. Cancers are composed of clonal cells (all are the progeny of a single cell) and have lost control of their tissue organization and architecture. In addition to the natural history, a number of physical properties help to distinguish between benign and malignant tumours (Table 1.2). However, there is no single histological feature that defines a cancer nor indeed that separates benign from malignant tumours. In general, benign tumours are rarely life-threatening but may cause health problems on account of their location (by pressure or obstruction of adjacent organs) or by overproduction of hormones. In contrast malignant tumours usually follow a progressive course and unless successfully treated are frequently fatal.

Is it *in situ* or invasive?

Invasive cancers extend into the surrounding stroma (see Plate 1.1). However tumours that exhibit all the microscopic features of cancers but do not breach the original basement membrane are termed *in situ* (non-invasive) cancers. Examples include *in situ* breast cancer confined to the mammary ducts (ductal carcinoma *in situ* or DCIS) or lobules (lobular carcinoma *in situ* or LCIS) (see Plate 1.2). Similar pre-invasive *in situ* cancers have been found in many organs (e.g. cervix, anus, prostate, bronchus) and are believed to represent a stage in the progression from dysplasia to cancer (see Plate 1.3).

Histopathologist's nomenclature: name that cancer

The histopathologists' lexicon often can be a tool for obfuscation, but follow a few simple rules and you can translate their lingo. The suffix -oma usually denotes a benign tumour (although it simply means 'swelling' and some -omas are not tumours, e.g. xanthoma). If a tumour is malignant the suffix -carcinoma (Greek for crab) is used for epithleial cancers or -sarcoma (Greek for flesh) for connective tissue cancers. The prefix is determined by the cells of origin of the tumour (e.g. adeno- for glandular epithelium), qualified by the tissue of origin (e.g. prostatic adenocarcinoma). There are numerous exceptions to this systematic nomenclature; for example leukaemias and lymphomas are malignant tumours of bone marrow and lymphoid tissue, respectively. As a general rule neoplasms are classified according to the type of normal tissue they most closely resemble. The four major categories are: epithelial, connective tissue, lymphoid and haemopoietic tissue, and germ cells (Tables 1.3–1.6). The latter arise in totipotential cells, and can develop into any cell type. Germ cell tumours contain a variety of different mature and/or immature tissues from different embryonic germ layers, and these are given names with the root terato- (Greek for monster). In addition, as with most fields of medicine where physicians try to leave their mark, there are a number of eponymous names (e.g. Hodgkin's disease). (Thomas Hodgkin (of Guy's Hospital) described seven cases in 1832 of the tumour that bears his name but re-examination in 1926 revealed that the diagnosis was inaccurate in four of the seven cases.)

Table 1.3 Nomenclature of epithelial tumours.

Epithelium	Benign tumour	Malignant tumour
Squamous	Squamous papilloma	Squamous carcinoma
Glandular	Adenoma	Adenocarcinoma
Transitional	Transitional papilloma	Transitional carcinoma
Liver	Hepatic adenoma	Hepatocellular carcinoma
Skin	Papilloma	Squamous cell carcinoma Basal cell carcinoma
Skin melanocyte	Naevus	Malignant melanoma

Table 1.4 Nomenclature of connective tissue tumours.

Tissue	Benign tumour	Malignant tumour
Bone	Osteoma	Osteosarcoma
Cartilage	Chondroma	Chondrosarcoma
Fat	Lipoma	Liposarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Blood vessel	Angioma	Angiosarcoma
Fibrous tissue	Fibroma	Fibrosarcoma

Table 1.5 Nomenclature of haematological tumours.

Tissue	Malignant tumour
Node lymphocyte	Lymphoma
Marrow lymphocyte	Lymphocytic leukaemia
Granulocyte	Myeloid leukaemia
Plasma cell	Myeloma

Table 1.6 Nomenclature of germ cell tumours.

Tissue	Benign tumour	Malignant tumour (male)	Malignant tumour (female)
Germ cell	Mature teratoma/dermoid cyst	Non-seminomatous germ cell tumour/malignant teratoma	Immature teratoma/embryonal carcinoma
	–	Seminoma	Dysgerminoma

Tumour grading

Tumours are graded according to the degree of tissue differentiation. Cancers that closely resemble their tissue of origin are graded as well differentiated cancers. Cancers that look nothing like the original tissue and have histological features of aggressive growth with high mitotic rates are graded as poorly differentiated cancers. The grade of a tumour is of prognostic significance.

In the case of breast cancer, the Scarff–Bloom–Richardson system is usually used to grade cancers based upon three features: the frequency of cell mitosis, tubule formation, and nuclear pleomorphism. Each of these features is assigned a score ranging from 1 to 3 (1 indicating slower cell growth and 3 indicating faster cell growth). The scores of each of the cells' features are then added together for a final sum that will range between 3 and 9. A tumour with a final sum of 3, 4 or 5 is considered a grade 1 tumour (well differentiated). A sum of 6 or 7 is considered a grade 2 tumour (moderately differentiated), and a sum of 8 or 9 is a grade 3 tumour (poorly differentiated). The five-year overall survival for grades 1, 2 and 3 are 95%, 75% and 50%, respectively.

In addition, pathologists may identify other features that relate to the natural behaviour of a tumour, such as lymphovascular invasion, which usually denotes a worse prognosis. The molecular

properties of a cancer can also influence the biology, prognosis and treatment of a tumour. For example, the gene expression prolife of a breast cancer may be determined by gene expression microarray chip technology and the results assist clinicians in optimizing adjuvant therapy (see Plate 1.4).

Unknown primary identification (standard histological techniques)

Occasionally patients present with metastatic cancer without an obvious primary tumour site and, in addition to a careful clinical and radiological examination, the pathologist may provide a clue to the origins of the cancer. Most unknown primary cancers are adenocarcinoma (60%), and the remainder are poorly differentiated carcinomas (30%) and squamous cell carcinomas (5%). Light microscopy may provide pointers, for example the presence of melanin pigment favours melanoma, whilst mucin production is common in gastrointestinal, breast and lung cancers but less common in ovarian cancers and is rare in renal cell and thyroid cancers. Immunocytochemical staining of tissue samples can aid the pathologist in tissue identification. For example, the presence of oestrogen and progesterone receptors favours a diagnosis of breast cancer, whilst prostate-specific antigen and prostatic acid phosphatase staining points to prostatic adenocarcinoma. Similarly, cytokeratin expression patterns may provide helpful hints about the origin of metastatic cancers (Box 1.3 and see Plate 1.5). Cell surface immunophenotyping is a sophistication of immunocytochemistry that is frequently applied to haematological malignancies. The pattern of immunoglobulin, T-cell receptor and cluster designation (CD) antigen expression on the surface of lymphomas is helpful in their diagnosis and classification. Immunophenotyping can be achieved by immunohistochemical staining, immunofluorescent staining or flow cytometry.

