LECTURES FOR MEDICAL STUDENTS
ONCOLOGY SYLLABUS

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Sept, 2024

OVERVIEW

What is cancer??

* Cancer is a singular word that embraces a vast diversity of diseases that can occur in any organ system throughout the animal kingdom.
* The unique characteristic of cancer is the proliferation of cells of a type different from, if ever so slightly, the normal complement of the organism. The proliferation may be rapid or slow, the accumulation of cells may be massive or miniscule.
* The essence of the matter, however, is that aberrant cells, distinct from the ordinary evolution of cell types, appear, and accumulate.
* Thus, a cancer differs from hypertrophy and hyperplasia, which involve normal cells

- A cancer cell does not obey the complex rules of architecture and function that govern the usual placement and behavior of cells within a tissue.
- Cancer is distinguished from other abnormal cellular growths that lead to benign tumors in its characteristic independence from the

* Benign tumors expand and compress but do not attack or invade adjacent tissues.
* Accumulated cancer cells make a tissue that ignores the anatomic barriers of adjacent cell membranes and basement membranes.
* Through chemical and mechanical means, the cancer cell insinuates itself between and into the space of the normal cells, killing them by chemical and physical means.
* The cancer cell is partially or absolutely insensitive to such normal constraints and may continue its invasiveness indefinitely.
* Up on reaching a circulatory conduit, either a lymphatic or capillary vessel, a process that may not be entirely haphazard, cancer cells often penetrate the wall as part of their invasive behavior.
* They then may be carried by the lymphatic or venous circulation to remote sites where the possibility of adherence, extravasation, and colonization can occur, establishing metastases.
* In the absence of an intervening event, and given enough time, with few exceptions, the cancer process, as described, can lead to such

The 10 hallmarks of cancer:

The formation and growth of cancer constitute a multistep process, during which sequentially occurring gene mutations result in the formation of a cancerous cell.

For cells to initiate carcinogenesis successfully, they require key characteristics, collectively referred to as the hallmarks of cancer.

1. Genome instability and mutation

Multistep carcinogenesis results from successive clonal expansions of pre-malignant cells, each expansion being triggered by acquisition of a random enabling genetic mutation. Under normal circumstances, cellular DNA repair mechanisms are so effective that almost all spontaneous mutations are corrected without producing phenotypic changes, keeping the overall mutation rates very low. In cancer cells, the accumulation of mutations can be accelerated by compromising the surveillance systems that normally monitor genomic integrity and force genetically damaged cells into either senescence or apoptosis. They can therefore become more sensitive to mutagenic actions or

2. Resisting cell death

There are three principal mechanisms through which cell death occurs in healthy tissues: apoptosis, autophagy and necrosis.

2.A Apoptosis

This is programmed cell death. It is frequently found at markedly reduced rates in cancers, particularly those of high grade or those resistant to treatment. The cellular apoptotic system has regulatory elements that sense intrinsic and extrinsic pro-apoptotic signals and initiate a cascade of proteolysis and cell disassembly with nuclear fragmentation, chromosomal condensation, and shrinking of the cell with loss of intercellular contact, followed by cellular fragmentation and the formation of apoptotic bodies that are phagocytized by neighboring cells. The most important regulator of apoptosis is the TP53 tumor suppressor gene, often described as the 'guardian of the genome', as it is able to induce apoptosis in response to sufficient levels of genomic damage. The largest initiator of apoptosis via TP53 is cellular injury, particularly that due to DNA damage from chemotherapy, oxidative damage and ultraviolet (UV) radiation

2.B Autophagy

This is a catabolic process during which cellular constituents are degraded by lysosomal machinery within the cell. It is an important physiological mechanism; it usually occurs at low levels in cells but can be induced in response to environmental stresses, particularly radiotherapy and cytotoxic chemotherapy, which induce elevated levels of autophagy that are cytoprotective for malignant cells, thus impeding rather than perpetuating the killing actions of these stress situations. Severely stressed cancer cells have been shown to shrink via autophagy to a state of reversible dormancy.

2.C Necrosis

This is the premature death of cells and is characterized by the release of cellular contents into the local tissue microenvironment, in marked contrast to apoptosis, where cells are disassembled in a step-by-step fashion and the resulting cellular fragments are phagocytized. Necrotic cell death results in the recruitment of inflammatory immune cells, promotion of angiogenesis, and release of stimulatory factors that increase cellular proliferation and tissue invasion, thereby enhancing

3. Sustaining proliferative signaling

Cancer cells can sustain proliferation beyond what would be expected for normal cells; this is typically due to growth factors, which are able to bind to cell surface-bound receptors that activate an intracellular tyrosine kinase-mediated signaling cascade, ultimately leading to changes in gene expression and promoting cellular proliferation and growth. Sustained proliferative capacity can result from over-production of growth factor ligands or receptors and production of structurally altered receptors, which can signal in the absence of ligand binding and activation of intracellular signaling pathway components, so that signaling is no longer ligand-dependent.

3.A The cell cycle

The cell cycle is composed of four ordered, strictly regulated phases referred to as G1 (gap 1), S (DNA synthesis), G2 (gap 2) and M (mitosis) (Fig. 33.2). The quiescent state called G0 . The first gap phase (G1) prior to the initiation of DNA synthesis represents the period of commitment that separates M and S phases as cells prepare for DNA duplication. Cells in G0 and G1 are receptive to growth signals, but once they have passed a restriction point, they are committed to enter DNA synthesis (S phase). Cells demonstrate arrest at different points in G1 in response to different inhibitory growth signals. Mitogenic signals promote progression through G1 to S phase, utilizing phosphorylation of the retinoblastoma gene product (pRB, p. 40). Following DNA synthesis, there is a second gap phase (G2) prior to mitosis (M), allowing cells to repair errors that have occurred during DNA replication and thus

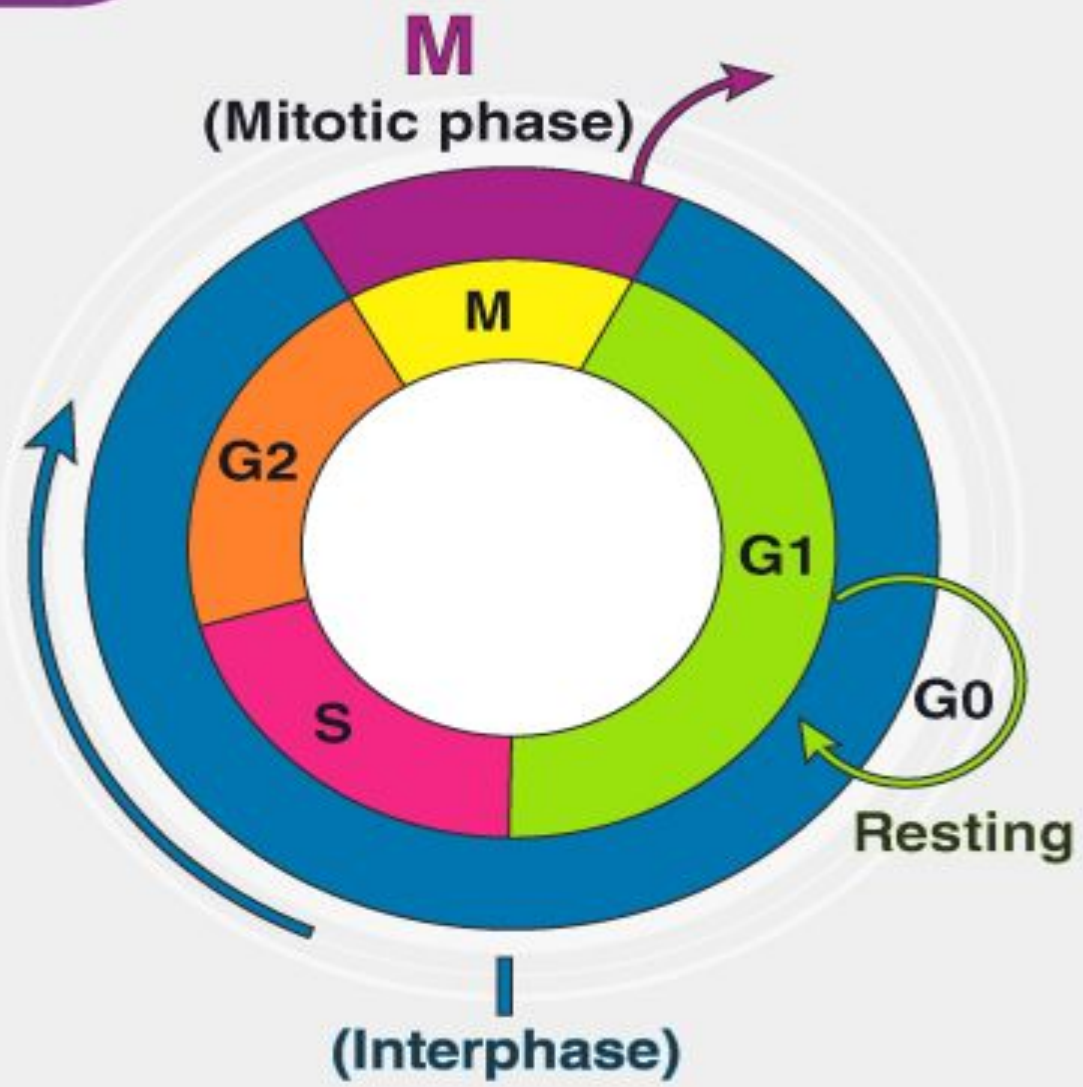
3.B Cell cycle regulation

The cell cycle is orchestrated by a number of molecular mechanisms: most importantly, by cyclins and cyclin-dependent kinases (CDKs). Cyclins bind to CDKs and are regulated by both activating and inactivating phosphorylation, with two main checkpoints at G1/S and G2/M transition. The genes that inhibit progression play an important part in tumor prevention and are referred to as tumor suppressor genes (e.g. TP53, TP21, TP16 genes). The products of these genes deactivate the cyclin–CDK complexes and are thus able to halt the cell cycle. The complexity of cell cycle control is susceptible to dysregulation, which may produce a malignant phenotype.

3.C Stimulation of the cell cycle

Many cancer cells produce growth factors, which drive their own proliferation by a positive feedback known as autocrine stimulation. Examples include transforming growth factor-alpha (TGF-α) and platelet-derived growth factor (PDGF). Other cancer cells express growth factor receptors at increased levels due to gene amplification or express abnormal receptors that are permanently activated. This results in abnormal cell growth in response to physiological growth factor stimulation or even in the absence of growth factor stimulation (ligand-independent signalling). The epidermal growth factor receptor (EGFR) is often over-expressed in lung and gastrointestinal tumours and the human epidermal growth factor receptor 2 (HER2)/neu receptor is frequently over-expressed in breast cancer. Both receptors activate the

CELL CYCLE



4. Evading growth suppressors:

In healthy tissues, cell-to-cell contact in dense cell populations acts as an inhibitory factor on proliferation. This contact inhibition is typically absent in many cancer cell populations. Growth-inhibitory factors can modulate the cell cycle regulators and produce activation of the CDK inhibitors, causing inhibition of the CDKs. Mutations within inhibitory proteins are common in cancer. Loss of restriction by disruption of pRB regulation can be found in human tumors, which produces a loss of restraint on transition from G1 to S phase of the cell cycle. Disruption of TP53 function will have downstream effects on p21 that alter the coordination of DNA repair with cycle arrest, and that result in the affected cell accumulating genomic defects.

5. Enabling replicative immortality:

For cancer cells to evolve into macroscopic tumors, they need to acquire the ability for unlimited proliferation. Telomeric DNA sequences, which protect and stabilize chromosomal ends, play a central role in conferring this limitless replicative potential. During replication of normal cells, telomeres shorten progressively as small fragments of telomeric DNA are lost with successive cycles of replication. This shortening process is thought to represent a mitotic clock and eventually prevents the cell from dividing further. Telomerase, a specialized polymerase enzyme, adds nucleotides to telomeres, allowing continued cell division and thus preventing premature arrest of cellular replication. The telomerase enzyme is almost absent in normal cells but is expressed at significant levels in many human cancers.

Oncogenesis. The multistep origin of cancer, showing events implicated in cancer initiation, progression, invasion and metastasis.

