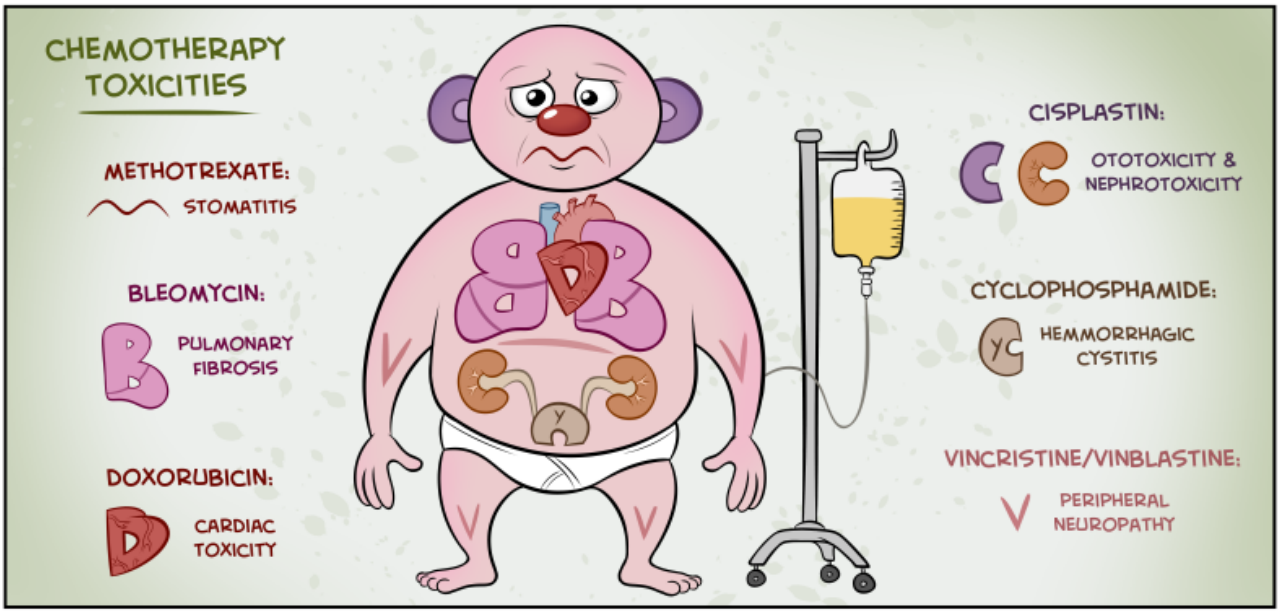


Oncogenes

Oncogenes are cancer promoting genes that are derived from normal genes (proto-oncogenes). Proto-oncogenes play an important physiological role in cellular growth. They are implicated in the development of up to 20% of human cancers.

Proto-oncogenes may become oncogenes via the following processes:

- Mutation (point mutation)
- Chromosomal translocation
- Increased protein expression

Only one mutated copy of the gene is needed for cancer to occur - a dominant effect

Classification of oncogenes

- Growth factors e.g. Sis
- Transcription factors e.g. Myc
- Receptor tyrosine kinase e.g. RET *(MEN type IIA and IIB)*
- Cytoplasmic tyrosine kinase e.g. Src
- Regulatory GTPases e.g. Ras

Tumour suppressor genes

Tumour suppressor genes restrict or repress cellular proliferation in normal cells. Their inactivation through mutation or germ line incorporation is implicated in renal, colonic, breast, bladder and many other cancers. One of the best known tumour suppressor genes is p53. **p53** gene offers protection by causing apoptosis of damaged cells. Other well-known genes include **BRCA** 1 and 2.

See 'Genetics and Surgical Disease' in Pathology Chapter…

Oncoviruses

- Viruses which cause cancer
- These may be detected on blood test and prevented by vaccine

These are the main types of oncoviruses and their diseases:

Oncovirus	Cancer
Epstein-Barr virus	Burkitt's lymphoma Hodgkin's lymphoma Post transplant lymphoma Nasopharyngeal carcinoma
Human papillomavirus 16/18	Cervical cancer Anal cancer Penile cancer Vulval cancer Oropharyneal cancer
Human herpes virus 8	Kaposi's sarcoma
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma
Human T-lymphotropic virus 1	Tropical spastic paraparesis Adult T cell leukaemia

Extravasation Injury

Chemotherapy may be complicated by extravasation reactions in up to 6% of cases. The following chemotherapy agents are recognised causes of extravasation reactions; doxorubicin, vincristine, vinblastine, adriamycin, cisplatin, mitomycin and mithramycin.

