LECTURE NOTES

Oncology

MARK BOWER
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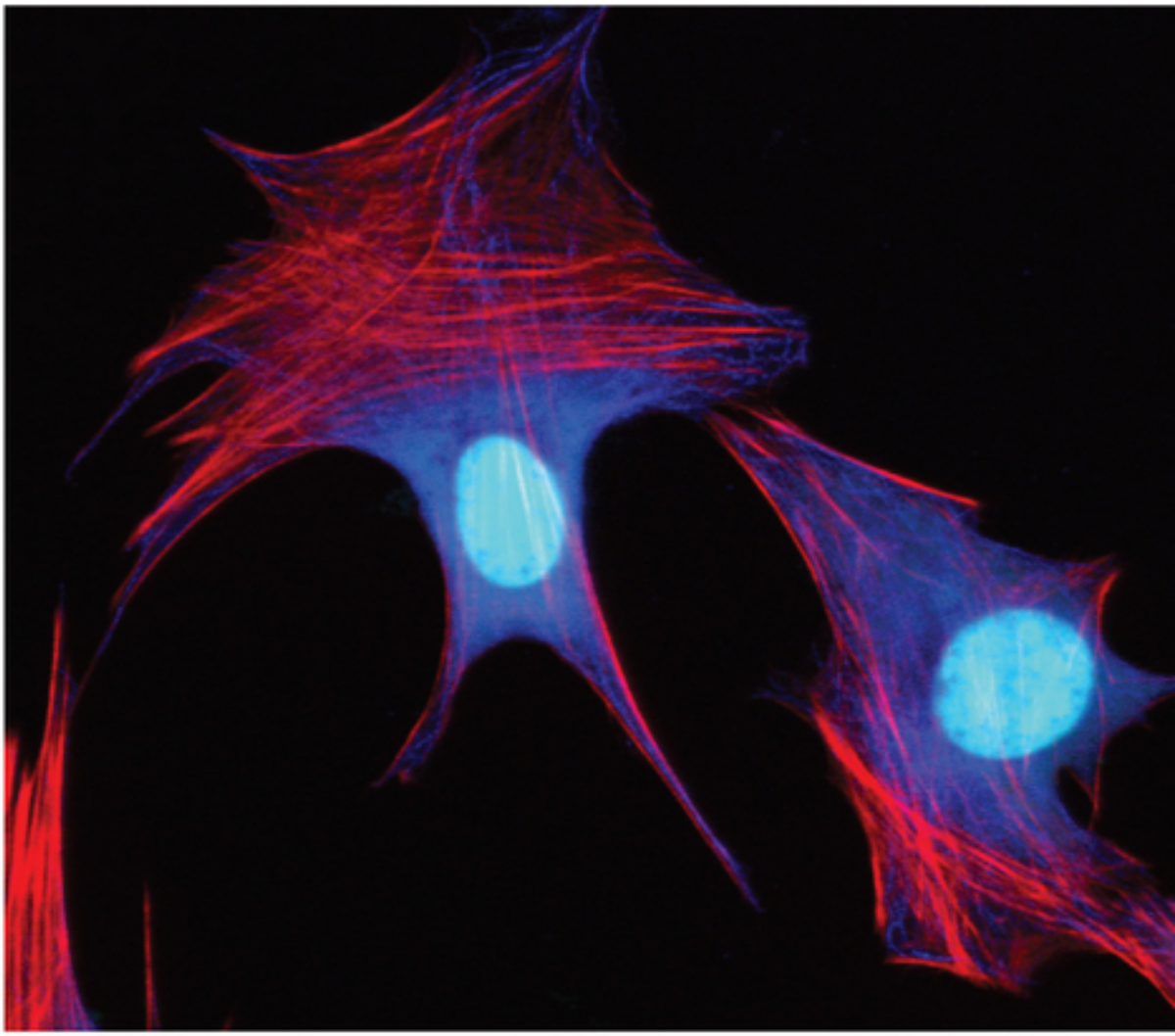
2nd edition



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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 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).

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

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:

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 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
- 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).