Principles of Surgical Oncology and Pathology

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Introduction

The *Edwin Smith papyrus* contains the earliest written record of cancer. It is an ancient Egyptian script from ~1700 BC with the collected teachings of *Imhotep* for conditions such as fractures and skin abscesses. While the script is written in a style comparable to a modern surgical textbook, the treatment offered for cancer in this manuscript is atypically short and dismal: "there is none". Thankfully, times have changed. While surgery was the first discipline to treat cancer, these days cancer patients are taken care of by a multidisciplinary team (MDT) of specialists consisting of oncologists, surgeons, specialist nurses, physiotherapists, pathologists and palliative care specialists.

Terminology

Basic pathological terminology taught in preclinical years is often forgotten by clinical years. Being well-versed with this terminology will put you at an advantage.

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Dysplasia

Dysplasia is not a pathological process but a descriptive term used by pathologists for *disordered growth and architecture* of a tissue as seen under a microscope. Features of dysplasia are shown in Fig. 12.1. Although dysplastic tissues may already contain *neoplastic cells*, these cannot metastasise and the changes may even be reversed in early stages. The importance of recognising dysplasia is that it is a **premalignant state** and the term **intraepithelial neoplasia** is preferred instead of dysplasia in some organs such as the cervix.

Neoplasms, Tumour and Cancer

- **Neoplasm** (*new growth*): an abnormal mass of tissue, formed due to the uncontrolled proliferation of cells. Cells continue to divide after the cessation of growth signals. The word **tumour** (*swelling*) is often used synonymously.
- **Neoplasia:** the process by which a neoplasm is formed
- **Cancer:** a *malignant* neoplasm

In order to describe a neoplasm, the nature of the tumour (benign or malignant) and its histological origin must be known.

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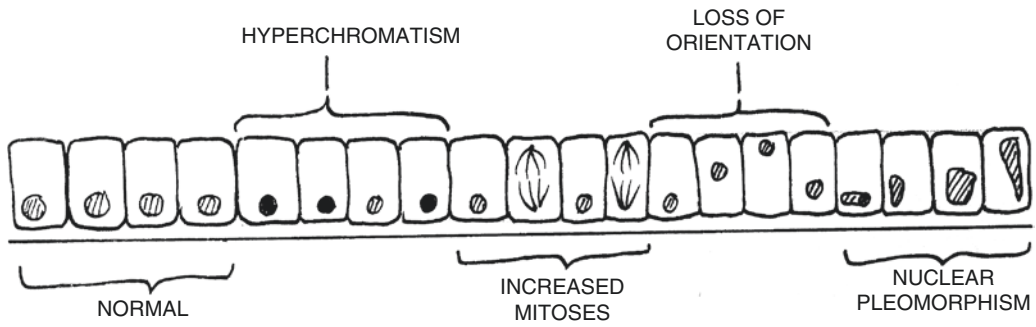

Fig. 12.1 Schematic representation of features of dysplasia as would be seen under the microscope

Table 12.1 Benign and malignant neoplasms

Benign	Malignant
No local invasion or metastasis	Local tissue invasion and metastasis
Usually slow rate of growth	Usually erratic or rapid growth
Well circumscribed	Poorly circumscribed
Good prognosis but can compress vital organs	Often poor prognosis
Histologically well-differentiated	Histologically poorly-differentiated
Often encapsulated	If encapsulated, invasion through capsule is seen

Tumour Behaviour: Benign/Malignant

All solid neoplasms are composed of *neoplastic cells*. However, neoplasms can be classified as either benign or malignant. Although there are several differences between the two (see Table 12.1), the key distinguishing criterion is the ability of malignant neoplasms to **invade and metastasise.**

Histogenesis

Microscopic examination and staining are used to assess the tissue of origin of tumours. The four main tissues from which tumours can arise are epithelial, connective, lymphoid/haematopoietic and germline tissue. The majority of tumours arise from epithelial tissue as epithelial cells line the internal and external body surfaces and are thus the most exposed to carcinogens. Epithelial tissue can be further subdivided mainly into either glandular or squamous.

Nomenclature

Some broad rules govern the naming of neoplasms. Benign tumours are usually named by adding the suffix *–oma* to the name of the tissue. For example, a lipoma is a benign tumour of adipose tissue. Malignant tumours from mesenchyme and epithelia are distinguished by the terms *carcinoma* and *sarcoma*, respectively. For example, an osteosarcoma is a malignant bone tumour. Prefixes indicate the tissue type. Commonly used nomenclature is shown in Table 12.2. Some important exceptions to the above rules are melanomas, neuroblastomas and glioblastomas, which are all malignant tumours.