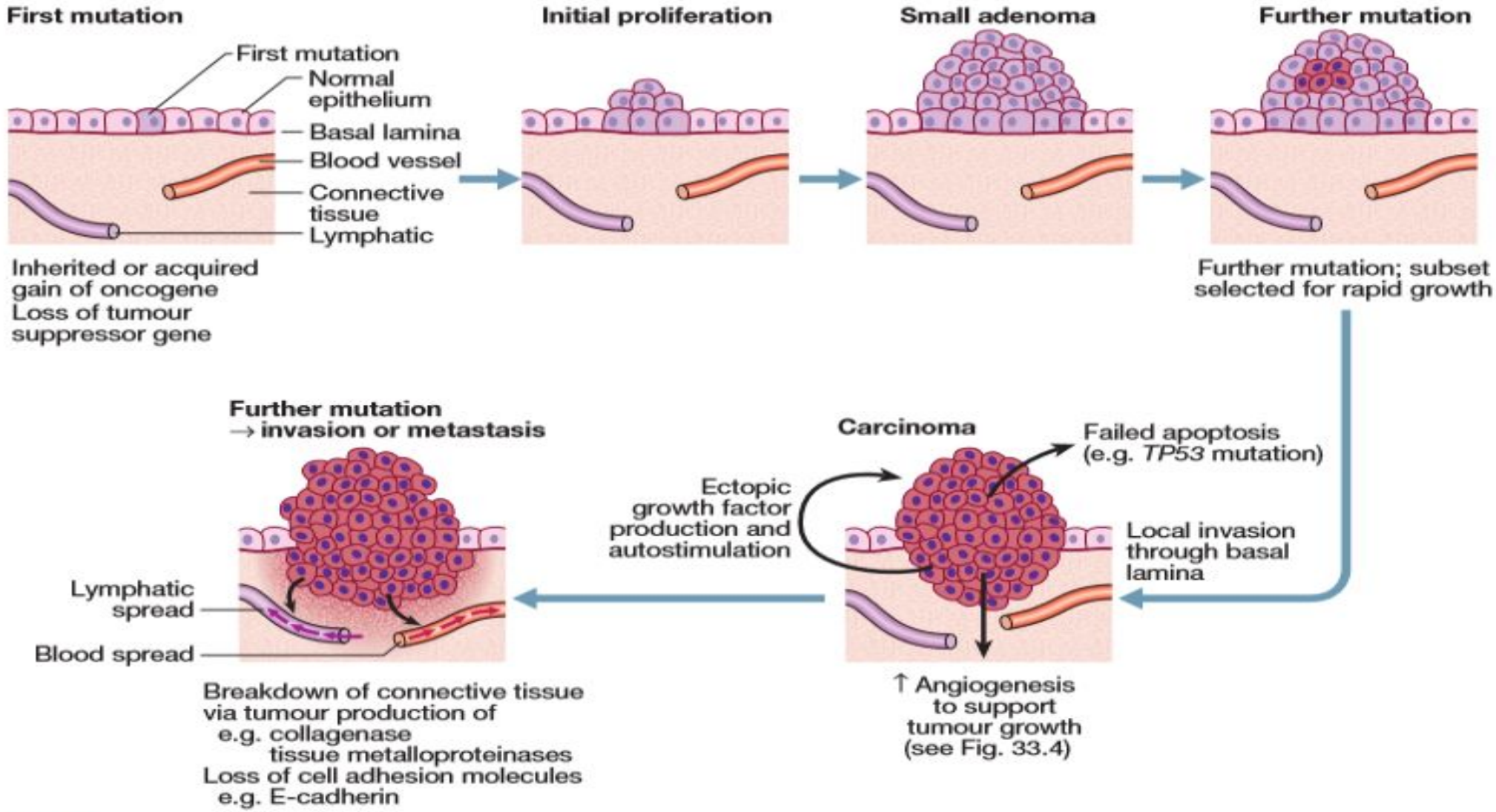
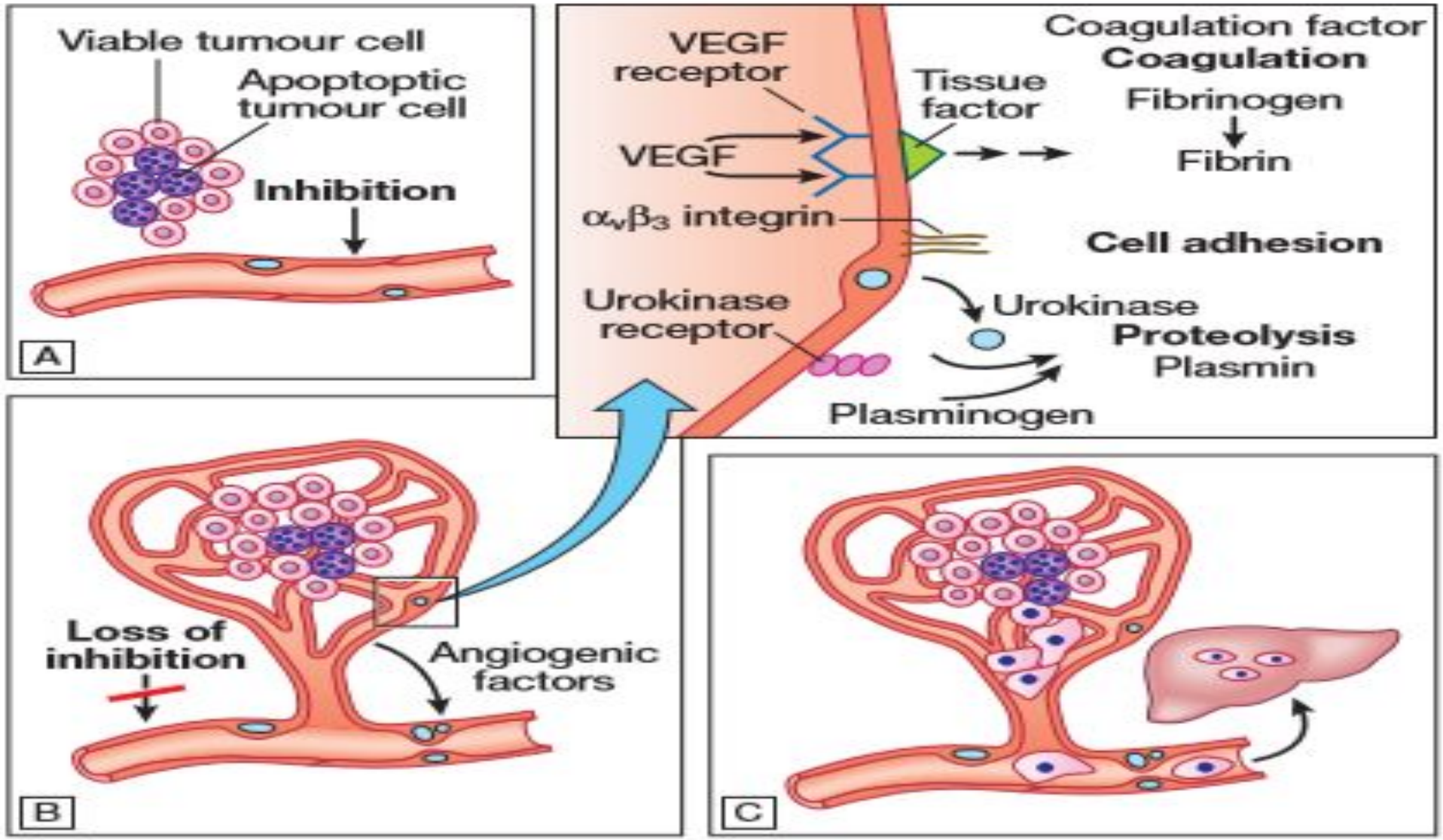


Fig. 33.3 Oncogenesis. The multistep origin of cancer, showing events implicated in cancer initiation, progression, invasion and metastasis.

6. Inducing angiogenesis:

All cancers require a functional vascular network to ensure continued growth and will be unable to grow beyond 1 mm3 without stimulating the development of a vascular supply. Tumors require sustenance in the form of nutrients and oxygen, as well as an ability to evacuate metabolic waste products and carbon dioxide. This entails the development of new blood vessels, which is termed angiogenesis (Figs 33.3 and 33.4). Angiogenesis is dependent on the production of angiogenic growth factors, of which vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are the best characterized. During tumor progression, an angiogenic switch is activated and remains on, causing normally quiescent vasculature to sprout new vessels continually that help sustain expanding tumor growth. Angiogenesis is governed by a balance of pro-angiogenic stimuli and angiogenesis inhibitors, such as thrombospondin (TSP)-1, which binds to transmembrane receptors on endothelial cells and evokes suppressive signals. A number of cells can contribute to the maintenance of a functional tumor vasculature and therefore sustain angiogenesis. These include pericytes and a variety of bone marrow-derived cells such as macrophages, neutrophils, mast cells and myeloid progenitors.

Angiogenesis, invasion and metastasis



7. Activating invasion and metastasis:

Invasion and metastasis are complex processes involving multiple discrete steps; they begin with local tissue invasion, followed by infiltration of nearby blood and lymphatic vessels by cancer cells. Malignant cells are eventually transported through haematogenous and lymphatic spread to distant sites within the body, where they form micrometastases that will eventually grow into macroscopic metastatic lesions (see Fig. 33.3). Cadherin-1 (CDH1) is a calcium-dependent cell–cell adhesion glycoprotein that facilitates assembly of organized cell sheets in tissues, and increased expression is recognised as an antagonist of invasion and metastasis. In situ tumors usually retain CDH1 production, whereas loss of CDH1 production due to downregulation or occasional mutational inactivation of CDH1 has been observed in human cancers, supporting the theory that CDH1 plays a key role in suppression of invasion and metastasis. Cross-talk between cancer cells and cells of the surrounding stromal tissue is involved in the acquired capability for invasive growth and metastasis. Mesenchymal stem cells in tumor stromal have been found to secrete CCL5, a protein chemokine that helps recruit leucocytes into inflammatory sites. With the help of particular T-cell-derived cytokines (interleukin (IL)-2 and interferon-gamma (IFN-γ)), CCL5 induces proliferation and activation of natural killer cells and then acts reciprocally on cancer cells to stimulate invasive behavior. Macrophages at the tumor periphery can foster local invasion by supplying matrix-degrading enzymes such as metalloproteinases and cysteine cathepsin proteases

8. Reprogramming energy metabolism:

Under aerobic conditions, oxidative phosphorylation functions as the main metabolic pathway for energy production; cells process glucose, first to pyruvate via glycolysis and thereafter to carbon dioxide in the mitochondria. While under anaerobic conditions, glycolysis is favoured to produce adenosine triphosphate (ATP). Cancer cells can reprogram their glucose metabolism to limit energy production to glycolysis, even in the presence of oxygen. This has been termed 'aerobic glycolysis'. Upregulation of glucose transporters, such as GLUT1, is the main mechanism through which aerobic glycolysis is achieved. This reprogramming of energy metabolism appears paradoxical, as overall energy production from glycolysis is significantly lower (18-fold) than that from oxidative phosphorylation. One explanation may be that the increased production of glycolytic intermediates can be fed into various biosynthetic pathways, including those that generate the nucleosides and

9. Tumor-promoting inflammation:

Almost all tumors show infiltration with immune cells on pathological investigation and historically this finding was thought to represent an attempt of the immune system to eradicate the cancer. It is now clear that tumor-associated inflammatory responses promote tumor formation and cancer progression. Cytokines are able to alter blood vessels to permit migration of leucocytes (mainly neutrophils), in order to permeate from the blood vessels into the tissue, a process known as extravasation. Migration across the endothelium occurs via the process of diapedesis, where chemokine gradients stimulate adhered leucocytes to move between endothelial cells and pass through the basement membrane into the surrounding tissues. Once within the tissue interstitium, leucocytes bind to extracellular matrix proteins via integrins and CD44 to prevent their loss from the site.