Up to 30% of extravasation reactions may be complicated by the development of ulceration.

When an extravasation reaction is suspected, the **infusion should be stopped** and the infusing device aspirated. The extremity should be elevated. ***As a general rule cold compresses have been shown to reduce the incidence of subsequent ulceration with doxorubicin. Warm compresses have been found to be beneficial in extravasation of vinca alkaloids.***

Dimethylsulfoxide may be infused in some cases, ideally within 5 hours of the event occurring. No conclusive evidence exists to support the use of corticosteroids or sodium bicarbonate for extravasation injuries.

Extravasation of total parenteral nutrition **(TPN)** solutions is usually managed by the local administration of **hyaluronidase** to the infusion site.

Chemotherapy Agents

Class	Example	Mode of action
Antimetabolites	5 FU	S Phase specific drug, mimics uracil and is incorporated into RNA
Anthracyclines*	Doxorubicin	Inhibits DNA and RNA synthesis by **intercalating base pairs**
Topoisomerase inhibitors**	Etoposide	Inhibits topoisomerase II, prevents efficient DNA coiling
Platinum	Cisplatin	Crosslinks DNA, this then distorts molecule and induces apoptosis (similar to alkylating agents)
Alkylating agent	Cyclophosphamide	Phosphoramide mustard forms DNA crosslinks and then cell death
Taxanes	Docetaxal	Disrupts microtubule formation

**=Main adverse effect cardiotoxicity*

***=Irinotecan is a similar drug which works by inhibition of topoisomerase I*

Chordoma

Chordoma is a rare slow-growing bone tumour. Their favored origin is remnants of the notochord.

Chordomas can arise anywhere from the skull base to the sacrum. The two most common locations are the skull base and sacrum.

There are three histological variants of chordoma: classical (or "conventional"), chondroid and de-differentiated.

- The histological appearance of classical chordoma is of a lobulated tumor composed of groups of cells separated by fibrous septa. The cells have small round nuclei and abundant vacuolated cytoplasm.
- Chondroid chordomas histologically show features of both chordoma and chondrosarcoma.

The 10-year tumor free survival rate for sacral chordoma was 46%. Chondroid chordomas appear to have a more indolent clinical course.

In most cases, complete surgical resection followed by radiation therapy offers the best chance of long-term control. Unfortunately, the lesion has a close proximity to the spine itself and this can compromise resection margins.

Chordomas are relatively radioresistant, requiring high doses of radiation to be controlled. The proximity of chordomas to vital neurological structures such as the brain stem and nerves limits the dose of radiation that can safely be delivered. Therefore, highly focused radiation such as proton therapy and carbon ion therapy are more effective than conventional x-ray radiation.

Secondary Malignant Tumours of Bone

Metastatic lesions affecting bone are more common than primary bone tumours.
75% cases will affect those over the age of 50.

The typical tumours that spread to bone include:

- Breast
- Bronchus
- Renal
- Thyroid
- Prostate

The commonest bone sites affected are:

- Vertebrae (usually thoracic)
- Proximal femur
- Ribs
- Sternum
- Pelvis
- Skull

Pathological fracture

Osteolytic lesions are the greatest risk for pathological fracture
The risk and load required to produce fracture varies according to bone site. Bones with lesions that occupy 50% or less will be prone to fracture under loading (Harrington). When 75% of the bone is affected the process of torsion about a bony fulcrum may produce a fracture.

Mirel's Scoring system *used to help determine the risk of fracture*

Score points	Site	Radiographic appearance	Width of bone involved	Pain
1	Upper extremity	Blastic	Less than 1/3	Mild
2	Lower extremity	Mixed	1/3 to 2/3	Moderate
3	Peritrochanteric	Lytic	More than 2/3	Aggravated by function