Tumour Biology

A basic understanding of tumour biology helps in the management of patients with cancer.

Neoplasia: Aetiology and Mechanisms

Fundamentally, cancer is caused by DNA mutations. The overall effect is an increase the activity of oncogenes and/or a decrease the activity of tumour suppressor genes. These mutations can occur as a result of complex interactions between environmental and genetic factors. For example, inherited genetic makeup may enhance or decrease susceptibility to the DNA-damaging effects of environmental toxins, radiation, infection or hormonal imbalances. Thus, cancer is multifactorial.

Table 12.2 Nomenclature of epithelial and connective tissue tumours

Tissue of origin	Benign	Malignant
Epithelium		
Glandular epithelium	Adenoma	Adenocarcinoma
Squamous epithelium	Squamous papilloma Acanthoma	Squamous cell carcinoma
Connective tissue		
Adipose tissue	Lipoma	Liposarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Bone	Osteoma	Osteosarcoma
Fibrous tissue	Fibroma	Fibrosarcoma
Blood vessel	Angioma	Angiosarcoma

Hallmarks of Cancer

A widely accepted model of cancer development is the "multistep process" which suggests that multiple genetic changes need to take place in a stepwise manner for a cell to become cancerous. These mutations lead to the cells acquiring key characteristics called the **hallmarks of cancer** ([1]; see box below), which offer them a selective growth advantage over their neighbours.

Hallmarks of Cancer

1. Resisting cell death
2. Sustaining proliferative signalling
3. Evading growth suppressors
4. Limitless replicative potential
5. Inducing angiogenesis
6. Activating invasion and metastasis
7. Reprogramming of energy metabolism
8. Evasion of the immune system

Invasion and Metastasis

Metastasis of primary tumours to secondary sites, and the subsequent loss of organ function is the major cause of morbidity and mortality in cancer patients.

Metastatic Cascade Metastasis is a highly complex process involving several stages, which remain to be fully understood. Despite the complexity of the process, cancer cells regularly metastasise. While the rates and sites of metastasis may differ between cancers, there are core similarities in the mechanism of the process. Briefly, cells reduce the expression of cell-adhesion molecules allowing them to break free from their neighbours. The subsequent release of enzymes (such as matrix metalloproteinases) permits local tissue destruction and invasion by malignant cells. Intravasation into nearby blood vessels allows spread to a distant site, though cells in the blood stream must avoid detection by the immune system. A secondary focus is set up after extravasation.

Routes of Metastasis There are two main routes of metastasis:

- **Lymphatic spread** is the main route for carcinomas and typically follows the arterial supply.
- **Haematogenous spread** (especially via veins) is important for sarcomas and is often a late route for the spread of carcinomas.

Sites of Metastasis Different tumours metastasise to different organs. For example, gastrointestinal malignancies often spread to the liver via the portal vein, while breast carcinomas typically spread to the lungs and brain. The biology is not well understood. It is important to know the five main tumours which commonly metastasise to bone, as this is a common question:

Bony Metastases
(Mnemonic: **KP** crisps and a **BLT** sandwich)
1. **K**idney
2. **P**rostate
3. **B**reast
4. **L**ung
5. **T**hyroid

Clinical Features

Patients are usually asymptomatic until the tumour becomes large enough to cause signs and symptoms:

- **Local invasion and mass effects:** compression of organs or invasion into a hollow tube organ. Obstruction of the superior vena cava can be an oncological emergency if there is airway compromise.
- **Palpable mass**: often detected on clinical examination
- **Constitutional symptoms**: unexplained fever, weight loss, anaemia
- **Metastatic effects**: depend on the site of metastasis. Bony metastases can cause bone pain and even fractures.
- **Paraneoplastic syndromes**: these are "non-metastatic" effects due to ectopic hormone production or the immune response to the tumours. Ectopic ACTH production by small cell lung cancer can lead to Cushing's syndrome.
- Some patients will be picked up through screening programmes.

Assessment Before Treatment

Several investigations need to be carried out before treatment can begin. Most importantly, there must be unequivocal histological/cytological confirmation of malignancy along with an assessment of the stage. The histological assessment provides information on the tumour type and guides appropriate treatment.

Diagnostic Investigations

Simpler diagnostic tests are used before more invasive tests are carried out.

Blood Tests FBC, U&Es, LFTs and **tumour markers**.