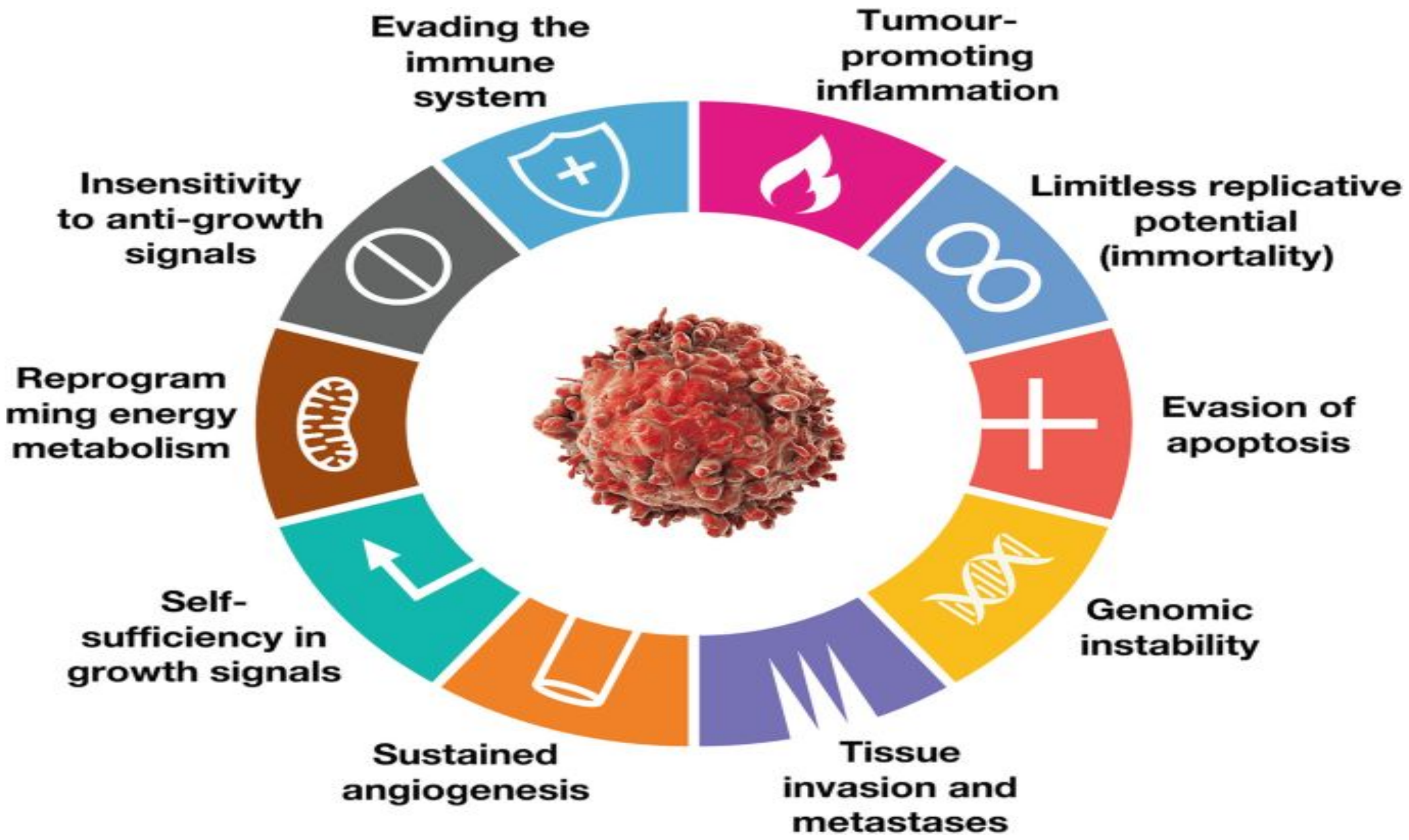
As well as cell-derived mediators, several cellular biochemical cascade systems consisting of pre-formed plasma proteins act in parallel to initiate and propagate the inflammatory response. Other bioactive molecules, such as growth factors and pro-angiogenic factors, may be released by inflammatory immune cells into the surrounding tumor microenvironment.

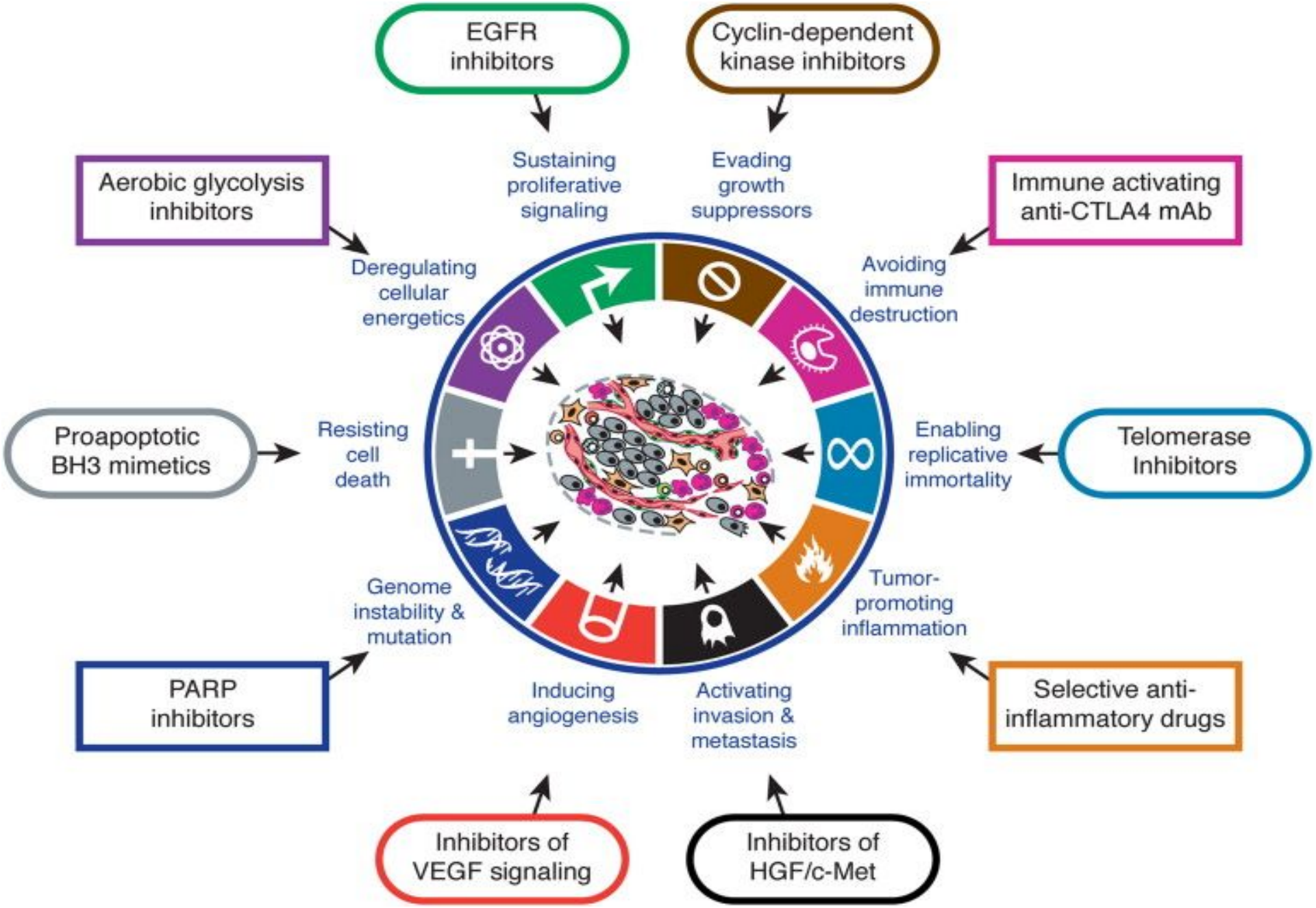
In particular, the release of reactive oxygen species, which are actively mutagenic, will accelerate the genetic evolution of surrounding cancer

10. Evading immune destruction:

The immune system operates as a significant barrier to tumor formation and progression, and the ability to escape from immunity is a hallmark of cancer development. Cancer cells continuously shed surface antigens into the circulatory system, prompting an immune response that includes cytotoxic T-cell, natural killer cell and macrophage production. The immune system is thought to provide continuous surveillance, with resultant elimination of cells that undergo malignant transformation. However, deficiencies in the development or function of CD8+ cytotoxic T lymphocytes, CD4+ Th1 helper T cells or natural killer cells can each lead to a demonstrable increase in cancer incidence. Also, highly immunogenic cancer cells may evade immune destruction by disabling components of the immune system. This is done through recruitment of inflammatory cells, including regulatory T cells and myeloid-derived suppressor cells, both actively immunosuppressive against the actions of cytotoxic lymphocytes.

Cancers develop and progress when there is loss of recognition by


Evading the immune system
Tumour-promoting inflammation
Insensitivity to anti-growth signals
Limitless replicative potential (immortality)
Reprogram ming energy metabolism
Evasion of apoptosis
Self-sufficiency in growth signals
Genomic instability
Sustained angiogenesis
Tissue invasion and metastases


EGFR inhibitors
Cyclin-dependent kinase inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Aerobic glycolysis inhibitors
Immune activating anti-CTLA4 mAb
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

Risk factors for cancer

The majority of cancers do not have a single cause but rather are the result of a complex interaction between genetic factors and exposure environmental carcinogens. These are often tumor type-specific but some general principles do apply.

So two factors interplay with each other, environmental and genetic factors.

A. Environmental factors:

Environmental triggers for cancer have mainly been identified through epidemiological studies that examine patterns of distribution of cancers in patients in whom age, sex, presence of other illnesses, social class, geography and so on differ. Sometimes, these give strong pointers to the molecular or cellular causes of the disease, such as the association between aflatoxin production within contaminated food supplies and hepatocellular carcinomas. For many solid cancers, such as breast and colorectal, however, there is evidence of a multifactorial pathogenesis, even when there is a principal environmental cause.

33.1 Environmental factors that predispose to cancer

Environmental aetiology	Processes	Diseases
Occupational exposure (see 'Radiation' below)	Dye and rubber manufacturing (aromatic amines) Asbestos mining, construction work, shipbuilding (asbestos) Vinyl chloride (PVC) manufacturing Petroleum industry (benzene)	Bladder cancer Lung cancer and mesothelioma Liver angiosarcoma Acute leukaemia
Chemicals	Chemotherapy (e.g. melphalan, cyclophosphamide)	Acute myeloid leukaemia
Cigarette smoking	Exposure to carcinogens from inhaled smoke	Lung and bladder cancer
Viral infection	Epstein–Barr virus Human papillomavirus Hepatitis B and C viruses	Burkitt's lymphoma and nasopharyngeal cancer Cervical cancer Hepatocellular carcinoma
Bacterial infection	*Helicobacter pylori*	Gastric MALT lymphomas, gastric cancer
Parasitic infection	Liver fluke (*Opisthorchis sinensis*) *Schistosoma haematobium*	Cholangiocarcinoma Squamous cell bladder cancer
Dietary factors	Low-roughage/high-fat content diet High nitrosamine intake Aflatoxin from contamination of *Aspergillus flavus*	Colonic cancer Gastric cancer Hepatocellular cancer
Radiation	UV exposure Nuclear fallout following explosion (e.g. Hiroshima) Diagnostic exposure (e.g. CT) Occupational exposure (e.g. beryllium and strontium mining) Therapeutic radiotherapy	Basal cell carcinoma Melanoma Non-melanocytic skin cancer Leukaemia Solid tumours, e.g. thyroid Cholangiocarcinoma following Thorotrast usage Lung cancer Medullary thyroid cancer Sarcoma
Inflammatory diseases	Ulcerative colitis	Colon cancer
Hormonal	Use of diethylstilbestrol Oestrogens	Vaginal cancer Endometrial cancer Breast cancer

(CT = computed tomography; MALT = mucosa-associated lymphoid tissue; UV = ultraviolet)

B. Genetic factors:

A number of inherited cancer syndromes are recognised that account for 5–10% of all cancers . In general they result from inherited mutations in genes that regulate cell growth, cell death and apoptosis. Examples include the BRCA1, BRCA2 and AT (ataxia telangiectasia) genes that cause breast and some other cancers, the FAP gene that causes bowel cancer and the RB gene that causes retinoblastoma. Although carriers of these gene mutations have a greatly elevated risk of cancer, none has 100% penetrance and additional modulating factors, both genetic and environmental, are likely to be operative.

Exploration of a possible genetic contribution is a key part of cancer management, especially with regard to ascertaining the risk for an affected patient's offspring.