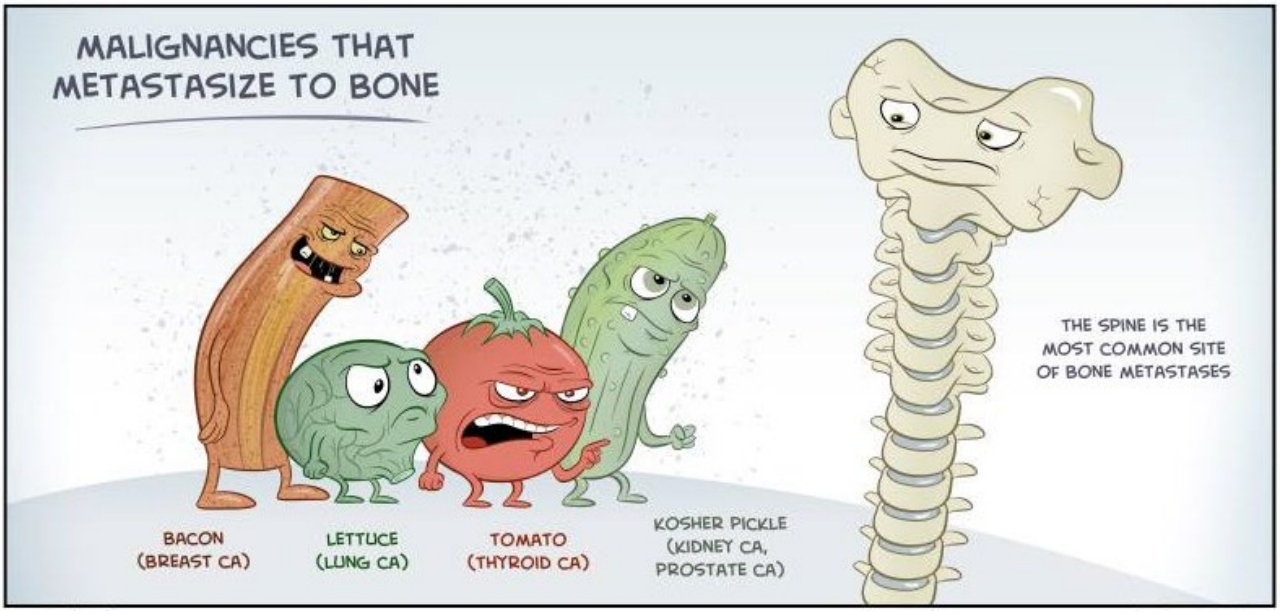
Depending upon the score the treatment should be as follows:

Score	Risk of fracture	Treatment
9 or greater	Impending (33%)	Prophylactic fixation
8	Borderline	Consider fixation
7 or less	Not impending (4%)	Non operative management

Where the lesion is an isolated metastatic deposit consideration should be given to excision and reconstruction as the outcome is better.

Non operative treatments

Hypercalcaemia: Treat with re hydration and bisphosphonates.
Pain: Opiate analgesics and radiotherapy.
Some tumours such as breast and prostate will benefit from chemotherapy and or hormonal agents.



Lung cancer

Lung cancers may be classified according to histological subtypes. The main distinction is between small cell and non-small cell lung cancer. Non-small cell lung cancer is the most common variant and accounts for 80% of all lung cancers.

Non-small cell lung cancer	Small cell lung carcinoma
These share common features of prognosis and management. Paraneoplastic features and early disease dissemination are **less likely than** with small cell lung carcinoma. They comprise the following tumours: • **Adenocarcinoma** (40% cases) *most common lung cancer type encountered in **never smokers.*** • **Squamous cell carcinoma** (25% cases) *more **slow** growing and are typically centrally located* • **Large cell carcinoma** (10% cases)	Small cell lung carcinomas are comprised of cells with a neuro endocrine differentiation. The neuroendocrine hormones may be released from these cells with a wide range of paraneoplastic associations. These tumours are strongly associated with **smoking** and will typically arise in the larger airways. They **disseminate early** in the course of the disease and although they are usually chemosensitive this seldom results in long lasting remissions.

Lung Cancer: Non-Small Cell Management

Management

- Only 20% suitable for surgery
- Mediastinoscopy performed prior to surgery as CT does not always show mediastinal lymph node involvement
- Curative or palliative radiotherapy
- Poor response to chemotherapy

Surgery contraindications

- Assess general health
- Stage IIIb or IV (i.e. metastases present)
- FEV1 < 1.5 litres is considered a general cut-off point*
- Malignant pleural effusion
- Tumour near hilum
- Vocal cord paralysis
- SVC obstruction

** However if FEV1 < 1.5 for lobectomy or < 2.0 for pneumonectomy then some authorities advocate further lung function tests as operations may still go ahead based on the results*

Notes and Mnemonics

Contraindications to lung cancer surgery include:

- SVC obstruction
- FEV < 1.5
- Malignant pleural effusion
- Vocal cord paralysis *(implies extracapsular spread to mediastinal nodes and is an indication of inoperability).*