Box 1.3: Cytokeratins

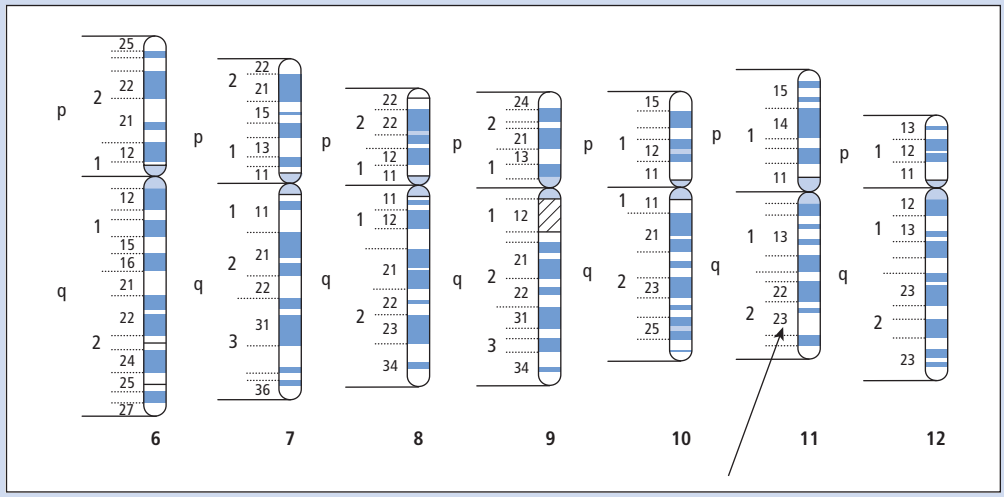
Cytokeratins are intermediate filament proteins expressed in pairs comprising a type I (cytokeratins 9–20) and a type II (cytokeratins 1–8) cytokeratin. Different tissues express different pairs and immunocytochemical staining for cytokeratins can help identify the likely tissue origins of cancers cells. For example in disseminated peritoneal metastases, CK7 expression favours an ovarian origin, whilst lack of CK7 is more common in colorectal cancer (Figure 1.3).

Unknown primary identification (special histological techniques)

The study of intracellular organelles by electron microscopy may identify the cellular origin of a tumour; for example, the presence of melanosomes in melanomas and dense core neurosecretory granules in neuroendodermal tumours. Further laboratory techniques to aid diagnosis include molecular studies of DNA rearrangements that characterize malignancies. Monoclonal immunoglobulin gene rearrangements are present in B-cell malignancies and rearrangements of T-cell receptors occur in T-cell tumours. In addition, a number of chromosomal translocations involving the immunoglobulin genes (heavy chain on chromosome 14q32, light chains on 2p12 and 22q11) and T-cell receptor genes (TCRα on 14q11, TCRβ on 7q35, TCRγ on 7p15, TCRδ on 14q11) occur in malignancies arising from these cell types. For instance, low-grade follicular lymphomas rearrange the Bcl-2 gene on 18q21 (e.g. t(14;18)(q32;q21)), most Burkitt lymphomas rearrange the Myc gene on 8q24 (e.g. t(8;14)(q24;q32)) and most mantle cell lymphomas rearrange Bcl-1 on 11q13 (e.g. t(11;14)(q13;q32)). These rearrangements may be detected by karyotype analysis of mitotic chromosome preparations or by molecular techniques including Southern blotting and polymerase chain reaction (Box 1.4 and Table 1.7). Less commonly these same methods may assist the diagnosis of solid tumours that are associated with specific chromosomal abnormalities such as the i(12p) isochromosome found in germ cell tumours and the t(11;22)(q24;q12) translocation seen in Ewing's sarcoma and peripheral neuroectodermal tumours. In addition to translocations, gene amplification may be detected and may have prognostic

Box 1.4: The language of chromosomes – karyotype nomenclature

Each arm of a chromosome is divided into one to four major regions, depending on chromosomal length; each band, positively or negatively stained, is given a number, which rises as the distance from the centromere increases. The normal male is designated as 46,XY and the normal female as 46,XX.



For example, 11q23 designates the chromosome (11), the long arm (q), the second region distal to the centromere (2) and the third band (3) in that region.

Polyploid
Cell with more than one complete chromosome set or with multiples of the basic number of chromosomes characteristic of the species; in humans this would be 69,92, etc.

Aneuploid
Individual with one or more chromosomes in addition or missing from the complete chromosome set; for example trisomy 21 (47,XX +21).

Deletion
The loss of a chromosome segment from a normal chromosome.

Duplication
An extra piece of chromosome segment which may be attached to the same homologous chromosome or transposed to another chromosome in the genome.

Inversion
A change in linear sequence of the genes in a chromosome that results in the reverse order of genes in a chromosome segment. Inversions may be pericentric (two breaks on either side of the centromere) or paracentric (both breaks on the same arm).

Isochromosome
breaks in one arm of a chromosome followed by duplication of the other arm of the chromosome to produce a chromosome with two arms that are both short (p) or both long (q) arms.

Translocations
Translocations are the result of the reciprocal exchange of terminal segments of non-homologous chromosomes.

Table 1.7 Examples of chromosomal abnormalities in cancers.

Chromosome defect	Karyotype	Tumour	Candidate gene
Monosomy	45,XY –22	Meningioma	NF2
Trisomy	47,XX +7	Papillary renal carcinoma	MET
Deletion	46,XY del(11)(p13)	Wilms' tumour	WT1
Duplication	46,XX dup(2)(p23-24)	Neuroblastoma	n-Myc
Inversion	46,XY inv(16)(p13q22)	Acute myeloid leukaemia (M4Eo)	MYH11/core-binding factor b
Isochromosome	47,XX i(12p)	Testicular germ cell tumour	
Translocation	46,XX t(9;22)(q34;q11)	Chronic myeloid leukaemia	bcr/abl

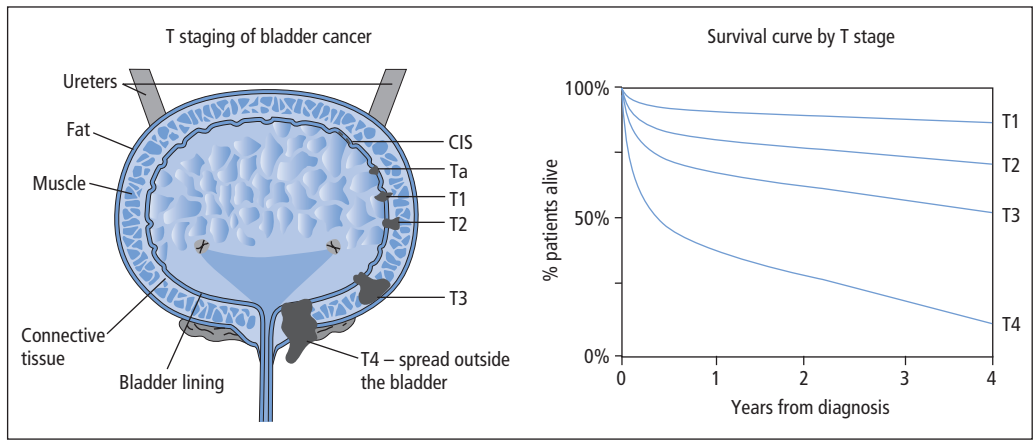


Figure 1.1 T-stage classification for bladder cancer and influence on survival. CIS, carcinoma *in situ*.

significance, e.g. the amplification of the n-Myc oncogene in neuroblastoma is an adverse prognostic variable.