33.2 Inherited cancer predisposition syndromes

Syndrome	Malignancies	Inheritance	Gene
Ataxia telangiectasia	Leukaemia, lymphoma, ovarian, gastric, brain, colon	AR	*AT*
Bloom's syndrome	Leukaemia, tongue, oesophageal, colonic, Wilms' tumour	AR	*BLM*
Breast/ovarian	Breast, ovarian, colonic, prostatic, pancreatic	AD	*BRCA1, BRCA2*
Cowden's syndrome	Breast, thyroid, gastrointestinal tract, pancreatic	AD	*PTEN*
Familial adenomatous polyposis	Colonic, upper gastrointestinal tract	AD	*APC, MUTYH*
Familial atypical multiple mole melanoma (FAMMM)	Melanoma, pancreas	AD	*CDKN2A (TP16)*
Fanconi anaemia	Leukaemia, oesophageal, skin, hepatoma	AR	*FACA, FACC, FACD*
Gorlin's syndrome	Basal cell skin, brain	AD	*PTCH*
Hereditary diffuse gastric cancer	Diffuse gastric cancer	AD	*E-cadherin*
Hereditary non-polyposis colon cancer (HNPCC)	Colonic, endometrial, ovarian, pancreatic, gastric	AD	*MSH2, MLH1, MSH6, PMS1, PMS2*
Li–Fraumeni syndrome	Sarcoma, breast, osteosarcoma, leukaemia, glioma, adrenocortical	AD	*TP53*
Multiple endocrine neoplasia (MEN) 1	Pancreatic islet cell, pituitary adenoma, parathyroid adenoma and hyperplasia	AD	*MEN1*
MEN 2	Medullary thyroid, phaeochromocytoma, parathyroid hyperplasia	AD	*RET*
Neurofibromatosis 1	Neurofibrosarcoma, phaeochromocytoma, optic glioma	AD	*NF1*
Neurofibromatosis 2	Vestibular schwannoma	AD	*NF2*
Papillary renal cell cancer syndrome	Renal cell cancer	AD	*MET*
Peutz–Jeghers syndrome	Colonic, ileal, breast, ovarian	AD	*STK11*
Prostate cancer	Prostate	AD	*HPC1*
Retinoblastoma	Retinoblastoma, osteosarcoma	AD	*RB1*
von Hippel–Lindau syndrome	Haemangioblastoma of retina and CNS, renal cell, phaeochromocytoma	AD	*VHL*
Wilms' tumour	Nephroblastoma, neuroblastoma, hepatoblastoma, rhabdomyosarcoma	AD	*WT1*
Xeroderma pigmentosum	Skin, leukaemia, melanoma	AR	*XPA, XPC, XPD (ERCC2), XPF*

(AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system)

Investigations

When a patient is suspected of having cancer, a full history should be taken; specific questions should be included as to potential risk factors such as smoking and occupational exposures or potential complications of the disease.

A thorough clinical examination is essential to identify sites of metastases, and to discover any other conditions that may have a bearing on the management plan.

In order to make a diagnosis and to plan the most appropriate management, information is needed on:

- the type of tumor
- the extent of disease, as assessed by staging investigations
- the patient's general condition and any comorbidity.

The overall fitness of a patient is often assessed by the Eastern Cooperative Oncology Group (ECOG) performance status scale .The outcome for patients with a performance status of 3 or 4 is worse in almost all malignancies than for those with a status of 0–2, and this has a strong influence on the approach to treatment in the individual p

33.3 Eastern Cooperative Oncology Group (ECOG) performance status scale

0	Fully active, able to carry on all usual activities without restriction and without the aid of analgesics
1	Restricted in strenuous activity but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains patients who are fully active, as in grade 0, but only with the aid of analgesics
2	Ambulatory and capable of all self-care but unable to work. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, unable to carry out any self-care and confined totally to bed or chair

Staging:

The process of staging determines the extent of the tumor; it entails clinical examination, imaging and, in some cases, surgery, to establish the extent of disease involvement.

The outcome is recorded using a standard staging classification that allows comparisons to be made between different groups of patients.

Therapeutic decisions and prognostic predictions can then be made using the evidence base for the disease.

One of the most commonly used systems is the TNM system, T (tumor), N (regional lymph nodes), M (metastatic sites) approach of the International Union against Cancer (UICC)

Histology:

To know the tumor type.

Histological analysis of a biopsy or resected specimen is pivotal in clinching the diagnosis and in deciding on the best form of management.

The results of histological analysis are most informative when combined with knowledge of the clinical picture; biopsy results should therefore be reviewed and discussed within the context of a multidisciplinary team meeting, MDT.

* Four steps to reach the final histopathological diagnosis.

1. Light microscopy
2. Immunohistochemistry
3. Electron Microscopy
4. Genetic and molecular testing.

1. Light microscopy:

Examination of tumor samples by light microscopy remains the core method of cancer diagnosis and, in cases where the primary site is unclear, may give clues to the origin of the tumor:

- Signet-ring cells favour a gastric primary.
- Presence of melanin favors melanoma.
- Mucin is common in gut/lung/breast/endometrial cancers, but particularly common in ovarian cancer and rare in renal cell or thyroid cancers.
- Psammoma bodies are a feature of ovarian cancer (mucin +) and thyroid cancer (mucin –).

2. Immunohistochemistry:

Immunohistochemical (IHC) staining for tumor markers can provide useful diagnostic information and can help with treatment decisions.

Commonly used examples of IHC in clinical practice include:

- Estrogen (ER) and progesterone (PR) receptors. Positive results indicate that the tumor may be sensitive to hormonal manipulation.
- Alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) with or without placental alkaline phosphatase (PLAP). These favor germ-cell tumors. • Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP). These favor prostate cancer.
- Carcinoembryonic antigen (CEA), cytokeratin and epithelial membrane antigen (EMA). These favor epithelial carcinomas.
- HER2 receptor. Breast cancers that have high levels of expression of HER2 indicate that the tumor may respond to trastuzumab (Herceptin), an antibody directed against the HER2 receptor.

The pattern of immunoglobulin, T-cell receptor and cluster designation (CD) antigen expression on the surface is helpful in the diagnosis and classification of lymphomas. This can be achieved by IHC staining of biopsy samples or flow cytometry

3. Electron microscopy:

Electron microscopy (EM) can sometimes be of diagnostic value.

Examples include the visualization of melanosomes in amelanotic melanoma and dense core granules in neuro-endocrine tumors.

EM may help to distinguish adenocarcinoma from mesothelioma, as the ultrastructural properties of these two diseases are different (mesothelioma appears to have long, narrow, branching microvilli while adenocarcinomas appear to have short, stubby microvilli).

EM is also useful for differentiating spindle-cell tumors (sarcomas, melanomas, squamous cell cancers) from small round-cell tumors, again due to their ultrastructural differences

4. Cytogenetic and molecularb analysis:

Some tumors demonstrate typical chromosomal changes that help in diagnosis.

The utilization of fluorescent in situ hybridization (FISH) techniques can be useful in Ewing's sarcoma and peripheral neuro-ectodermal tumors where there is a translocation between chromosome 11 and 22–t(11;22)(q24;q12). In some cases, gene amplification can be detected via FISH (e.g. determining over-expression of HER2/neu).

Molecular analysis such as next generation sequencing can determine the particular molecular derangement and a specific alteration which could be targeted later on by specific treatment called targeted therapy. An example of this is EGFR mutation in lung adenocarcinoma.

Imaging

Imaging plays a critical role in oncology, not only in locating the primary tumor but also in staging the disease and determining the response to treatment. The imaging modality employed depends primarily on the site of the disease and likely patterns of spread, and may require more than one modality.

1. Ultrasound :

Ultrasound is useful in characterizing lesions within the liver, kidney, pancreas and reproductive organs. It can be used for guiding biopsies of tumors in breast and liver. Endoscopic ultrasound is helpful in staging upper gastrointestinal and pancreatic cancers, involving a special endoscope with an ultrasound probe attached

2. Computed tomography:

Computed tomography (CT) is a key investigation in cancer patients and is particularly useful in imaging the thorax and abdomen. With modern scanners it is possible to visualize the large bowel if it is prepared (CT colonography), allowing accurate detection of colorectal cancers and adenomas ≥ 10 mm.

3. Magnetic resonance imaging:

Magnetic resonance imaging (MRI) has a high resolution and is the preferred technique for brain and pelvic imaging. It is widely employed

4. Positron emission tomography:

Positron emission tomography (PET) visualizes metabolic activity of tumor cells and is widely used, often in combination with CT (PET–CT), to evaluate the extent of the disease, particularly in the assessment of potential distant metastasis (Fig. 33.5). It can accurately assess the severity and spread of cancer by detecting tumor metabolic activity following injection of small amounts of radioactive tracers such as fluorodeoxyglucose (FDG). In addition to having a role in diagnosis, PET can be used in some patients to assess treatment response.

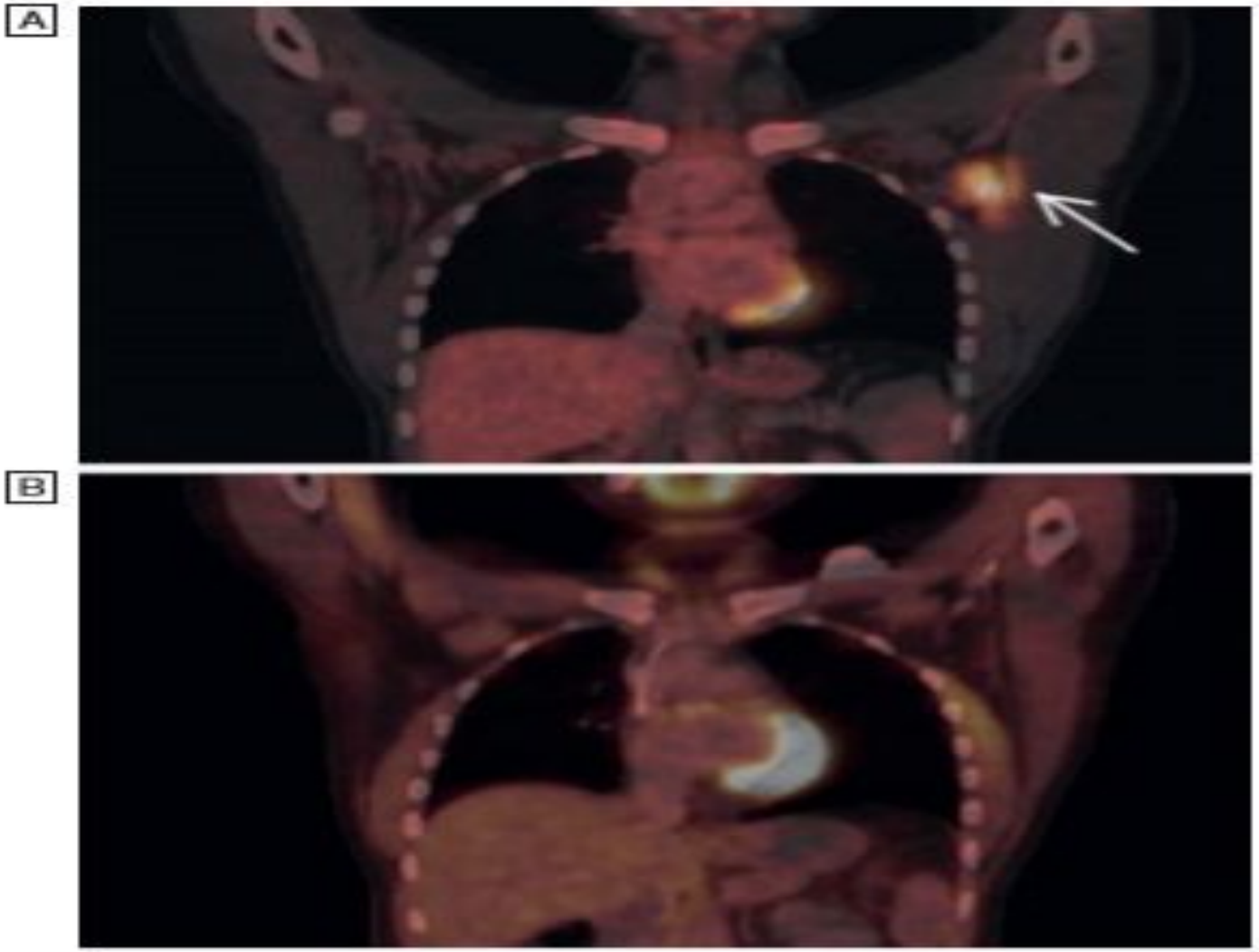


Fig. 33.5 Positron emission tomography–computed tomography (PET–CT) images. A There is a neoplastic lesion (arrow) in the left axilla, evidenced by the increased uptake of fluorodeoxyglucose (FDG) tracers. B Imaging after chemotherapy, demonstrating that the abnormal uptake has disappeared and indicating a response to treatment. *Courtesy of Dr J. Wilsdon, Freeman Hospital, Newcastle upon Tyne.*

Tumor Markers

Many cancers produce substances called tumor markers, which can assist in diagnosis and surveillance.

