Chapter 7

Tumours

New growths are so common and widespread that their consideration must at least pass through the mind in most clinical situations. It therefore behoves the student, both for examinations and, still more importantly, for future practical doctoring, to have a standard scheme with which to tabulate the pathology, diagnosis, treatment and prognosis of neoplastic disease.

Pathology

When considering the tumours affecting any organ, this simple classification should be used:

1 Benign.

2 Malignant:

(a) primary;

(b) secondary.

It is surprising how often failure to remember this basic scheme leads one to omit such an elementary fact that common tumours of brain and bone are secondary deposits.

For each particular tumour, the following headings should be used:

- Incidence.
- Age distribution.
- Sex distribution.
- Geographical distribution (where relevant).
- Predisposing factors.
- Macroscopic appearances.
- Microscopic appearances.
- Pathways of spread of the tumour.
- Prognosis.

Clinical features and diagnosis

A malignant tumour may manifest itself in four ways.

1 The effects of the *primary tumour* itself.

2 The effects produced by *secondary deposits*.

3 The general effects of *malignant disease*.

4 *Paraneoplastic syndromes*. These are remote effects caused by hormone or other tumour-cell products, which are most common in carcinoma of the lung, particularly small cell tumours. For example, ectopic adrenocorticotrophic hormone (ACTH) production may present like Cushing's syndrome, and ectopic parathormone (PTH) production may present with hypercalcaemia and its symptoms.

The only common exceptions to this scheme are primary tumours of the central nervous system (CNS), which seldom produce secondary deposits.

Diagnosis is always made by history, clinical examination and, where necessary, special investigations.

Let us now, as an example, apply this scheme to carcinoma of the lung – the commonest lethal cancer in the UK.

History

- *The primary tumour* may present with cough, haemoptysis, dyspnoea and pneumonia (sometimes recurrent pneumonia due to partial bronchial obstruction).
- *Secondary deposits* in bone may produce pathological fracture or bone pains; cerebral metastases may produce headaches or drowsiness; liver deposits may result in jaundice.
- *General effects of malignant disease*: the patient may present with malaise, lassitude or loss of weight.
- *Paraneoplastic syndromes*, such as
  (a) ectopic hormone production (e.g. PTH, ACTH)
  (b) myasthenia-like syndrome (Eaton–Lambert syndrome*)
  (c) hypertrophic pulmonary osteoarthropathy (HPOA) and finger clubbing.

Examination

- *The primary tumour* may produce signs in the chest.
- *Secondary deposits* may produce cervical lymph node enlargement, hepatomegaly or obvious bony deposits.
- *The general effects of malignancy* may be suggested by pallor or weight loss.

Special investigations

- *The primary tumour*: chest X-ray, computed tomography (CT), bronchoscopy, cytology of sputum and needle biopsy.
- *Secondary deposits*: isotope bone scan, bone X-ray and ultrasound of liver.
- *General manifestations of malignancy*: a blood count may reveal anaemia. The erythrocyte sedimentation rate (ESR) may be raised.
- *Paraneoplastic hormone production*: hormone assay.

* Lealdes M Eaton (1905–58), Professor of neurology at the Mayo Clinic; Edward Lambert (b. 1915), Professor of Physiology and Neurology, Mayo Clinic, Rochester.

This simple scheme applied to any of the principal malignant tumours will enable the student to present a very full clinical picture of the disease with little mental effort.

Tumour markers

These are blood chemicals (often fetal proteins) produced by the malignant cells. Some tumours have a characteristic marker associated with them, such as α-fetoprotein (AFP) in hepatoma and teratoma, prostate-specific antigen (PSA) in carcinoma of the prostate (see Box 7.1 "Tumor markers"). Tumour markers may indicate malignant change in a benign condition, and are useful in postoperative monitoring. If a marker was raised pretreatment, it should fall when the disease is controlled, but will rise again if recurrence occurs. Some tumours produce excess amounts of the appropriate hormone, such as medullary carcinoma of the thyroid and calcitonin, in which case hormone assay may be used to detect tumour activity.

Treatment

The treatment of malignant disease should be considered under two headings:

1 *Curative*: an attempt is made to ablate the disease completely.

2 *Palliative*: although the disease is incurable or has recurred after treatment, measures can still be taken to ease the symptoms of the patient.

In this section, we shall summarize the possible lines of treatment for malignant disease in general; in subsequent chapters, the management of specific tumours will be considered in more detail.

Curative treatment

1 *Surgery* (e.g. carcinoma of the lung or colon).

2 *Radiotherapy* alone (e.g. tumours of the mouth and pharynx).