How to stage a tumour

In addition to the histological grade of a tumour, an important criterion in treatment decisions and the major determinant of outcome is the extent of spread or stage of a cancer (Figure 1.1). Staging a tumour is essentially an anatomical exercise that uses a combination of clinical examination and radiology. A uniform staging system is employed for most tumour sites that is based upon the size of the primary **T**umour, the presence of regional lymph **N**odes and of distant **M**etastases. The details of this **TNM** classification vary between different tumour sites. As always there are exceptions, including the staging system for lymphomas that was originally set out following a conference at the University of Michigan in Ann Arbour. It is known as the Ann Arbour Staging System and most radiologists assume that it is named after a person rather than a town, so this is a chance to score points at the X-ray meetings.

Radiology techniques

Staging depends to a large extent upon radiology and this is the most commonly used tool to evaluate the response of cancers to therapies. Anatomical imaging by plain films, computed tomography (CT), ultrasound and magnetic resonance imaging (MRI) are the standard methods. Using the correct

terms impresses other clinicians and may make a trip to the radiology department less daunting for junior doctors requensting an investigation. X-rays measure radiodensity (radiolucency and radioopacity) and ultrasound measures echogenicity and echoreflectivity, whilst CT scans report attenuation values measured in Hounsfield units and MRI reports signal intensity.

Computed tomography

CT scanning is the production of three-dimensional images using X-rays that have been directed through tissues and the images produced depend on the density of the tissues. CT was developed in the 1970s by Sir Godfrey Hounsfield and Allan McLeod Cormack who shared the Nobel Prize in 1979. The first CT scanner built at EMI Central Research Laboratories is said to have been funded by the success of the Beatles who were signed to the EMI label. CT measures the attenuation of different tissues to ionizing radiation and calculates a mean value for a volume of tissue known as a voxel. This is displayed on a two-dimensional image as a single pixel. The attenuation is calculated relative to water which has a Hounsfield unit (HU) value of 0, so high attenutation tissues have a positive HU value (e.g. bone +400 HU) and low attenuation tissues a negative HU value (e.g. fat –120 HU). Different window settings are used to look at different ranges of the Hounsfield greyscale. For example, in the bone windows setting the lungs will look uniformly black whilst in the lung windows the bones look uniformly white. Intravenous iodinated contrast agents improve the sensitivity and specificity of CT but are contraindicated in patients with asthma or allergies to contrast.

Magnetic resonance imaging

Unlike CT, MRI does not use ionizing radiation but instead a powerful magnetic field aligns the spin of protons, especially hydrogen atom protons, in water and fat. A radiofrequency pulse then energizes the protons and the gradual release of this energy from the protons as they relax back to their original magnetic alignment may be detected as radiofrequency signals. The signal intensity relates to the concentration of mobile hydrogen nuclei in tissues. T1 (longitudinal relaxation or spin-lattice) and T2 (transverse relaxation or spin-spin) relaxation time constants depend on the physical properties of the tissues. If you want to impress the neuroradiologists (not always a useful ploy in the authors' experience), water such as cerebrospinal fluid (CSF) is black (low signal intensity) on T1 images and white (high signal intensity) on T2 images (Figure 1.2). Whilst CT is a good tool to examine tissues composed of high atomic weight elements such as bone, MRI is better suited to non-calcified tissues. For similar reasons CT contrast agents usually are composed of high atomic number atoms such as iodine or barium, whilst MRI contrast agents such as gadolinium are paramagnets that have magnetic properties only in the presence of an externally applied magnetic field. MRI is generally superior for imaging the brain, whilst CT is better for solid tumours of the chest and abdomen as it is faster and generates fewer motion artifacts. MRI is also better suited to patients who may require many examinations because it does not carry the risks of ionizing radiation. MRI is, however, contraindicated in patients with metallic objects such as pacemakers *in situ* and it is also quite claustrophobic and noisy in the scanner.

Positron emission tomography

Positron emission tomography (PET) is a functional imaging modality that detects γ-rays emitted by positrons (positively charged electrons) emitting radionuclide tracers. Positrons have a short half-life and are generated by cyclotrons. Common positron-labelled radionuclides include fluorine (^{18}F), carbon (^{11}C), oxygen (^{15}O) and nitrogen (^{13}N). In oncology the most frequently used tracer is ^{18}F-fluorodeoxyglucose (FDG), a short half-life glucose analogue that is taken up into actively metabolizing cells including cancer cells and following intracellular phosphorylation is trapped in these cells. Hence the distribution in the body of

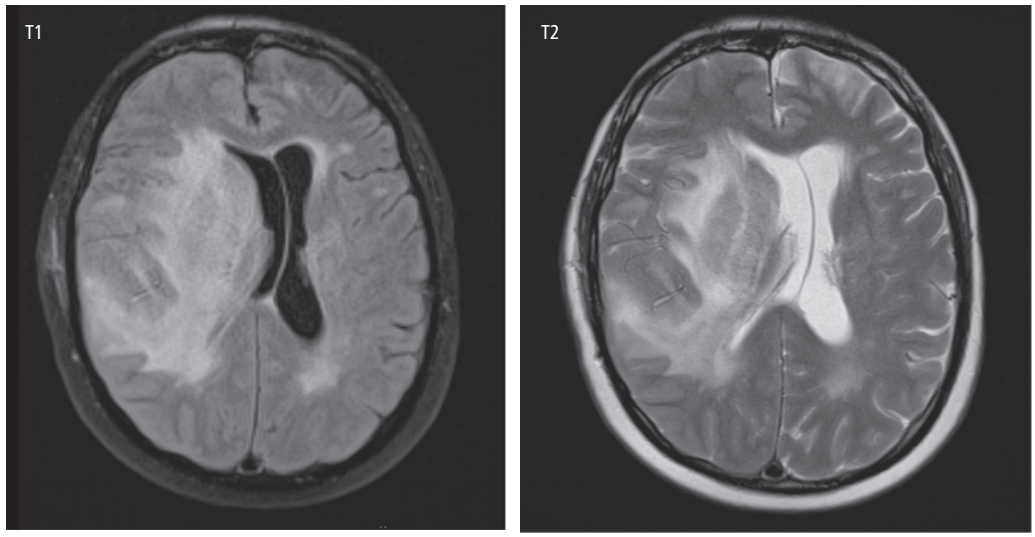


Figure 1.2 T1 and T2 MRI scan images of a primary cerebral lymphoma mass, showing a large right basal ganglia lesion with midline shift, compression of the right lateral ventricle and peritumoral oedema. In the T1 image the CSF is black (low attenuation) and the bone is white (high attenuation), whilst in the T2 image the CSF is white (high attenuation) and the bone is black (low attenuation).

FDG reflects glucose uptake within the body. This means that PET scanning may differentiate between residual masses and active disease in lymphoma. As a consequence FDG-PET scanning is used in both staging and monitoring cancer treatment (Figure 1.3 and see Plate 1.6).