Some are useful in population screening, diagnosis, determining prognosis, response evaluation, detection of relapse and imaging of metastasis. Unfortunately, most tumor markers are neither sufficiently sensitive nor sufficiently specific to be used in isolation for diagnosis and need to be interpreted in the context of the other clinical features.

Some can be used for antibody-directed therapy or imaging, however, where they have a greater role in diagnosis.

33.5 Commonly used serum tumour markers

Name	Natural occurrence	Tumours
Alpha-fetoprotein (AFP)	Glycoprotein found in yolk sac and fetal liver tissue. Transient elevation in liver diseases. Has a role in screening during pregnancy for the detection of neural tube defects and Down's syndrome	Ovarian non-seminomatous germ cell tumours (80%), testicular teratoma (80%), hepatocellular cancer (50%)
Beta-2-microglobulin	A human leucocyte antigen (HLA) common fragment present on surface of lymphocytes, macrophages and some epithelial cells. Can be elevated in autoimmune disease and renal glomerular disease	Non-Hodgkin lymphoma, myeloma
Calcitonin	32-amino-acid peptide from C cells of thyroid. Used to screen for MEN 2	Medullary cell carcinoma of thyroid
Cancer antigen 125 (CA-125)	Differentiation antigen of coelomic epithelium (Müller's duct). Raised in any cause of ascites, pleural effusion or heart failure. Can be raised in inflammatory conditions	Ovarian epithelial cancer (75%), gastrointestinal cancer (10%), lung cancer (5%) and breast cancer (5%)
CA-19.9	A mucin found in epithelium of fetal stomach, intestine and pancreas. It is eliminated exclusively via bile and so any degree of cholestasis can cause levels to rise	Pancreatic cancer (80%), mucinous tumour of the ovary (65%), gastric cancer (30%), colon cancer (30%)
Carcinoembryonic antigen (CEA)	Glycoprotein found in intestinal mucosa during embryonic and fetal life. Elevated in smokers, cirrhosis, chronic hepatitis, ulcerative colitis, pneumonia	Colorectal cancer, particularly with liver metastasis, gastric cancer, breast cancer, lung cancer, mucinous cancer of the ovary
Human chorionic gonadotrophin (hCG)	Glycoprotein hormone, 14 kD α subunit and 24 kD β subunit from placental syncytiotrophoblasts. Used for disease monitoring in hydatidiform mole and as the basis of a pregnancy test	Choriocarcinoma (100%), hydatidiform moles (97%), ovarian non-seminomatous germ cell tumours (50–80%), seminoma (15%)
Placental alkaline phosphatase (PLAP)	Isoenzyme of alkaline phosphatase	Seminoma (40%), ovarian dysgerminoma (50%)
Prostate-specific antigen (PSA)	Glycoprotein member of human kallikrein gene family. PSA is a serine protease that liquefies semen in excretory ducts of prostate. Can be elevated in benign prostatic hypertrophy and prostatitis	Prostate cancer (95%)
Thyroglobulin	Matrix protein for thyroid hormone synthesis in normal thyroid follicles	Papillary and follicular thyroid cancer

Presenting problems in oncology

* In the early stages of cancer development, the number of malignant cells is small and the patient is usually asymptomatic.
* With tumor progression, localized signs or symptoms develop due to mass effects and/or invasion of local tissues.
* With further progression, symptoms may occur at distant sites as a result of metastatic disease or from non-metastatic manifestations due to production of biologically active hormones by the tumor or as the result of an immune response to the tumor.
* Although the incidence of cancer increases with patient age, the approach to investigation and management is similar at all ages.

33.6 Local features of malignant disease

Symptom	Typical site or possible tumour
Haemorrhage	Stomach, colon, bronchus, endometrium, bladder, kidney
Lump	Breast, lymph node (any site), testicle
Bone pain or fracture	Bone (primary sarcoma, secondary metastasis from breast, prostate, bronchus, thyroid, kidney)
Skin abnormality	Melanoma, basal cell carcinoma (rodent ulcer)
Ulcer	Oesophagus, stomach, anus, skin
Dysphagia	Oesophagus, bronchus, gastric
Increasing constipation, abdominal discomfort or pain	Colon, rectum, ovary
Airway obstruction, stridor, cough, recurrent infection	Bronchus, thyroid
Odynophagia, early satiety, vomiting	Bronchus, stomach, oesophagus, colon, rectum
Abdominal swelling (ascites)	Ovary, stomach, pancreas

33.7 Non-metastatic manifestations of malignant disease

Feature	Common cancer site associations
Weight loss and anorexia	Lung, gastrointestinal tract
Fatigue	Any
Hypercalcaemia	Myeloma, breast, kidney
Prothrombotic tendency	Ovary, pancreas, gastrointestinal tract
SIADH **Ectopic ACTH**	Small cell lung cancer
Lambert–Eaton myasthenic syndrome	Small cell lung cancer
Subacute cerebellar degeneration	Small cell lung cancer, ovarian cancer
Acanthosis nigricans	Stomach, oesophagus
Dermatomyositis/polymyositis	Stomach, lung

(ACTH = adrenocorticotrophic hormone; SIADH = syndrome of inappropriate antidiuretic hormone (vasopressin) secretion)

33.9 Ectopic hormone production by tumours

Hormone	Consequence	Tumours
ACTH	Cushing's syndrome	SCLC
Erythropoietin	Polycythaemia	Kidney, hepatoma, cerebellar haemangioblastoma, uterine fibroids
FGF-23	Hypophosphataemic osteomalacia	Mesenchymal tumours
PTHrP	Hypercalcaemia	NSCLC (squamous cell), breast, kidney
Vasopressin (ADH)	Hyponatraemia	SCLC

(ACTH = adrenocorticotrophic hormone; ADH = antidiuretic hormone; FGF = fibroblast growth factor; NSCLC = non-small cell lung cancer; PTHrP = parathyroid hormone-related protein; SCLC = small cell lung cancer)

Metastatic disease

Metastatic disease is the major cause of death in cancer patients and the principal cause of morbidity.

For the majority, the aim of treatment is palliative but treatment of a solitary metastasis can occasionally be curative.

1. Brain metastases:

* Brain metastases occur in 10–30% of adults and 6–10% of children with cancer, and are an increasingly important cause of morbidity.
* Tumors that typically metastasize to the brain are lung, breast, renal cell, melanoma, and colon cancer .
* Most involve the brain parenchyma but can also affect the cranial nerves, the blood vessels and other intracranial structures.

Clinical features:

Presentation is with headaches (40–50%), focal neurological dysfunction (20–40%), cognitive dysfunction (35%), seizures (10–20%) and papilloedema (< 10%).

Investigations and management:

The diagnosis can be confirmed by CT or contrast-enhanced MRI.

Treatment options include:

* High-dose glucocorticoids (dexamethasone 4 mg 4 times daily) for tumor-associated edema.
* Anticonvulsants for seizures,
* Whole-brain radiotherapy and chemotherapy.
* Surgery may be considered for single sites of disease and can be curative.
* Stereotactic radiotherapy may also be considered for solitary site involvement where surgery is not possible

2. Lung metastases:

* These are common in breast cancer, colon cancer and tumours of the head and neck.
* The presentation is usually with a lesion on chest X-ray or CT.
* Solitary lesions require investigation, as single metastases can be difficult to distinguish from a primary lung tumour.
* Patients with two or more pulmonary nodules can be assumed to have metastases.
* The approach to treatment depends on the extent of disease in the lung and elsewhere.
* For solitary lesions, surgery should be considered, with a generous wedge resection.
* Radiotherapy, chemotherapy or endocrine therapy can be used as systemic treatment and is dependent on the underlying primary cancer diagnosis

3. Liver metastases:

* Metastatic cancer in the liver can represent the sole or life limiting component of disease for many with colorectal cancer, ocular melanoma, neuro-endocrine tumors (NETs) and, less commonly, other tumor types.
* The most common clinical presentations are with right upper quadrant pain due to stretching of the liver capsule, jaundice, deranged liver function tests or an abnormality detected on imaging.
* In selected cases, resection of the metastasis can be contemplated. In colorectal cancer, successful resection of metastases improves 5-year survival from 3% to 30–40%.
* Other techniques, such as chemoembolization or radiofrequency ablation, can also be used, provided the number and size of metastases remain small.
* If these are not feasible, symptoms may respond to systemic chemotherapy

4. Bone metastases:

* Bone is the third most common organ involved by metastasis, after lung and liver.
* Bone metastases are a major clinical problem in patients with myeloma and breast or prostate cancers, but other tumors that commonly metastasize to bone include those of the kidney and thyroid.
* Bone metastases are an increasing management problem in other tumor types that do not classically target bone, due to the prolonged survival of patients generally.
* Accordingly, effective management of bony metastases has become a focus in the treatment of patients with many incurable cancers.

Clinical features :

The main presentations are with pain, pathological fractures and spinal cord compression The pain tends to be progressive and worst at night, and may be partially relieved by activity, but subsequently becomes more constant in nature and is exacerbated by movement.

Most pathological fractures occur in metastatic breast cancer (53%); other tumor types associated with fracture include the kidney (11%), lung (8%), thyroid (5%), lymphoma (5%) and prostate (3%).

Investigations:

The most sensitive way of detecting bone metastases is by isotope bone scan. This can have false-positive results in healing bone, particularly as a flare response following treatment and false negative results occur in multiple myeloma due to suppression of osteoblast activity.

Plain X-ray films are therefore preferred for any sites of bone pain, as lytic lesions may not be detected by a bone scan. In patients with a single lesion, it is especially important to perform a biopsy to obtain a tissue diagnosis, since primary bone tumors may look very similar to metastases on X-ray.

PET CT scan has a very high sensitivity and specificity for detecting bone metastases. Some other specific type such as PSMA PET CT scan for prostate cancer.

Management:

The main goals of management are:

- pain relief
- preservation and restoration of function
- skeletal stabilization
- local tumor control (e.g. relief of tumor impingement on normal structure).

Surgical intervention may be warranted where there is evidence of skeletal instability (e.g. anterior or posterior spinal column fracture) or an impending fracture (e.g. a large lytic lesion on a weight-bearing bone with more than 50% cortical involvement).

Intravenous bisphosphonates (pamidronate, zoledronic acid or denosumab) are widely used for bone metastases and are effective at improving pain and in reducing further skeletal related events, such as fractures and hypercalcaemia.

In certain types of cancer, such as breast and prostate, hormonal therapy may be effective. Radiotherapy, in the form of external beam may be very effective in controlling pain and preventing fracture.

5. Malignant pleural effusion:

This is a common complication of cancer and 40% of all pleural effusions are due to malignancy. The most common causes are lung and breast cancers, and the presence of an effusion indicates advanced and incurable disease. The presentation may be with dyspnea, cough or chest discomfort, which can be dull or pleuritic in nature.

Investigations and management

* Pleural aspirate is the key investigation and may show the presence of malignant cells. Malignant effusions are commonly blood-stained and are exudates with a raised fluid to serum LDH ratio (> 0.6) and a raised fluid to serum protein ratio (> 0.5).

* Treatment should focus on palliation of symptoms and be tailored to the patient's physical condition and prognosis.

Aspiration alone may be an appropriate treatment in frail patients with a limited life expectancy .

Those who present with malignant pleural effusion as the initial manifestation of breast cancer, small cell lung cancer, germ cell tumors or lymphoma should have the fluid aspirated and should be given systemic chemotherapy to try to treat disease in the pleural space.