Tumour Markers
These are serum proteins produced by tumours that are detectable at higher concentrations in the serum of patients with certain cancers. Although different proteins have been used as diagnostic or prognostic biomarkers, the relatively low sensitivities and specificities of tumour marker tests mean that they should not be used in isolation. Indeed, their main value is to monitor the course of illness and efficacy of treatment. Some frequently used tumour markers include CEA, CA 19-9, CA 15-3, and hCG.

Imaging Imaging is used not only in diagnosis but also in assessing the stage of a cancer (see below) and to monitor the response of a tumour to treatment. Various modalities are available including plain film imaging, ultrasound, CT, MRI, radioisotope imaging and PET scans. The choice will depend on the type of tumour in question and the risk of ionising radiation.

Histology and Cytology Histological analysis requires a tissue sample, which may be obtained from a biopsy sample (see below) or a resected specimen. H&E stains and light microscopy of the tumour samples are carried out to look for certain features. For example, adenocarcinomas exhibit glandular differentiation along with mucin production, whereas squamous cell carcinomas have evidence of keratinisation and the presence of desmosomes. Immunohistochemistry can also be performed such as in breast cancer for ER, PR and HER2. Differences in the staining pattern will affect the treatment offered. Pathologists will also perform **tumour grading**.

Cytology can also be used to diagnose malignancies. This involves examination of cells obtained from sputum and urine, or via fluid aspiration (from peritoneal fluid, pleural fluid or CSF, for example), fine-needle aspiration (FNA), and endoscopic brushings.

Tumour Grade

This is a measure of how closely the tumour resembles the tissue of origin i.e. the degree of differentiation. The grade is usually reported as a score from 1 to 3 which takes into account the rate of growth:

- **Grade 1:** well-differentiated and similar in appearance to the tissue of origin
- **Grade 3:** poorly differentiated with a high mitotic rate

Grade 2 tumours lie somewhere in between. The term **"anaplastic"** refers to tumours which are extremely poorly differentiated. Although tumour-specific grading systems do exist (such as the *Bloom-Richardson* grade for breast cancer), grading is subjective. However, higher-grade tumours have a **poorer prognosis**.

Staging Investigations

The stage of a cancer reflects the extent of spread of a tumour. Staging systems attempt to classify tumours into "stages" of their natural history based on uniform criteria. This is extremely important since it determines the most appropriate treatment plan and allows an assessment of prognosis. The stage of a cancer does not change after staging has been done—even after progression or regression.

Tumour Staging

The most commonly used tumour staging system is the **TNM staging system** devised by the International Union against Cancer (*Union Internationale Contre le Cancer, UICC*) and is based on the tumour size (**T**), the presence of involved lymph nodes (**N**) and whether there is any metastasis (**M**). The addition of numbers after each letter in the TNM system denotes the extent of disease (see Table 12.3). Specific staging systems exist for certain tumours such as the *Duke's staging* for colorectal cancer.

Table 12.3 Cancer staging

TNM staging system
Tumour size (T)
TX = not assessed T0 = primary unknown or no tumour Tis = carcinoma in situ T1-4 = number increases with the size of the tumour[a]
Lymph nodes (N)
NX = not assessed N0 = lymph nodes not involved N1-3 = number increases with increasing involvement[a]
Metastasis (M)
MX = not assessed M0 = no metastases M1 = metastases present

[a]Exact criteria depend on the tumour in question

A number of prefixes are often attached to the TNM stage:

- **cTNM**: **c**linical stage based on information from examination, imaging or biopsy before surgery
- **pTNM:** stage given after **p**athological examination
- **yTNM:** refers to a reassessment of stage after *neoadjuvant* therap**y**
- **rTNM:** used if a tumour is **r**e-staged if there has been a disease-free interval

Staging investigations may be performed as part of the diagnostic process and many different

Table 12.4 ECOG performance status score

Score	Description
0	Fully active, able to carry out all normal activities without restriction and without need of analgesia
1	Restricted in strenuous activity but is able carry out light work/pursue sedentary occupation
2	Ambulatory and able to self-care but unable to work. Mobile for **>50 %** of the day
3	Capable of limited self-care. Bed-bound for **>50 %** of the day
4	Completely disabled; incapable of self-care; permanently confined to bed or chair

modalities can be used. Imaging modalities like CT and MRI scans are also useful, especially for metastases. In general, surgical staging techniques have been replaced by more advanced imaging modalities such as PET/CT, which avoids unnecessary invasive procedures.

Performance Status

Assessing the **performance status** (i.e. overall fitness) of the patient is important in determining the treatment. Scoring systems like the European Cooperative Oncology Group (see Table 12.4) can be used.