Radio-isotope scanning

In addition to PET scanning other functional images may be used in the diagnosis and staging of specific cancers, using isotope-labelled radionuclide tracer elements (Table 1.8 and Figure 1.4). The isotope-labelled tracers that are used diagnostically may also be used therapeutically. Bone scintigraphy uses bisphosphonates labelled with ^{99}Tc and is more sensitive than X-rays for detecting metastases.

Performance status

In addition to the histological grade and the stage of a cancer, the general health of patients will determine how long they survive and may influence treatment decisions. Scales that measure the performance status or functional capacity of patients include the ECOG (Eastern Co-operative Oncology Group) grading system and the Karnovsky scale (Table 1.9). The performance status, however estimated, is an important prognostic indicator for almost all tumour types.

Prognosis: it's not cancer is it doc?

Although a very significant stigma is attached to the diagnosis of cancer, for most of the general population the fear outweighs the reality and comparison with other more palatable illnesses yield results that are not always expected (Table 1.10).

Cancer epidemiology

Epidemiology in UK

Cancer is now the commonest cause of death in the UK (if cardiovascular and cerebrovascular diseases are classed separately).

- One in three people in the UK will develop a cancer (289 000/year)
- One in four die of cancer (150 000/year).

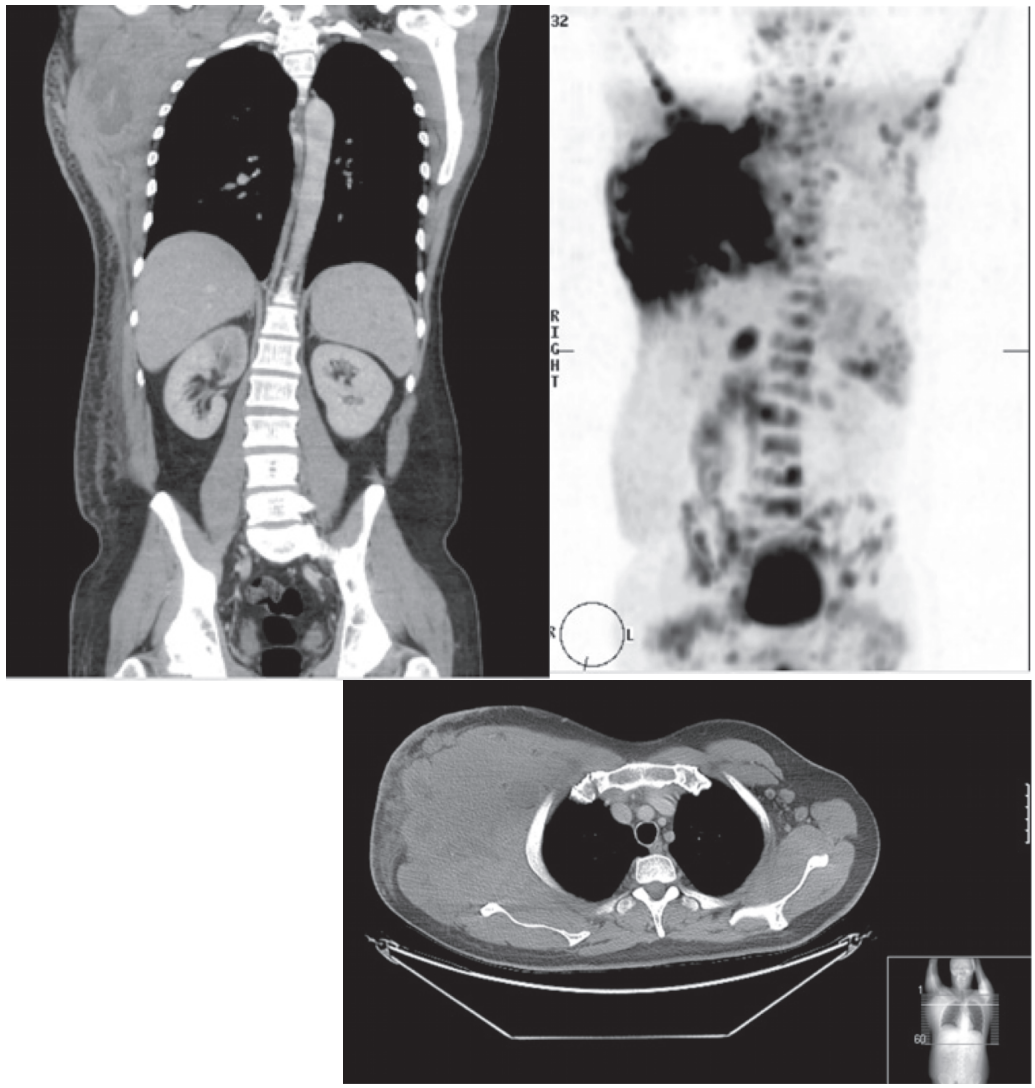


Figure 1.3 Coronal CT (top left), transverse CT (below) and FDG-PET (top right) scans demonstrating a huge right axillary and anterior chest wall mass due to Burkitt lymphoma. The FDG-PET also demonstrates extensive involvement of the other nodal groups, bones and right kidney upper pole (stage 4B).

Table 1.8 Commonly used isotopes in nuclear imaging in oncology.

Isotope	Half-life	Tracer	Oncological use
^{99}Tc (technetium)	6 hours	Methylene diphosphonate (MDP)	Bone scan
^{111}In (indium)	67 hours	Octreotide	Neuroendocrine tumours
^{131}I (iodine)	8 days	Sodium iodide	Thyroid cancer
^{131}I (iodine)	8 days	Meta-iodobenzylguanidine (MIBG)	Phaeochromocytoma neuroblastoma
^{67}Ga (gallium)	68 hours	Gallium citrate	Lymphoma

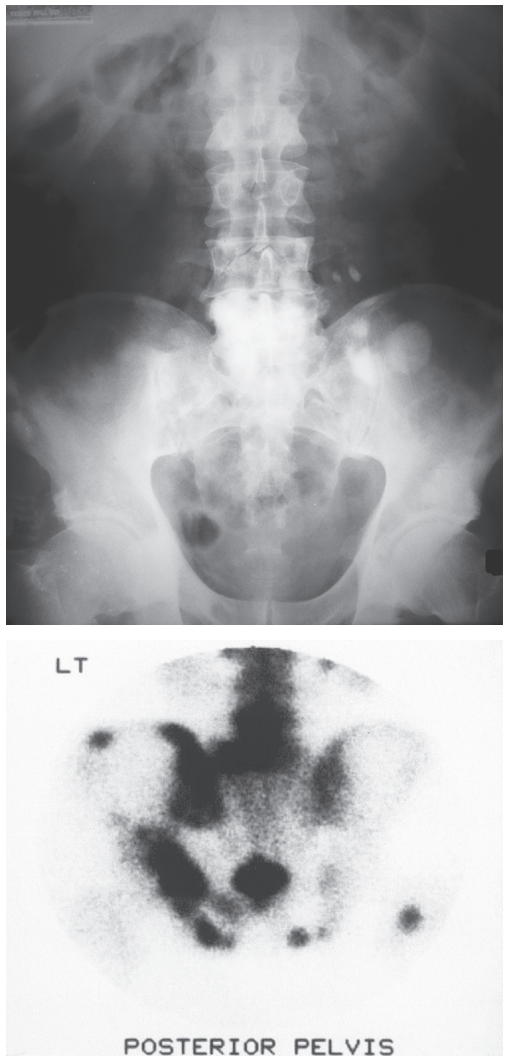


Figure 1.4 Plain pelvic radiograph (above) and corresponding area of technetium pyrophosphate bone scan (below) of a patient with sclerotic bone metastases from prostate cancer.