Treatment options for patients with recurrent pleural effusion include

Treatment of cancer:

Treatment of cancer comprises multi disceplins, including surgery, radiation therapy and systemic therapy.

(A) Surgical Treatment:

Surgery has a pivotal role in the management of cancer. There are three main situations in which it is necessary.

(I) Biopsy:

In the vast majority of cases, a histological or cytological diagnosis of cancer is necessary, and tissue will also provide important information such as tumour type and differentiation, to assist subsequent management. Cytology can be obtained with fine needle aspiration but a biopsy is usually preferred. This can be a core biopsy, an image-guided biopsy or an excision biopsy.

(2) Resection or Excision:

The main curative management of most solid cancers is surgical excision. In early, localized cases of colorectal, breast and lung cancer, cure rates are high with surgery.

This is called the curative surgery. Usually planned through a multidisciplinary team to get the best option for the patient.

(3) Palliative:

Surgical procedures are often the quickest and most effective way of palliating symptoms. Examples include the treatment of faecal incontinence with a defunctioning colostomy; fixation of pathological fractures and decompression of spinal cord compression; and the treatment of fungating skin lesions by 'toilet' surgery.

A more specialist role for surgery is in resection of residual masses after chemotherapy and, in very selected cases, resection of metastases.

(B) Systemic Chemotherapy:

* Chemotherapeutic drugs are classified by their mode of action. They have the greatest activity in proliferating cells and this provides the rationale for their use in the treatment of cancer. Chemotherapeutic agents are not specific for cancer cells, however, and the side-effects of treatment are a result of their antiproliferative actions in normal tissues such as the bone marrow, skin and gut.
* The dosing schedule and interval are determined by the choice of drugs and recovery of the cancer and normal tissues. For most common chemotherapy regimens, the treatment is administered every 21 or 28 days, which defines one cycle. A course of treatment often uses up to 6 cycles of treatment.
* Adverse effects of chemotherapy:

Most cytotoxics have a narrow therapeutic window or index and can have significant adverse effects. Considerable supportive therapy is often required to enable patients to tolerate therapy and achieve benefit.

(C) Radiation Therapy:

* Radiation therapy (radiotherapy) involves treating the cancer with ionising radiation; for certain localised cancers it may be curative. Ionising radiation can be delivered by radiation emitted from the decay of radioactive isotopes or by high-energy radiation beams, usually X-rays.

* The majority of treatments are delivered by linear accelerators, which produce electron or X-ray beams of high energy that are used to target tumour tissue. The biological effect of ionising radiation is to cause lethal and sublethal damage to DNA. Since normal tissues are also radiosensitive, treatment has to be designed to maximise exposure of the tumour and minimise exposure of normal tissues.

* Both normal and malignant tissues vary widely in their sensitivity to radiotherapy. Germ cell tumours and lymphomas are extremely radiosensitive and relatively low doses are adequate for cure, but most cancers require doses close to or beyond that which can be tolerated by adjacent normal structures.

* The side-effects of radiotherapy depend on the normal tissues treated, their radiosensitivity and the dose delivered, including: nausea, vomiting, stomatitis,

(D) Hormone Therapy:

Hormone therapy is most commonly used in the treatment of breast cancer and prostate cancer. Breast tumours that are positive for expression of the oestrogen receptor (ER) respond well to anti-oestrogen therapy, and assessment of ER status is now standard in the diagnosis of breast cancer. Several drugs are now available that reduce oestrogen levels or block the effects of oestrogen on the receptor. When targeted appropriately, adjuvant hormone therapy reduces the risk of relapse and death at least as much as chemotherapy, and in advanced cases can induce stable disease and remissions that may last months to years, with acceptable toxicity.

Hormonal manipulation may be effective in other cancers. In prostate cancer, hormonal therapy (e.g. luteinising hormone releasing hormone (LHRH) analogues such as goserelin and/or anti-androgens such as bicalutamide) aimed at reducing androgen levels can provide good long-term control of advanced disease.

(F) Biological Therapy:

Advances in knowledge about the molecular basis of cancer have resulted in the development of a new generation of treatments to block the signalling pathways responsible for the growth of specific tumours. This has created the potential to target cancer cells more selectively, with reduced toxicity to normal tissues. Examples:

(1) Gefitinib/erlotinib:

These agents inhibit the activity of the EGFR, which is overexpressed in many solid tumours. However, the drugs' activity does not depend on the amount of receptor over-expression but rather on factors such as gene copy number and mutation status.

(2) Imatinib Imatinib:

was developed to inhibit the BCR-ABL gene product, tyrosine kinase, that is responsible for chronic myeloid leukaemia (p. 958), and it does this extremely effectively. It is also active in malignant gastrointestinal stromal tumour (GIST), a type of sarcoma that has over-expression of another cell surface tyrosine kinase, c-kit. This agent has good tolerability and is particularly useful in GIST, where conventional

(3) Bevacizumab:

This is a humanised monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A), a key stimulant of angiogenesis in tumours. Bevacizumab has activity in colorectal, lung, breast, renal and ovarian cancers, although the licence was subsequently revoked for breast cancer; while bevacizumab slows the rate of progression of metastatic breast cancer, it had little impact on survival or improved quality of life.

(4) Trastuzumab :

Trastuzumab (Herceptin) targets the HER2 receptor, an oncogene that is over-expressed in around one-third of breast cancers and in a number of other solid tumours (e.g. gastric cancer). It is effective as a single-agent therapy, but also improves survival in patients with advanced breast cancer when used in conjunction with chemotherapy. Unfortunately, trastuzumab can induce cardiac failure by an unknown biological mechanism, especially in combination with doxorubicin.

Specific Cancers

(1) Breast Cancer:

Globally, the incidence of breast cancer is second only to that of lung cancer, and the disease represents the leading cause of cancer-related deaths among women. Invasive ductal carcinoma with or without ductal carcinoma in situ (DCIS) is the most common histology, accounting for 70%, whilst invasive lobular carcinoma accounts for most of the remaining cases.

DCIS: constitutes 20% of breast cancers detected by mammography screening. It is multifocal in one-third of women and has a high risk of becoming invasive (10% at 5 years following excision only). Pure DCIS does not cause lymph node metastases, although these are found in 2% of cases where nodes are examined, owing to undetected invasive cancer.

Lobular carcinoma in situ (LCIS) is a predisposing risk factor for developing cancer in either breast (7% at 10 years).

Risk Factors:

Both genetic and hormonal factors play a role; about 5–10% of breast cancers are hereditary and occur in patients with mutations of BRCA1, BRCA2, AT or TP53 genes.

Prolonged oestrogen exposure associated with early menarche, late menopause and use of hormone replacement therapy (HRT) has been associated with an increased risk.

Other risk factors include obesity, alcohol intake, nulliparity and late first pregnancy. There is no definite evidence linking use of the contraceptive pill to breast cancer

Also previous radiation exposure to chest during early treatment of Hodgkin's lymphoma.

Clinical features:

(1)Breast cancer usually presents as a result of mammographic screening or as a palpable mass with nipple discharge in 10% and pain in 7% of patients.

(2)Less common presentations include inflammatory carcinoma with diffuse induration of the skin of the breast, and this confers an adverse prognosis.

(3)Around 40% of patients will have axillary nodal disease, with likelihood correlating with increasing size of the primary tumour.

(4)Distant metastases are infrequently present at diagnosis and the most common sites of spread are bone (70%), lung (60%), liver (55%), pleura (40%), adrenals (35%), skin (30%) and brain (10–20%).

Investigations:

Following clinical examination, patients should have imaging with mammography or ultrasound evaluation, and a biopsy using fine needle aspiration for cytology or core biopsy for histology.

Histological assessment should be carried out to assess tumour type and to determine oestrogen and progesterone receptor (ER/PR) status and HER2 status.

If distant spread is suspected, CT of the thorax and abdomen and an isotope bone scan are required.

Molecular subtyping is being used to classify tumours into four major subtypes: luminal A, luminal B, HER2 type and basal-like (often called ‘triple negative’, as these tumours are ER-, PR- and HER2-negative). This may allow more targeted selection of therapies in future.

Management:

Surgery:

is the mainstay of treatment for most patients, and this can range from a lumpectomy, where only the tumour is removed, to mastectomy, where the whole breast is removed. Breast-conserving surgery is as effective as mastectomy if complete excision with negative margins can be achieved. Lymph node sampling is performed at the time of surgery.

Adjuvant radiotherapy: is given to reduce the risk of local recurrence to 4–6%.

Adjuvant hormonal therapy : improves disease-free and overall survival in pre- and post-menopausal patients who have tumours that express ER. Patients at low risk, with tumours that are small and ER-positive, require only adjuvant hormonal therapy with tamoxifen. Patients with tumours that are ER-positive and who are pre-menopausal should

Adjuvant chemotherapy:

is considered for patients at higher risk of recurrence. Factors that increase the risk of recurrence include a tumour of > 1 cm, a tumour that is ER-negative or the presence of involved axillary lymph nodes. Such patients should be offered adjuvant chemotherapy, which improves disease-free and overall survival. The role of adjuvant treatment has been studied by meta-analyses and data support the use of adjuvant trastuzumab, a humanised monoclonal antibody to HER2, in addition to standard chemotherapy for women with early HER2-positive breast cancer.

Metastatic disease:

management includes radiotherapy to palliate painful bone metastases and second-line endocrine therapy with aromatase inhibitors, which inhibit peripheral oestrogen production in adrenal and adipose tissues. Advanced ER-negative disease may be treated with combination chemotherapy.

(2) Lung cancer:

Aetiology:

Cigarette smoking is by far the most important cause of lung cancer. It is thought to be directly responsible for at least 90% of cases, the risk being proportional to the amount smoked and to the tar content of cigarettes. The death rate from the disease in heavy smokers is 40 times that in non-smokers. Risk falls slowly after smoking cessation but remains above that in non-smokers for many years. It is estimated that 1 in 2 smokers dies from a smoking-related disease, about half in middle age. The effect of 'passive' smoking is more difficult to quantify but is currently thought to be a factor in 5% of all lung cancer deaths. Exposure to naturally occurring radon is another risk.

The incidence of lung cancer is slightly higher in urban than in rural dwellers, which may reflect differences in atmospheric pollution (including tobacco smoke) or occupation, since a number of industrial materials are associated with lung cancer.

In recent years, the strong link between smoking and ill health has led

Incidence:

The incidence of lung cancer increased dramatically during the 20th century as a direct result of the tobacco epidemic In women, smoking prevalence and deaths from lung cancer continue to increase, and more women now die of lung cancer than breast cancer in the USA and the UK.

Pathology:

Lung cancers arise from the bronchial epithelium or mucous glands.

The following are the t

17.62 Common cell types in lung cancer

Cell type	%
Adenocarcinoma	35–40
Squamous	25–30
Small-cell	15
Large-cell	10–15

Clinical features:

Lung cancer presents in many different ways, reflecting local, metastatic or paraneoplastic tumour effects.

(1) Cough: This is the most common early symptom. It is often dry but secondary infection may cause purulent sputum. A change in the character of a smoker's cough, particularly if associated with other new symptoms, should always raise suspicion of lung cancer.

(2) Hemoptysis: Hemoptysis is common, especially with central bronchial tumours. Although it may be caused by bronchitic infection, hemoptysis in a smoker should always be investigated to exclude a lung cancer. Occasionally, central tumours invade large vessels, causing sudden massive hemoptysis that may be fatal.

(3) Bronchial obstruction: This is another common presentation. The clinical and radiological manifestations depend on the site and extent of the obstruction, any secondary infection and the extent of coexisting lung disease. Complete obstruction causes collapse of a lobe or lung, with breathlessness, mediastinal displacement and dullness to percussion with reduced breath sounds. Partial bronchial obstruction may cause a monophonic, unilateral wheeze that fails to clear with

*** Pneumonia that recurs at the same site or responds slowly to treatment, particularly in a smoker, should always suggest an underlying lung cancer. Stridor (a harsh inspiratory noise) occurs when the larynx, trachea or a main bronchus is narrowed by the primary tumour or by compression from malignant enlargement of the subcarinal and paratracheal lymph nodes.

(4) Breathlessness: Breathlessness may be caused by collapse or pneumonia, or by tumour causing a large pleural effusion or compressing a phrenic nerve and leading to diaphragmatic paralysis.