Treatment and Management

There are three main treatment options:

- Surgery
- Radiotherapy
- Chemotherapy

These can aim to be either ***curative*** or ***palliative*** and this should be recorded in the notes as a legal requirement. There are four main approaches to treatment for cancer:

- **Palliative therapy** is usually the indication for patients with widespread metastasis with the goal of improving symptoms and the quality of life.
- **Adjuvant therapy:** surgical treatment can be used to reduce the bulk of the tumour. However, not all the local disease may be cleared and adjuvant *chemotherapy* or *radiotherapy* can be offered afterwards with the aim of eradicating micrometastases and improving survival.
- **Neo-adjuvant therapy:** sometimes the tumour is too large to operate and chemotherapy or radiotherapy can be administered before the surgery (neo-adjuvant). The aim is to reduce the tumour bulk to either reduce the requirement for surgery or increase the chance of successful surgery.
- **Preventive therapy:** An increased understanding of the genetics of cancer has allowed prophylactic treatments to be offered to individuals at high risk of developing cancer before the cancer develops.

Surgical Oncology

There are four main roles for surgery in oncological practice:

Prevention of Cancer

A good example is provided by *familial adenomatous polyposis*, a rare autosomal dominant disorder caused by mutations in the APC gene. It is characterised by hundreds of adenomatous polyps throughout the colon. Total proctocolectomy prevents the inevitable development of carcinoma.

Diagnosis and Staging

Although FNA and fluid aspiration can provide cytological diagnostic samples, a **biopsy** is usually preferred. This can be obtained by several procedures and the approach will depend on the type and location of tumour and the risk of contamination. Needle-track metastases can occur along the path of the surgical instrument.

Core Needle Biopsy (CNB) This uses a needle similar to a FNA needle. The needle withdraws small "cores" of tissue that are representative of the tumour. The needle is inserted into the tumour guided either by palpation or ultrasound.

Open Biopsy An open biopsy is the main surgical approach. There are two types of surgical biopsies: ***excisional biopsies*** remove the entire suspected tumour and are generally preferable to ***incisional biopsies*** where only part of the suspected tumour is removed. Excisional biopsies allow a better examination of the tissue architecture and thus can better guide further treatment. However, incisional biopsies are often required if the tumour is fixed to the local surroundings making excision too difficult.

Treatment of Cancer

Surgery often has very high cure rates at the early stage of disease for colorectal and breast cancers. Some key points include:

A surgical "cure" for cancer aims for total **excision** of the macroscopic tumour tissue. Technically, this means an ***en-block resection*** that involves the removal of the primary tumour with clear **resection margins** (grossly and microscopically), adjacent organs (if necessary), regional lymphatics and biopsy scars (as these are considered contaminated).

The length of the resection margin is usually based on the biology of the tumour and available adjuvant modalities. For example, limited resection would be acceptable in tumours that are more responsive to chemotherapy/radiotherapy as this allows a better cosmetic result.

Establishing nodal involvement is important for staging. Lymph node removal can reduce the metastatic risk but can cause secondary lymphoedema.

A **sentinel node biopsy** provides a less radical approach. The sentinel node is a theoretical group of lymph nodes to which a malignancy would be expected to spread first. The surgeon may either inject a dye or a radioactive colloid around the tumour: this drains to the lymph nodes, which can be visualised directly or using a radioactive monitor. One to three sentinel nodes are often removed at surgery and if no metastasis is involved, then no further nodal clearance is undertaken and the risk of lymphoedema is reduced.

It is believed that the systemic dissemination of cancer can occur early even in patients without evidence of regional lymph node involvement (**micrometastases**). Indeed, since the surgical manipulation of any malignant tumour causes the potential shedding and spread of cells, some surgical procedures have been designed to reduce this by initially dividing the blood supply before mobilising a tumour (**no-touch technique**).

Micrometastases
Small numbers of tumour cells can metastasise early and form "micrometastases", microscopic tumour deposits which are generally not detectable. To eradicate any possible micrometastatic disease, adjuvant chemotherapy or radiotherapy is often administered.

Palliation

Surgery can be used to improve the symptoms of patients where cure is not the main intent. There may be several occasions where this can be used. Examples include the debulking of tumours, which may be causing nerve root compression, and the fixation of pathological fractures.

Surgeons' Favourite Questions for Students
1. What are some of the common cancers that metastasise to bone?
2. What is the difference between neoadjuvant and adjuvant therapy?
3. What is the most common staging system currently in practice? Can you think of an example where an alternative staging system is still in place?

4. How would you classify symptoms caused by malignancy?
5. What is the performance status and how is it measured?

Reference

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.