The top ten cancers diagnosed in the UK excluding non-melanomatous skin cancers are shown in Table 1.11.

Global epidemiology

The incidence of different types of cancer varies geographically according to the risk factors and demographics of the local population (Figure 1.5). However, there is a general correlation between

Table 1.9 Functional capacity grading (ECOG) and Karnovsky performance scales.

ECOG functional capacity grading	
0	Asymptomatic
1	Symptomatic but fully ambulant
2	Symptomatic, ambulant >50% waking hours
3	Symptomatic, confined to bed >50% waking hours
4	Symptomatic, bedfast
Karnovsky performance status score (%)	
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms
80	Normal activity with effort; some signs or symptoms
70	Care for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but able to care for most of needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated but death not imminent
20	Very sick; hospitalization necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly

Table 1.10 Survival rates for various diseases.

	Myocardial infarction	Hodgkin's disease	Heart failure (NYHA III/IV)	Metastatic breast cancer
1-year survival rate	75%	90%	50%	60%
5-year survival rate	45%	85%	15%	20%

NYHA, New York Heart Association grading scale.

increasing wealth and increasing cancer incidence. This is attributable to tobacco use, diet and increased longevity in wealthy populations. There are intriguing exceptions, for example the Gulf states of Kuwait, Qatar, Bahrain, United Arab Emirates and Saudi Arabia have lower cancer incidences than would be predicted from their per capita gross national product.

Table 1.11 The 12 most common cancers diagnosed in UK.

Tumour	As percentage of all cancers diagnosed
Breast	15%
Lung	13%
Colorectal	13%
Prostate	12%
Non-Hodgkin's lymphoma	3.6%
Bladder	3.5%
Melanoma	3.3%
Stomach	2.7%
Oesophageal	2.7%
Pancreas	2.6%
Kidney	2.5%
Leukaemia	2.5%

Cancer charities

Cancer charities

The UK has 640 cancer charities to counter the disease. Their expenditure increases awareness of cancer, improves diagnosis and treatment capability, and provides care for patients with the disease. The total income generated by the top 20 UK cancer charities in 2004 was £758m, and the average charitable efficiency was 64% providing £488m for spending on patients' care and research. The two largest UK cancer charities, the Imperial Cancer Research Fund (ICRF) and the Cancer Research Campaign (CRC) merged to form Cancer Research UK (CRUK) in 2002. CRUK is the largest volunteer-supported cancer research organization in the world, with 3000 scientists and an annual scientific spend of more than £339 million – raised almost entirely through public donations.

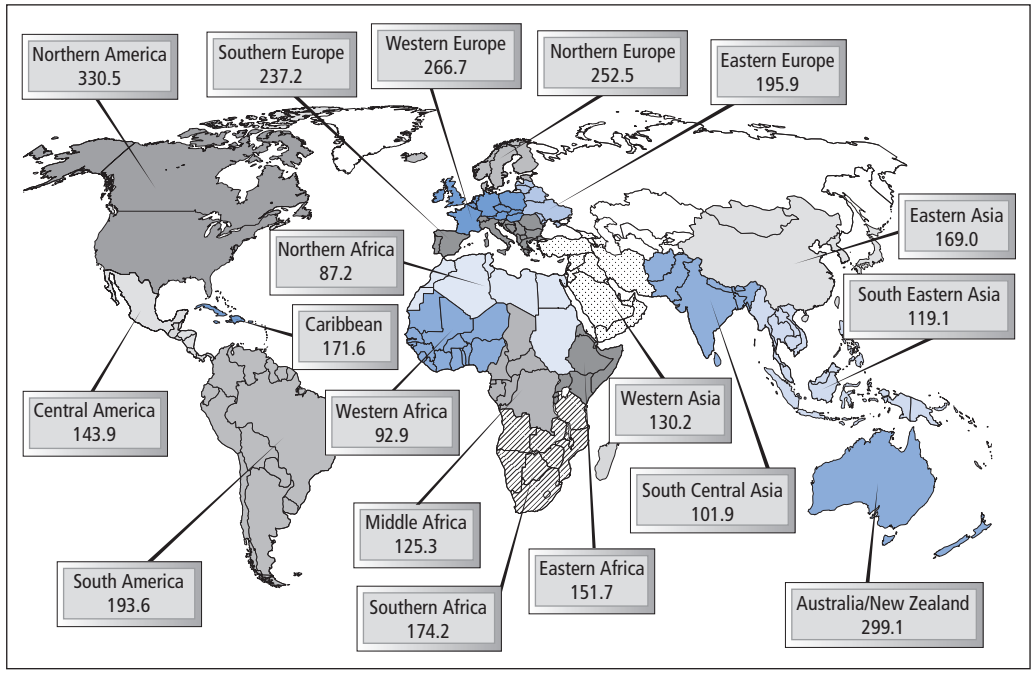


Figure 1.5 Figure of cancer incidences by global region.

Table 1.12 Rock star cancer deaths.

	Year of death	Age	Cause of death
Richard Wright (Pink Floyd)	2008	65	Cancer (type undisclosed)
Eartha Kitt	2008	81	Colon cancer
Johnny Ramone	2004	55	Prostate cancer
Little Eva	2003	60	Cervical cancer
George Harrison	2001	58	Non-small cell lung cancer
Joey Ramone	2001	49	Non-Hodgkin's lymphoma
Ian Dury	2000	58	Colorectal cancer
Dusty Springfield	1999	60	Breast cancer
Carl Wilson (Beach Boys)	1998	52	Lung cancer
Eva Cassidy	1996	33	Melanoma
Frank Zappa	1993	53	Prostate cancer
Freddy Mercury	1991	45	Kaposi's sarcoma
Mel Appleby (Mel & Kim)	1990	24	Spinal tumour
Bob Marley	1981	36	Melanoma

Cancer hospitals

Philanthropists and social reformers during the 19th century tried to provide free medical care for the poor. William Marsden, a young surgeon opened a dispensary for advice and medicines in 1828. His grandly named London General Institution for the Gratuitous Cure of Malignant Diseases – a simple four-storey house in one of the poorest parts of the city – was conceived as a hospital to which the only passport should be poverty and disease and where treatment was provided free of charge. The demand for Marsden's free services was overwhelming and by 1844 his dispensary, now called the Royal Free Hospital, was treating 30 000 patients a year. In 1846 when his wife died of cancer, Marsden opened a small house in Cannon Row, Westminster, for patients suffering from cancer. Within 10 years the institution moved to Fulham Road and became known as the Cancer Hospital, of which Marsden was the senior surgeon. The hospital was incorporated into the National Health Service in 1948 and renamed the Royal Marsden Hospital in 1954. Although other cancer hospitals have been established in Manchester (the Christie Hospital) and Glasgow (the Beatson Hospital), the Royal Marsden Hospital remains the most renown. With the recent emphasis on multidisciplinary approaches to cancer, single specialty hospitals are less in vogue and the majority of cancer departments are within large teaching hospitals.