(5) Pain and nerve entrapment: Pleural pain may indicate malignant pleural invasion, although it can occur with distal infection. Intercostal nerve involvement causes pain in the distribution of a thoracic dermatome. Cancer in the lung apex may cause Horner's syndrome (ipsilateral partial ptosis, enophthalmos, miosis and hypohidrosis of the face) due to involvement of the sympathetic nerves to the eye at or above the stellate ganglion. Pancoast's syndrome (pain in the inner aspect of the arm, sometimes with small muscle wasting in the hand) indicates malignant destruction of the T1 and C8 roots in the lower part

(6) Mediastinal spread: Involvement of the oesophagus may cause dysphagia. If the pericardium is invaded, arrhythmia or pericardial effusion may occur. Superior vena cava obstruction by malignant nodes causes suffusion and swelling of the neck and face, conjunctival edema, headache and dilated veins on the chest wall and is most commonly due to lung cancer. Involvement of the left recurrent laryngeal nerve by tumors at the left hilum causes vocal cord paralysis, voice alteration and a 'bovine' cough (lacking the normal explosive character). Supraclavicular lymph nodes may be palpably enlarged or identified using ultrasound; if so, a needle aspirate may provide a simple means of cytological diagnosis.

(7) Metastatic spread: This may lead to focal neurological defects, epileptic seizures, personality change, jaundice, bone pain or skin nodules. Lassitude, anorexia and weight loss usually indicate metastatic spread.

(8) Finger clubbing: Overgrowth of the soft tissue of the terminal phalanx, leading to increased nail curvature and nail bed fluctuation, is often seen.

(9) Hypertrophic pulmonary osteoarthropathy (HPOA): This is a painful periostitis of the distal tibia, fibula, radius and ulna, with local

(10) Non-metastatic extrapulmonary effects: The syndrome of inappropriate antidiuretic hormone secretion (SIADH) and ectopic adrenocorticotrophic hormone secretion are usually associated with small-cell lung cancer. Hypercalcaemia may indicate malignant bone destruction or production of hormone-like peptides by a tumour. Associated neurological syndromes may occur with any type of lung cancer.

Investigations:

The main aims of investigation are to confirm the diagnosis, establish the histological cell type and define the extent of the disease.

(1) Imaging: Lung cancer produces a range of appearances on chest X-ray, from lobar collapse to mass lesions, effusion or malignant rib destruction. CT should be performed early, as it may reveal mediastinal or metastatic spread and is helpful for planning biopsy procedures, e.g. in establishing whether a tumour is accessible by bronchoscopy or percutaneous CT-guided biopsy.

(2) Biopsy and histopathology:

* Over half of primary lung tumours can be visualized and sampled directly by biopsy and brushing using a flexible bronchoscope. Bronchoscopy also allows an assessment of operability, from the proximity of central tumours to the main carina.
* For tumours that are too peripheral to be accessible by bronchoscope, the yield of 'blind' bronchoscopic washings and brushings from the radiologically affected area is low and percutaneous needle biopsy under CT or ultrasound guidance is a more reliable way to obtain a histological diagnosis. There is a small risk of iatrogenic pneumothorax, which may preclude the procedure if there is extensive coexisting COPD.
* In patients with a peripheral tumour and enlarged hilar or paratracheal lymph nodes on CT, bronchoscopy with EBUS-guided node sampling may allow both diagnosis and staging.
* In patients with pleural effusions, pleural aspiration and biopsy is the preferred investigation. Where facilities exist, thoracoscopy increases yield by allowing targeted biopsies under direct vision.
* In patients with metastatic disease, the diagnosis can often be

Staging:

Staging to guide treatment The propensity of small-cell lung cancer to metastasize early means these patients are usually not suitable for surgical intervention. In non-small-cell lung cancer (NSCLC), treatment and prognosis are determined by disease extent, so careful staging is required.

* CT is used early to detect obvious local or distant spread.
* Combined CT and whole-body PET is commonly used to detect occult but metabolically active metastases in bones and viscera.
* Brain MRI to detect brain metastases.
* Bone marrow biopsy are generally reserved for patients with clinical, haematological or biochemical evidence of tumour spread to these sites.

*** Then the stage is assigned according to the TNM staging system.

Treatment:

Surgical resection carries the best hope of long-term survival but some patients treated with radical radiotherapy and chemotherapy also achieve prolonged remission or cure. In over 75% of cases, treatment with the aim of cure is not possible or is inappropriate due to extensive spread or comorbidity. Such patients are offered palliative therapy and best supportive care. Radiotherapy and, in some cases, chemotherapy can relieve symptoms.

(1) Surgery:

Accurate pre-operative staging, coupled with improvements in surgical and post-operative care, now offers 5-year survival rates of over 75% in stage I disease (N0, tumour confined within visceral pleura) and 55% in stage II disease, which includes resection in patients with ipsilateral peribronchial or hilar node involvement.

(2) Radiotherapy:

While much less effective than surgery, radical radiotherapy can offer long-term survival in selected patients with localized disease in whom comorbidity precludes surgery. Radical radiotherapy is usually combined with chemotherapy when lymph nodes are involved (stage

(3) Chemotherapy:

*** Small cell lung carcinoma:

The treatment of small-cell carcinoma with combinations of cytotoxic drugs, sometimes with radiotherapy, can increase median survival from 3 months to well over a year. The use of combinations of chemotherapeutic drugs requires considerable skill and should be overseen by multidisciplinary teams of clinical oncologists and specialist nurses. Combination chemotherapy leads to better outcomes than single-agent treatment. Regular cycles of therapy, including combinations of intravenous cisplatin and etoposide, commonly used.

*** Non- Small cell carcinoma:

In NSCLC chemotherapy is less effective, though platinum based chemotherapy regimens offer 30% response rates and a modest increase in survival, and are widely used. Some non-small-cell lung tumours, particularly adenocarcinomas in non-smokers, carry detectable mutations, e.g. in the epidermal growth factor receptor (EGFR) gene. Tyrosine kinase inhibitors, such as erlotinib, afatinib, and

* Neoadjuvant chemotherapy:

In NSCLC there is some evidence that chemotherapy given before surgery may increase survival and can effectively 'down-stage' disease with limited nodal spread.

* Adjuvant chemotherapy:

Post-operative chemotherapy is now proven to enhance survival rates when operative samples show nodal involvement by tumour.

Prognosis:

The overall prognosis in lung cancer is very poor, 70% of patients dying within a year of diagnosis and only 6–8% surviving 5 years after diagnosis. The best prognosis is with well-differentiated squamous cell tumours that have not metastasized and are amenable to surgical resection.

Now with the introduction of the new targeted therapy, and immunotherapy by immune checkpoint inhibitors, the prognosis has dramatically improved with some clinical trials showed a 5- year

(3) Colorectal Cancer:

Although relatively rare in the developing world, colorectal cancer is the second most common malignancy and the second leading cause of cancer deaths in Western countries.

Risk Factors:

Both environmental and genetic factors are important in colorectal carcinogenesis. (A)Environmental factors:

Account for the wide geographical variation in incidence and the decrease in risk seen in migrants who move from high- to low-risk countries. Dietary factors are most important and also non-dietary risk factors play a role.

Dietary risk factors:

Risk factor	Comments
Increased risk	
Red meat*	High saturated fat and protein content Carcinogenic amines formed during cooking
Saturated animal fat*	High faecal bile acid and fatty acid levels May affect colonic prostaglandin turnover
Decreased risk	
Dietary fibre*	Effects vary with fibre type; shortened transit time, binding of bile acids and effects on bacterial flora proposed
Fruit and vegetables	Green vegetables contain anticarcinogens, such as flavonoids Little evidence for protection from vitamins A, C and E
Calcium	Binds and precipitates faecal bile acids
Folic acid	Reverses DNA hypomethylation
Omega-3 fatty acids	May be of modest benefit

*Evidence is inconsistent and a clear relationship is unproven.

i 21.71 Non-dietary risk factors for colorectal cancer

Medical conditions

- Colorectal adenomas (p. 827)
- Long-standing extensive ulcerative colitis or Crohn's colitis (p. 813), especially if associated with primary sclerosing cholangitis
- Ureterosigmoidostomy
- Acromegaly
- Pelvic radiotherapy

Others

- Obesity and sedentary lifestyle – may be related to diet
- Smoking (relative risk 1.5–3.0)
- Alcohol (weak association)
- Cholecystectomy (effect of bile acids in right colon)
- Type 2 diabetes (hyperinsulinaemia)
- Use of aspirin or NSAIDs (COX-2 inhibition) and perhaps statins associated with *reduced* risk

(COX-2 = cyclo-oxygenase 2; NSAIDs = non-steroidal anti-inflammatory drugs)

(B) Genetic Factors:

Colorectal cancer development results from the accumulation of multiple genetic mutations. There are also associated epigenetic influences, such as microRNA expression signature, and potential influences from non-coding genetic variation.

Currently, there are three main pathways of genetic instability and each is associated with histological, clinical and prognostic parameters:

*** *Chromosomal instability*: Mutations or deletions of portions of chromosomes arise, with loss of heterozygosity (LOH) and inactivation of specific tumour suppressor genes. In LOH, one allele of a gene is deleted but gene inactivation occurs only when a subsequent unrelated mutation affects the other allele. Chromosomal instability (CIN) occurs in around 85% of colorectal cancers.

***

******Microsatellite instability*: This involves germline mutations in one of six genes encoding enzymes involved in repairing errors that occur normally during DNA replication (DNA mismatch repair); these genes are designated hMSH2, hMSH6, hMLH1, hMLH3, hPMS1 and hPMS2. Replication errors accumulate and can be detected in 'microsatellites' of repetitive DNA sequences. They also occur in important regulatory genes, resulting in a genetically unstable phenotype and accumulation of multiple somatic mutations throughout the genome that eventually lead to cancer. Around 15% of sporadic cancers develop this way, as do most cases of hereditary non-polyposis colon cancer (HNPCC).**

****** CpG island methylator phenotype (CIMP):* This phenotype is found in approximately 20–30% of colorectal cancers and results in widespread gene hypermethylation. The result is functional loss of tumour suppressor genes.**

About 5–10% of colon cancers are caused by HNPCC. Pedigrees with this disorder have an autosomal dominant mode of inheritance and a positive family history of colon cancer occurring at a young age. The

Clinical features:

Symptoms vary, depending on the site of the carcinoma.

* In tumours of the left colon, fresh rectal bleeding is common and obstruction occurs early.
* Tumours of the right colon present with anaemia from occult bleeding or with altered bowel habit, but obstruction is a late feature.
* Colicky lower abdominal pain is present in two-thirds of patients and rectal bleeding occurs in 50%.
* A minority present with features of either obstruction or perforation, leading to peritonitis, localized abscess or fistula formation.
* Carcinoma of the rectum usually causes early bleeding, mucus discharge or a feeling of incomplete emptying.
* Between 10% and 20% of patients present with iron deficiency anaemia or weight loss.
* On examination, there may be a palpable mass, signs of anaemia or hepatomegaly from metastases. Low rectal tumours may be palpable on digital examination.

Investigations:

* Colonoscopy is the investigation of choice because it is more sensitive and specific than barium enema. Furthermore, lesions can be biopsied and polyps removed.
* Patients in whom colonoscopy is incomplete and those who are at high risk of complications can be investigated by CT colonography (virtual colonoscopy). This is a sensitive and non-invasive technique for diagnosing tumours and polyps of more than 6 mm diameter.
* When the diagnosis of colon cancer has been made, CT of the chest, abdomen and pelvis should be performed as a staging investigation, particularly to detect hepatic metastases.
* Pelvic MRI or endoanal ultrasound should be used for local staging of rectal cancer.
* Measurement of serum carcinoembryonic antigen (CEA) levels are of limited value in diagnosis, since values are normal in many patients, but CEA testing can be helpful during follow-up to monitor for recurrence.