3 *Cytotoxic chemotherapy* where the tumour is particularly sensitive to particular agents, such as teratoma of the testis to platinum compounds.

4 *A combination* of treatment modalities including surgery and/or radiotherapy and/or cytotoxic chemotherapy.

Tumour markers			
Marker	**Nature of marker**	**Malignant disease associated with rise in marker**	**Benign disease associated with rise in marker**
α-Fetoprotein (AFP)	Protein secreted by fetal liver	Hepatocellular carcinoma and testicular teratoma	Viral hepatitis (eg hepatitis C) and cirrhosis; pregnancy esp. if spinal cord abnormality
β-human chorionic gonadotrophin (β-HCG)	Protein normally produced by placenta.	Testicular teratoma and chorioncarcinoma	Pregnancy
Ca 15.3	Oncofetal antigen	Breast carcinoma	Hepatitis, cirrhosis, autoimmune diseases, benign lung disease
Ca 27.29	Glycoprotein MUC1 on epithelial cells	Breast carcinoma	Benign breast disease, ovarian cysts, and liver and kidney disease
Ca 19.9	Intracellular adhesion molecule related to Lewis blood group	Hepatocellular and cholangiocarcinoma. Also other colorectal and ovarian carcinoma	Pancreatitis, biliary disease, cirrhosis
Ca 125	Glycoprotein on coelomic epithelium during fetal development	Ovarian carcinoma	Pregnancy, ovarian cysts, pelvic inflammation, ascites, cirrhosis, pancreatitis
Carcinoembryonic antigen (CEA)	Oncofetal protein (protein secreted by fetal gut)	Advanced colorectal, breast and lung carcinomas	Peptic ulcer, inflammatory bowel disease, pancreatitis
Prostate-specific antigen (PSA)	Glycoprotein produced by epithelium of prostatic duct	Prostatic carcinoma	Prostatitis, benign prostatic hypertrophy and prostatic trauma

Palliative treatment

1 *Surgery*. The palliative excision of a primary lesion may be indicated, although secondary deposits may be present. For example, a carcinoma of the rectum may be excised to prevent pain, bleeding and mucus discharge, although secondary deposits may already be present in the liver. Irremovable obstructing growths in the bowel may be bypassed. Inoperable obstructing tumours of the oesophagus or cardia of the stomach may be intubated by means of a plastic tube or metal stent so that dysphagia can be relieved. The bile duct may be stented endoscopically via the duodenal papilla for the relief of jaundice and pruritus in patients with inoperable carcinomas of the head of pancreas. Surgery may also be used for pain relief by interrupting nerve pathways, e.g. cordotomy in which the contralateral spinothalamic tract within the spinal cord is divided.

2 *Radiotherapy*. Palliative treatment may be given to localized secondary deposits in bone, irremovable breast tumours, inoperable lymph node deposits, and so on. It is particularly indicated for localized irremovable disease.

3 *Hormone therapy*. Applicable in carcinoma of the breast and prostate.

4 *Cytotoxic chemotherapy*. A wide range of drugs have anticancer action, but this action is not specific; all the drugs damage normal dividing cells, especially those of the bone marrow, the gut, the skin and the gonads. They may be classified into the following:

(a) alkylating agents (e.g. cyclophosphamide, chlorambucil, busulphan);

(b) antimetabolites (e.g. 5-fluorouracil, methotrexate);

(c) plant alkaloids (e.g. vincristine, vinblastine);

(d) cytotoxic antibiotics (e.g. adriamycin, bleomycin, doxorubicin);

(e) platinum compounds (e.g. cisplatin, carboplatin);

(f) epipodophyllotoxins (e.g. etoposide).

(g) monoclonal antibodies (e.g. cetuximab, trastuzumab)

(h) taxanes (e.g. paclitaxel, docetaxel)

(i) others (e.g. imatinib, dacarbazine)

Multiple drugs are frequently used (combination chemotherapy) where their modes of action and toxicity profiles are different.

A balance must be made between the chances of regression of the tumour in relatively fit patients with tumours likely to be sensitive (e.g. breast, ovary, testis) and the toxic effects of the drug regimen.

5 *Drugs*. These are administered for pain relief (non-steroidal analgesics, opiates), hypnotics, tranquillizers and anti-emetics (e.g. chlorpromazine).

6 *Nerve blocks*, with phenol or alcohol for relief of pain.

7 *Maintenance of morale*. This is often impossible, but might be improved by cheerful and kindly attitude of medical and nursing staff.

Prognosis

The prognosis of any tumour depends on four main features:

1 extent of spread;

2 microscopic appearance;

3 anatomical situation; and

4 general condition of the patient.