Cancer celebrities

Celebrities influence public perceptions and behaviour inordinately and this is as true in oncology as elsewhere. Celebrities with cancer have contributed in three main ways: personal accounts bring patients' experiences into the limelight, reports of celebrity patients increase public awareness and may encourage health-seeking behaviour such as stopping smoking, and celebrity patients may support cancer charities and encourage donations. Prominent examples of patient's perspectives include John Diamond's account in *C: Because Cowards get Cancer, Too* and Ruth Picardie's *Before I Say Goodbye*, both moving accounts by accomplished journalists. Celebrity patients can influence the treatment choices that the public make. Following Nancy Reagan's mastectomy for localized breast cancer in 1987, there was a 25% fall in American women choosing breast-conserving surgery over mastectomy. Her husband's successful surgery for Dukes' B colon cancer whilst president in 1984 increased awareness and propelled the warning signs of colon cancer into the media. Similarly, the diagnosis and death from cervical

cancer in 2009 of Jade Goody, a *Big Brother* celebrity, led to an increased uptake of cervical cancer screening especially amongst young women in the UK. Successful cancer treatment is often most widely publicized and no article describing Lance Armstrong's seven consecutive Tour de France cycling victories is complete without a mention of his treatment for metastatic non-seminomatous germ cell tumour and his two children conceived with stored sperm banked prior to chemotherapy. Other celebrity patients have used their wealth and fame to establish and support charitable projects to support cancer research and treatment including Bob Champion, the steeple chase jockey treated for testicular cancer in the 1979, and Roy Castle, a lifelong non-smoker who was diagnosed with lung cancer in 1992. Of course, no one is immune to cancer; even rock stars whose deaths are more traditionally associated with suicide and substance abuse (Table 1.12).

Chapter 2

The scientific basis of cancer

Six steps to becoming a cancer

At a molecular level cancer cells are characterized by six acquired biological properties:

1. Self-sufficiency in growth stimuli (keep on doubling).
2. Insensitivity to inhibitory stimuli (don't stop doubling).
3. Evasion of apoptosis (don't die).
4. Immortalization (don't age).
5. Neoangiogenesis (feed themselves).
6. Invasion and metastasis (spread).

It is not certain, but probable, that all six features are necessary to a greater or lesser extent for a cell to posses malignant behaviour (Figure 2.1). Some single molecular changes in cancer cells may produce more than one of the six attributes (e.g. mutations of p53 may cause both avoidance of apoptosis and insensitivity to inhibitory stimuli). A number of mechanisms may contribute to the acquisition of these six properties, including genomic instability as a consequence of deficient DNA repair or loss of cell cycle arrest/death in response to DNA damage as well as epigenetic dysregulation of gene expression.

Lecture Notes: Oncology, 2nd edition. By M. Bower and J. Waxman. Published 2010 by Blackwell Publishing Ltd.

1. Autonomous growth signals

The instruction to a cell to grow and start dividing is communicated by extracellular growth factor ligands that bind to cell surface receptors. This usually results in the reversible phosphorylation of tyrosine, threonine or serine amino acid residues of the receptor. The transfer of these molecular switches from activated phosphorylated receptors to downstream signalling enzyme effectors and then to non-enzymatic second messengers in the cytoplasm and finally to nuclear transcription activators, is known as signal transduction (Figure 2.2). This cascade results in amplification of the initial stimulus. Cancers achieve self-sufficiency in growth factors and do not depend on these extracellular ligands for continued growth. The majority of dominant oncogenes act on this signal transduction mechanism by one of the following mechanisms:

- Overproducing growth factors, e.g. glioblastomas produce platelet-derived growth factor (PDGF)
- Overproducing growth factor receptors, e.g. epidermal growth factor receptor (EGFR/erbB) overexpression in breast cancers
- Mutations of the receptor or components of the signalling cascade that are constitutively active, e.g. mutations of Ras in lung and colonic cancers.

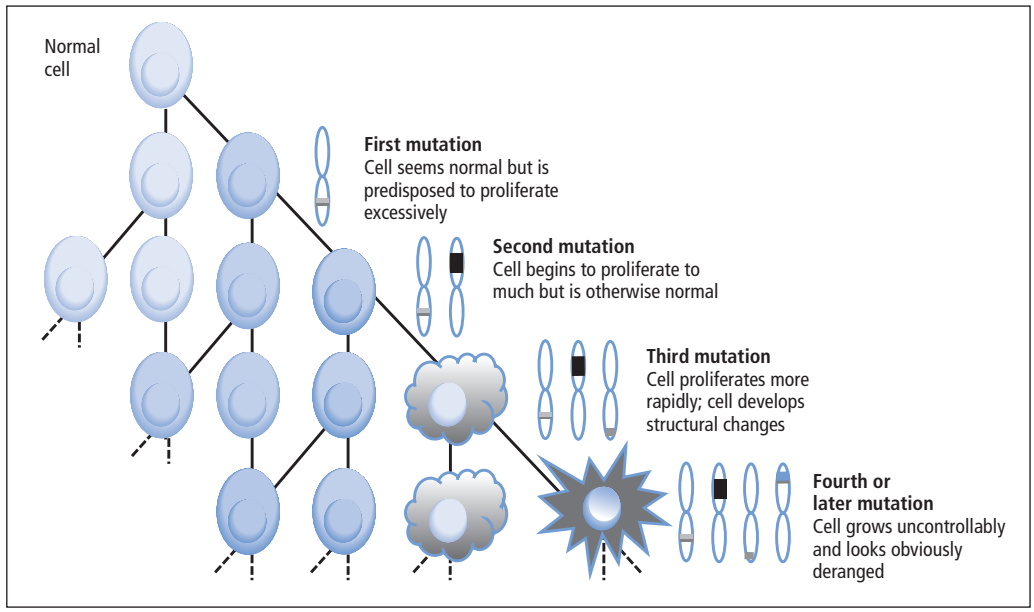


Figure 2.1 Stepwise accumulation of genetic mutations contributing to oncogenic phenotype.