Tissue Sampling

Tissue sampling is an important surgical process. Biopsy modalities vary according to the site, experience and subsequent planned therapeutic outcome

The modalities comprise:

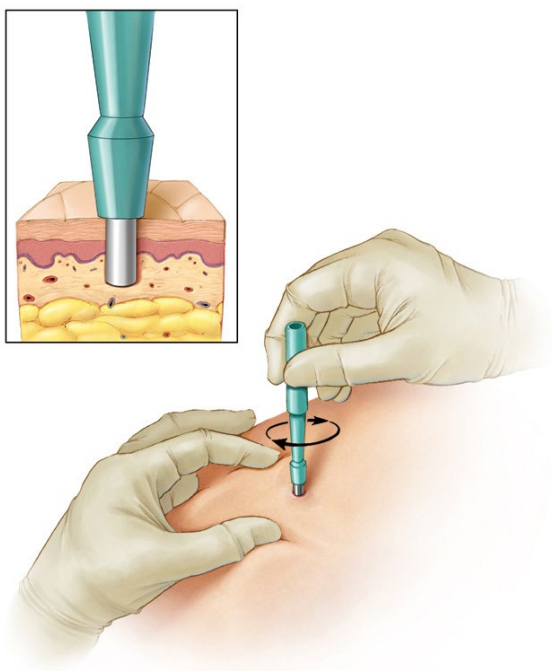
- Fine needle aspiration cytology
- Core biopsy
- Excision biopsy
- Tru cut biopsy
- Punch biopsy
- Cytological smears
- Endoscopic or laparoscopic biopsy

When the lesion is superficial the decision needs to be taken as to whether complete excision is desirable or whether excision biopsy is acceptable. In malignant melanoma for example the need for safe margins will mean that a more radical surgical approach needs to be adopted after diagnostic confirmation from excision biopsy than would be the case in basal cell carcinoma. Punch biopsies are useful in gaining histological diagnosis of unclear skin lesions where excision biopsy is undesirable such as in establishing whether a skin lesion is vasculitic or not.

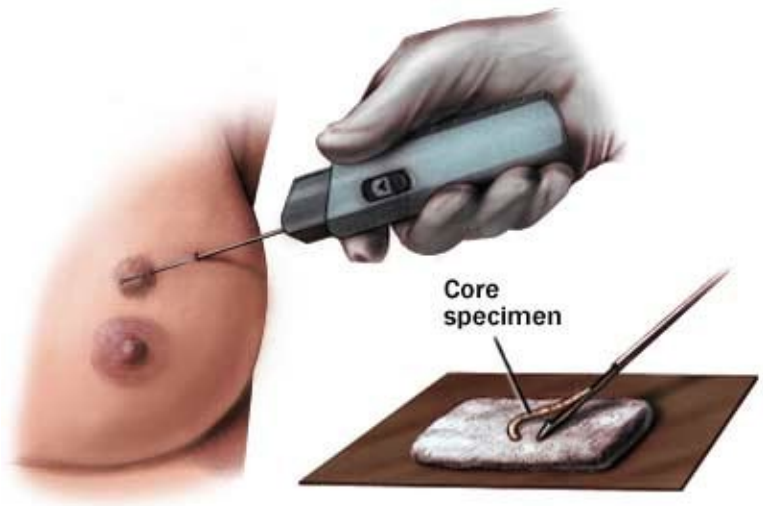
Fine needle aspiration cytology (FNAC) is an operator dependent procedure that may or may not be image guided and essentially involves passing a needle through a lesion whilst suction is applied to a syringe. The material thus obtained is expressed onto a slide and sent for cytological assessment. This test can be limited by operator inexperience and also by the lack of histological architectural information (e.g. Follicular carcinoma of the thyroid). Where a discharge is present a sample may be sent for cytology although in some sites (e.g. Nipple discharge) the information gleaned may be meaningless.

Tissue samples may be obtained by both core and tru cut biopsy. A core biopsy is obtained by use of a spring loaded gun with a needle passing quickly through the lesion of interest. A tru cut biopsy achieves the same objective but the needle moved by hand. When performing these techniques image guidance may be desirable (e.g. In breast lesions). Consideration needs to be given to any planned surgical resection as it may be necessary to resect the biopsy tract along with the specimen (e.g. In sarcoma surgery).

Visceral lesions may be accessed percutaneously under image guidance such as ultrasound guided biopsy of liver metastases. Or under direct vision such as a colonoscopic biopsy.



Punch biopsy



Core biopsy