Management:

Surgery:

* All patients should be discussed at a multidisciplinary team meeting.
* Those with locally advanced rectal cancer should be offered neoadjuvant radiotherapy or chemoradiotherapy to increase the subsequent chance of a complete (R0) surgical resection. A 1-week course of radiotherapy just prior to surgery reduces the risk of local recurrence in operable rectal cancer.
* The tumour should be removed, along with adequate resection margins and pericolic lymph nodes. Continuity should be restored by direct anastomosis, wherever possible.
* Carcinomas within 2 cm of the anal verge may require abdominoperineal resection and formation of a colostomy.
* All patients should be counselled pre-operatively about the possible need for a stoma.
* Total mesorectal excision reduces recurrence rates and increases survival in rectal cancer. Metastatic disease confined to liver or lung should be considered for resection, as this can be potentially curative if there is truly no disease at other sites.

Adjuvant therapy:

* About 30–40% of patients have lymph node involvement at presentation (Fig. 21.60) and are therefore at risk of recurrence.
* Most recurrences are within 3 years of diagnosis and affect the liver, lung, distant lymph nodes and peritoneum.
* Adjuvant chemotherapy with 5-fluorouracil/folinic acid or capecitabine, preferably in combination with oxaliplatin, can reduce the risk of recurrence in patients with stage III cancers and some high-risk stage II cancers.
* Post-operative radiotherapy reduces the risk of local recurrence in rectal cancer if operative resection margins are involved.

Palliative therapy:

Palliative chemotherapy with 5-fluorouracil/folinic acid, capecitabine, oxaliplatin or irinotecan improves survival. Patients with advanced metastatic disease may be treated with monoclonal antibodies using bevacizumab or cetuximab, either alone or together with chemotherapy.

Prevention and screening:

Secondary prevention aims to detect and remove lesions at an early or pre-malignant stage by screening the asymptomatic general population. Several potential methods exist:

* Population-based screening of people over the age of 50 years by regular faecal occult blood (FOB) testing reduces colorectal cancer mortality and increases the proportion of early cancers detected. The sensitivity and specificity of these tests need to be improved. Traditionally, serial stool testing with or without subsequent colonoscopy is the screening method of choice in the UK. •
* Colonoscopy remains the gold standard and allows preventative polypectomy but is expensive, requires bowel preparation and carries risks (perforation approximately 1 : 1000). Many countries lack the resources to offer this form of screening. •
* Flexible sigmoidoscopy is an alternative option and has been shown to reduce overall colorectal cancer mortality by approximately 35% (70% for cases arising in the rectosigmoid). It is recommended in the USA every 5 years in all persons over the age of 50.
* Screening for high-risk patients by molecular genetic analysis is an

(4) Lymphoma:

These neoplasms arise from lymphoid tissues, and are diagnosed from the pathological findings on biopsy as Hodgkin or nonHodgkin lymphoma.

The majority are of B-cell origin.

Non-Hodgkin lymphomas are classified as low- or high-grade tumours on the basis of their proliferation rate.

- High-grade tumours divide rapidly, are typically present for a matter of weeks before diagnosis, and may be lifethreatening with frequent risk of extranodal involvement.

- Low-grade tumours divide slowly, may be present for many months before diagnosis, and typically behave in an indolent fashion.

(A)Hodgkin lymphoma:

The histological hallmark of Hodgkin lymphoma (HL) is the presence of Reed–Sternberg cells: large, malignant lymphoid cells of B-cell origin. They are often present only in small numbers but are surrounded by large numbers of reactive non-malignant T cells, plasma cells and eosinophils.

Epidemiology and eti

23.53 Epidemiology and aetiology of Hodgkin lymphoma

Incidence

- Approximately 4 new cases/100 000 population/year

Sex ratio

- Slight male excess (1.5 : 1)

Age

- Median age 31 years; first peak at 20–35 years and second at 50–70 years

Aetiology

- Unknown
- More common in patients from well-educated backgrounds and small families
- Three times more likely with a past history of infectious mononucleosis but no definitive causal link to Epstein–Barr virus infection proven

Classification of Hodgkin's Lym

23.54 WHO pathological classification of Hodgkin lymphoma (HL)

Type	Histology classification	Proportion of HL
Nodular lymphocyte-predominant HL		5%
Classical HL	Nodular sclerosing	70%
	Mixed cellularity	20%
	Lymphocyte-rich	5%
	Lymphocyte-depleted	Rare

Staging:

23.55 Clinical stages of Hodgkin lymphoma (Ann Arbor classification)

Stage	Definition
I	Involvement of a single lymph node region (I) or extralymphatic* site (I_E)
II	Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side of (above or below) the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm with (III_E) or without (III) localised extralymphatic involvement or involvement of the spleen (III_S), or both (III_{SE})
IV	Diffuse involvement of one or more extralymphatic tissues, e.g. liver or bone marrow
Each stage is subclassified:	
A	No systemic symptoms
B	Weight loss >10%, drenching sweats, fever

*The lymphatic structures are defined as the lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches.

Nodular lymphocyte-predominant HL is slow-growing, localized and rarely fatal. It has biological features, such as CD20-positive Hodgkin cells, and clinical features that make it more akin to a low-grade B-cell non-Hodgkin lymphoma.

Clinical Features:

* There is painless, rubbery lymphadenopathy, usually in the neck or supraclavicular fossae; the lymph nodes may fluctuate in size.
* Young patients with nodular sclerosing disease may have large mediastinal masses that are surprisingly asymptomatic but may cause dry cough and some breathlessness.
* Isolated subdiaphragmatic nodes occur in fewer than 10% at diagnosis.
* Hepatosplenomegaly may be present but does not always indicate disease in those organs.
*Spread is contiguous from one node to the next, and extranodal disease, such as bone, brain or skin involvement, is rare

Investigations:

Treatment of HL depends on the stage at presentation; investigations therefore aim not only to diagnose lymphoma but also to determine the extent of disease.

- FBC may be normal. If a normochromic, normocytic anaemia or lymphopenia is present, this is a poor prognostic factor. An eosinophilia or a neutrophilia may be present.
- ESR may be raised.
- LDH measurements showing raised levels are an adverse prognostic factor.
- Chest X-ray may show a mediastinal mass.
- CT scan of chest, abdomen and pelvis permits staging. Bulky disease (> 10 cm in a single node mass) is an adverse prognostic feature.
- Positron emission tomography (PET) scanning identifies nodes involved with HL, which are 18fluorodeoxyglucose (FDG)-avid, and this allows more accurate staging and monitoring of response.
- Lymph node biopsy may be undertaken surgically or by percutaneous

Management:

(a) Early stage:

*Clinical trials have shown that patients with early-stage disease (stages IA and IIA) have better outcomes if limited cycles of chemotherapy are combined with radiotherapy, rather than using radiotherapy alone.

*The ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) is widely used.

*Standard therapy for early-stage patients without additional risk factors, such as bulk disease or high ESR, is two cycles of ABVD combined with 20 Gy radiotherapy to the involved sites of disease.

*Standard therapy for early-stage patients with additional risk factors is four cycles of ABVD combined with 30 Gy radiotherapy.

*Patients with advanced-stage disease are most commonly managed with chemotherapy alone. Standard treatment in the UK is 6–8 cycles of ABVD, followed by an assessment of response. Also more intensive regimens such as BEACOPP can be used.

Prognosis:

* Over 90% of patients with early-stage HL achieve complete remission when treated with chemotherapy followed by involved field radiotherapy, and the great majority are cured.

* Historically, between 50 and 70% of those with advanced-stage HL were cured.

(B) Non-Hodgkin lymphoma:

* Non-Hodgkin lymphoma (NHL) represents a monoclonal proliferation of lymphoid cells of B-cell (90%) or T-cell (10%) origin. The incidence of these tumours increases with age, to 62.8/million population per annum at age 75 years, and the overall rate is increasing at about 3% per year.
* Previous classifications were based principally on histological appearances. The current WHO classification stratifies according to cell lineage (T or B cells) and incorporates clinical features, histology, chromosomal abnormalities and concepts related to the biology of the lymphoma.
* Clinically, the most important factor is grade, which is a reflection of proliferation rate.
* High-grade NHL has high proliferation rates, rapidly produces symptoms, is fatal if untreated, but is potentially curable.
* Low-grade NHL has low proliferation rates, may be asymptomatic for many months or even years before presentation, runs an indolent

Clinical features:

* Unlike Hodgkin lymphoma, NHL is often widely disseminated at presentation, including in extranodal sites.
* Patients present with lymph node enlargement, which may be associated with systemic upset: weight loss, sweats, fever and itching.
* Hepatosplenomegaly may be present.
* Sites of extranodal involvement include the bone marrow, gut, thyroid, lung, skin, testis, brain and, more rarely, bone.
* Bone marrow involvement is more common in low-grade (50–60%) than high-grade (10%) disease.
* Compression syndromes may occur, including gut obstruction, ascites, superior vena cava obstruction and spinal cord compression.
* The same staging system is used for both HL and NHL, but NHL is more likely to be stage III or IV at presentation.

Investigations :

These are as for HL, but in addition the following should be performed:

- Bone marrow aspiration and trephine to identify bone marrow involvement.
- Immunophenotyping of surface antigens to distinguish T-cell from B-cell tumours. This may be done on blood, marrow or nodal material.
- Cytogenetic analysis to detect chromosomal translocations and molecular testing for T-cell receptor or immunoglobulin gene rearrangements.
- Immunoglobulin determination. Some lymphomas are associated with IgG or IgM paraproteins, which serve as markers for treatment response.
- Measurement of uric acid levels. Some very aggressive high-grade NHLs are associated with very high urate levels, which can precipitate renal failure when treatment is started.
- HIV testing. HIV is a risk factor for some lymphomas and affects treatment decisions.

Management:

(A) Low-grade NHL

The majority of patients (80%) present with advanced stage disease and will run a relapsing and remitting course over several years.

Asymptomatic patients may not require therapy and are managed by 'watching and waiting'.

Indications for treatment include marked systemic symptoms, lymphadenopathy causing discomfort or disfigurement, bone marrow failure or compression syndromes.

In follicular lymphoma, the options are:

- Radiotherapy. This can be used for localised stage I disease, which is rare.
- Chemotherapy. Most patients will respond to oral therapy with chlorambucil, which is well tolerated but not curative. More intensive intravenous chemotherapy in younger patients produces better quality of life but no survival benefit.
- Monoclonal antibody therapy. Humanised monoclonal antibodies

The anti-CD20 antibody rituximab has been shown to induce durable clinical responses in up to 60% of patients when given alone, and acts synergistically when given with chemotherapy. Rituximab (R) in combination with cyclophosphamide, vincristine and prednisolone (R-CVP), cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) or bendamustine (R-bendamustine) is commonly used as first-line therapy.

- Kinase inhibitors. Idelalisib is approved for relapsed follicular lymphoma and ibrutinib (p. 960) is approved for relapsed mantle cell lymphoma, a poor-prognosis lymphoma with low-grade histology but aggressive clinical behaviour. These targeted therapies are likely to become more widely used in low-grade lymphomas in the near future.

- Transplantation. High-dose chemotherapy and autologous HSCT can produce long remissions in patients with relapsed disease

(B) High Grade NHL:

Patients with diffuse large B-cell NHL need treatment at initial presentation:

* Chemotherapy:

  The majority (> 90%) are treated with intravenous combination chemotherapy, typically with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone).

* Monoclonal antibody therapy: When combined with CHOP chemotherapy, rituximab (R) increases the complete response rates and improves overall survival. R-CHOP is currently recommended as first-line therapy for those with stage II or higher diffuse large B-cell lymphoma.

* Radiotherapy: Stage I patients without bulky disease are treated with four cycles of CHOP or R-CHOP, followed by involved site radiotherapy. Radiotherapy is also indicated for a residual localised site of bulk disease after chemotherapy, and for spinal cord and other compression syndromes.

* HSCT: Autologous HSCT benefits patients with relapsed disease that is sensitive to salvage immunochemotherapy. As with HL, achieving PET

Prognosis:

Low-grade NHL runs an indolent remitting and relapsing course, with an overall median survival of 12 years. Transformation to a high-grade NHL occurs in 3% per annum and is associated with poor survival.

In diffuse large B-cell NHL treated with R-CHOP, some 75% of patients overall respond initially to therapy and 50% will have disease-free survival at 5 years.

Relapse is associated with a poor response to further chemotherapy (< 10% 5-year survival), but in patients under 65 years HSCT improves survival

الطلبة الأعزاء

هذا ملخص بسيط عن تخصص الأورام بما يتلاءم مع المنهاج الدراسي عندكم

نتمنى لكم التوفيق و النجاح