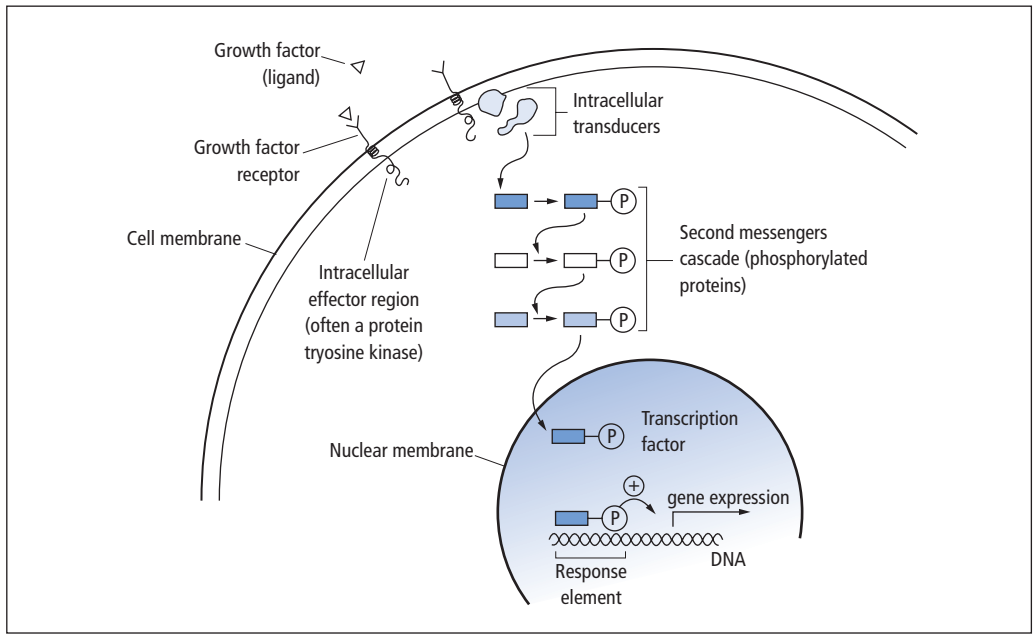


Figure 2.2 Signal transduction pathway.

2. Insensitivity to cell cycle checkpoints

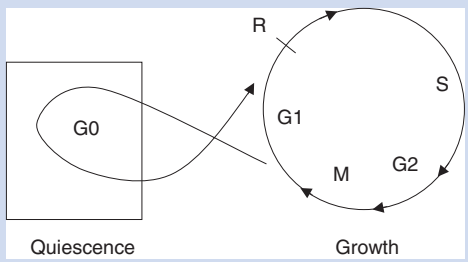
Many normal cells grow throughout their lifespan and the co-ordination of their growth, differentiation, senescence and death is controlled by the cell cycle. Antiproliferative signals may be received by cells as soluble growth inhibitors or fixed inhibitors in the extracellular matrix. They act on the cell cycle clock (Box 2.1), most frequently arresting transit through G1 into S phase. Cancer cells ignore these stop signals.

The co-ordination of the cell cycle and its arrest at checkpoints in response to DNA damage is achieved by sequential activation of kinase enzymes that ultimately phosphorylate and dephosphorylate the retinoblastoma protein (Rb). Periodic activation of these cyclin–cyclin-dependent kinase (CDK) complexes drives the cell cycle forward (Figure 2.3). Phosphorylation of Rb releases E2F, a transcription factor which is then able to promote the expression of a number of target genes resulting in cell proliferation. The brakes that balance this system are CDK inhibitors (CKIs). Interference in elements of the cell cycle regulatory process is a common theme in malignancy (see Table 2.2).

Box 2.1: The cell cycle

There are five cell cycle phases:

- **Quiescent phase (G0)**: Normal cells grown in culture will stop proliferating once they become confluent or are deprived of growth factors, and enter a quiescent state called G0. Most cells in normal tissue of adults are in a G0 state.
- **First gap phase (G1)** (duration 10–14 hours): This occurs prior to DNA synthesis. Cells in G0 and G1 are receptive to growth signals but once they have passed a restriction point (R), are committed to DNA synthesis (S phase).
- **Synthesis phase (S)** (duration 3–6 hours): During this phase DNA replication occurs and the cell becomes diploid.
- **Second gap phase (G2)** (duration 2–4 hours): This occurs after DNA synthesis and before mitosis (M) and completion of the cell cycle.
- **Mitosis (M)** (duration 1 hour).
  Cell division completes the cell cycle.



G1/S checkpoint

An important checkpoint or restriction point in the cell cycle occurs in G1 to ensure that errors in DNA are not replicated but instead are either repaired or that the cell dies by apoptosis. This is initiated by damaged DNA and is co-ordinated by p53, the gene that is probably most commonly mutated in cancers overall. Additional checkpoints are present in the S and G2 phases to allow cells to repair errors that occur during DNA duplication and thus prevent the propagation of these errors to daughter cells.

3. Evasion of apoptosis

Apoptosis is a pre-programmed sequence of cell suicide that occurs over 30–120 minutes. Apoptosis commences with condensation of cellular organelles and swelling of the endoplasmic reticulum. The plasma membrane remains intact but the cell breaks up into several membrane-bound apoptotic bodies, which are phagocytosed. Confining the process within the cell membrane reduces activation of both inflammatory and immune responses, so that programmed cell death does not cause autoimmune disease or inflammation. Amongst the molecules that control apoptosis are the Bcl-2 family that confusingly includes both pro-apoptosis members (e.g. Bax) and anti-apoptosis members (e.g. Bcl-2).

In mammalian cells two pathways initiate apoptosis (Figure 2.4):

1. **Intracellular triggers:** DNA damage leads via p53 to activation of pro-apoptotic members of the Bcl-2 family. This causes release of cytochrome c from mitochondria, which in turn activates the caspase (**c**leaves after **asp**artate prote**ase**) cascade.

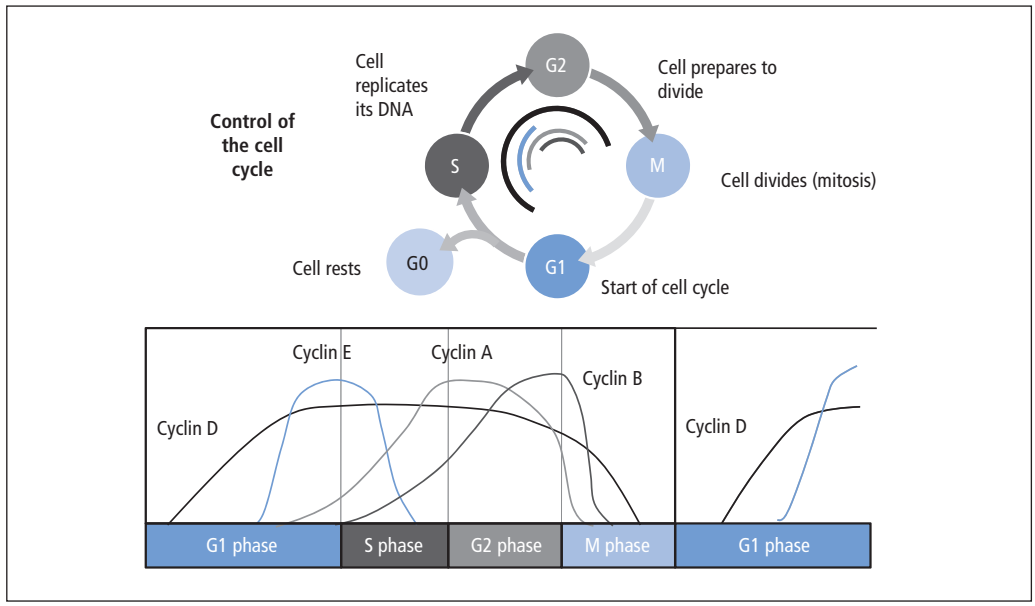


Figure 2.3 Oscillating levels of cyclins through the phases of the cell cycle.