The extent of spread (staging)

The extent of the tumour (its *staging*) on clinical examination, at operation and on studying the excised surgical specimen, is of great prognostic importance. Obviously, the clinical findings of palpable distant secondaries or gross fixation of the primary tumour are serious. Similarly, the local invasiveness of the tumour at operation and evidence of distant spread are of great significance. Finally, histological study may reveal involvement of the nodes, which had not been detected clinically, or microscopic extension of the growth to the edges of the resected specimen with consequent worsening of the outlook for the patient.

The TNM classification is an international system for tumour staging. Tumours are staged by scoring them according to the following:

Tumour characteristics – size, degree of invasion and so on.

Node involvement – regional nodes, distant nodes and so on.

Metastases – presence or absence.

An example of TNM staging as it relates to breast cancer is illustrated on in Chapter 35, p. 305. Some tumours have additional classifications which are more familiar to the clinician. Examples are Breslow's staging of local invasion of malignant melanoma (Chapter 9, p. 55) and Dukes' staging of rectal carcinoma (Chapter 26, p. 228).

Microscopic appearance (histological differentiation)

As a general principle, the prognosis of a tumour is related to its degree of histological differentiation (its *grading*) on the spectrum between well differentiated and anaplastic.

The spread of the tumour and its histological differentiation should be considered in conjunction with each other. A small tumour with no apparent spread at the time of operation may still have poor prognosis if it is highly anaplastic, whereas an extensive tumour is not incompatible with long survival of the patient after operation if the microscopic examination reveals a high degree of differentiation.

Anatomical situation

The site of the tumour may preclude its adequate removal and thus seriously affect the prognosis. For example, a tumour at the lower end of the oesophagus may be easily removable whereas an exactly similar tumour situated behind the arch of the aorta may be technically inoperable; a brain tumour located in the frontal lobe may be resected whereas a similar tumour in the brain stem will be a desperate surgical proposition.

General condition of the patient

A patient apparently curable from the point of view of the local condition may be inoperable because of poor general health. For example, gross congestive cardiac failure may convert what is technically an operable carcinoma of the rectum into a hopeless anaesthetic risk.

Screening

Screening is the process of testing individuals for a specific condition. It is commonly performed for tumours, but may be used in other contexts such as abdominal aortic aneurysm and hypertension. Effective screening for a given condition using a particular test has several prerequisites:

- The condition, if untreated, is sufficiently serious to warrant its prevention.
- The natural history of the condition should be understood.
- The condition has a recognizable early stage.
- Effective treatment is available.
- Treatment at an early stage could improve the prognosis, and is of more benefit than treatment started later in the disease.
- The screening test is simple, reliable and acceptable to the patient.
- The screening test should have minimal false-positive and false-negative outcomes (i.e. it should be both sensitive and specific). Incorrect diagnosis can have serious consequences.

In reality, cost-effective screening requires restricting the testing to those groups at highest risk of a condition. This may involve large-scale population screening or screening of families where a genetic predisposition exists.

Population screening

Examples of population screening include breast cancer screening by mammography, which is restricted to older women (over 50 years) and cervical cancer screening for women over 20 years. In cervical cancer, for example, a distinct progression exists from dysplasia through carcinoma *in situ* to invasive cancer. This progression may take 10 years. Hence, screening the population every three to five years by cervical smear cytology is cost-effective.

Screening for high-risk individuals

A number of cancer syndromes exist in which there is an inherited predisposition (e.g. familial

adenomatous polyposis (FAP)), or a familial risk (e.g. breast and ovarian cancer).

Inherited cancer syndromes. Like FAP, most inherited cancers are autosomal and dominantly inherited. In at-risk families, early identification may be possible through either genetic mapping of the cancer or early recognition of a component of the syndrome. In FAP, early colonoscopy may identify villous adenomas (polyps) while they are still dysplastic, before they become malignant, at which stage prophylactic colectomy is indicated. Alternatively, identification of the gene (located on chromosome 5q21) will also signify carriage.

Familial clustering. Many of the familial cancers are now being associated with mutations of specific genes. Incomplete expression of the gene may account for the sporadic incidence of the tumour. For breast cancer, two genes have been identified, *BRCA1* (chromosome 17q21) and *BRCA2* (chromosome 13q12). Mutations of either gene confer an 80% risk of breast cancer by the age of 70 years, together with an increased risk of ovarian cancer. Screening tests based on the detection of these genes differ from the other screening tests mentioned above, as they identify a tendency to malignancy and not premalignant change or early curable malignancy. There is no consensus at present as to the best management of such patients.