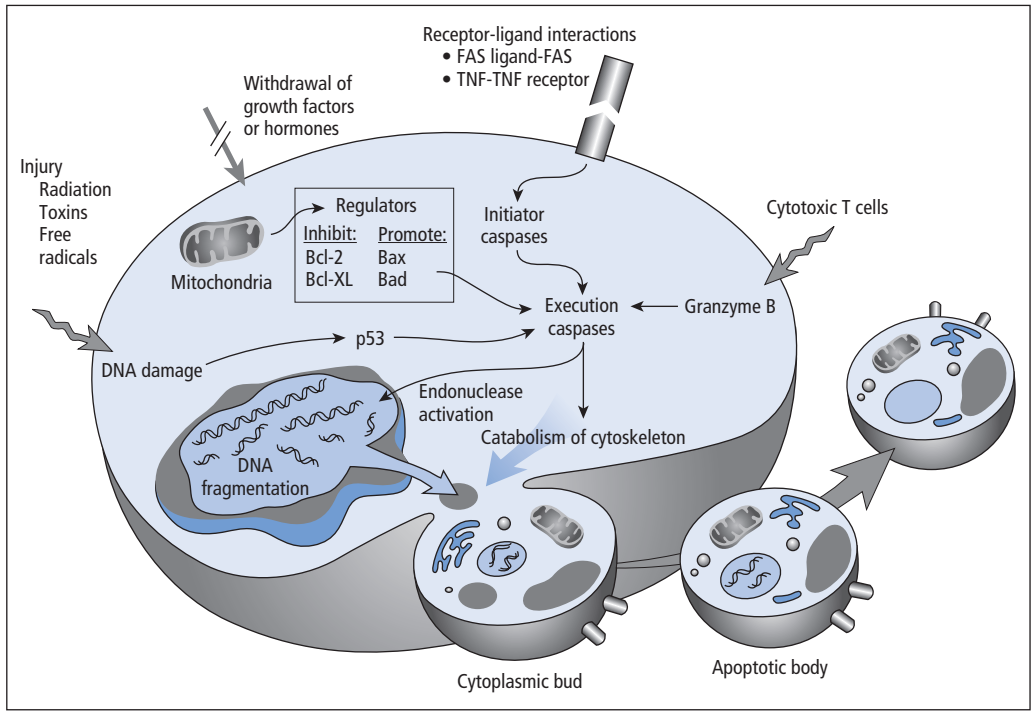


Figure 2.4 The apoptotic pathway.

2. **Extracellular triggers:** Binding of extracellular ligands to the cell surface death receptor superfamily (including CD95/Fas and tumour necrosis factor receptors) leads to a death-inducing cytoplasmic signalling complex that activates the caspase cascade.

Ultimately both pathways activate the caspase cascade, a series of protease enzymes that result in cell apoptosis. Evasion of this pathway is a prerequisite for malignant cell proliferation and a number of strategies to this end have been identified (see Table 2.2).

4. Immortalization

In culture, cells can divide a limited number of times, up to the 'Hayflick limit' (60–70 doublings in the case of human cells in culture), before the cell population enters crisis and dies off. This senescence is attributed to progressive telomere loss, which acts as a mitotic clock (Figure 2.5). Telomeres are the end segments of chromosomes and are made up of thousands of copies of a short 6 base pair sequence (TTAGGG). DNA replication always follows a 5′ to 3′ direction so that manufacturing the 3′ ends of the chromosomes cannot be achieved by DNA polymerases and each time a cell replicates its DNA ready for cell division, 50–100 base pairs are lost from the ends of chromosomes. Eventually the protective ends of chromosomes are eroded and end-to-end chromosomal fusions occur with karyotypic abnormalities and death of the affected cell.

Normal germ cells and cancer cells avoid this senescence, acquiring immortality in culture usually by upregulating the expression of human telomerase reverse transcriptase (hTERT) enzyme, which uses an RNA template and RNA-dependent DNA polymerase to add the 6 base pair sequence back onto the ends of chromosomes to compensate for the bases lost during DNA replication (see Table 2.2). Dyskeratosis congenita is an inherited condition, characterized by many abnormalities, including premature ageing and an increased risk of skin and gut cancers. It is due to mutations of components of the telomerase complex including the telomerase RNA and dyskerin.

5. Angiogenesis

All tissues including cancers require a supply of oxygen and nutrients. For cancers to grow larger

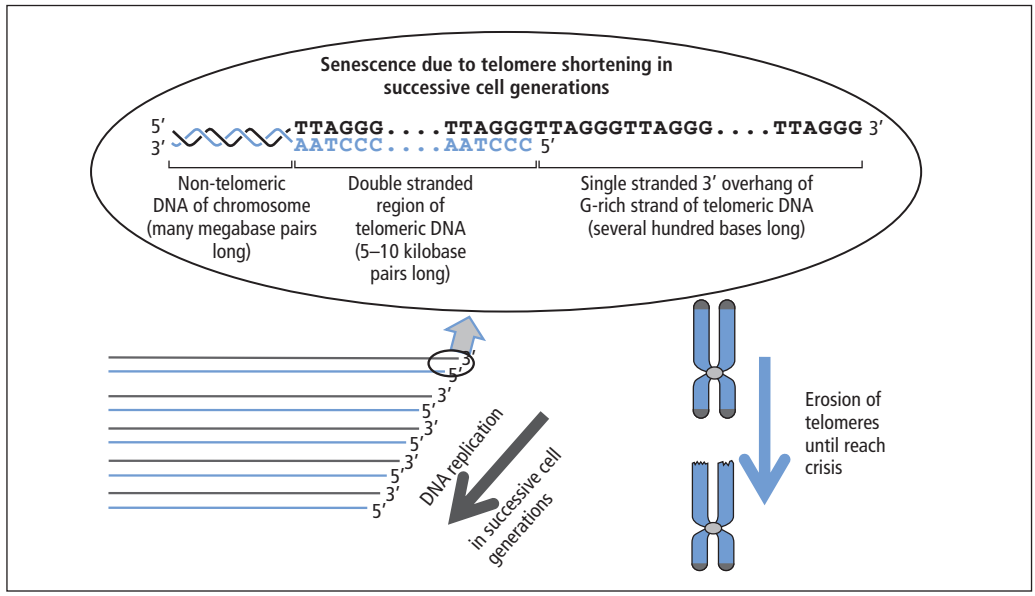


Figure 2.5 With every round of cell replication the chromosomes become shorter due to loss of the telomere repeats. Eventually this encroaches on the non-telomeric DNA of the chromosome and the cell enters crisis and dies.