23-33 Oncology

33 Oncology

1314 • ONCOLOGY Clinical examination of the cancer patient Observation Breast Lymph nodes Neck Supraclavicular Axillary Antecubital Inguinal Para-aortic Face Conjunctival pallor Icterus, jaundice Horner’s syndrome Cushingoid features Cardiovascular Superior vena cava (SVC) obstruction Atrial fibrillation Pericardial effusion Hypo-/hypertension Abdomen Surgical scars Umbilical nodule Mass in epigastrium Visible peristalsis Abdominal distension Ascites Hepatomegaly Splenomegaly Renal mass Pelvic or adnexal mass Respiratory Stridor Consolidation Pleural effusion • Skin changes • Ascites • Cushingoid appearance • Cachexia • Dehydration Hands Clubbing Signs of smoking Pallor Tylosis of palms Periphery Calf tenderness, venous thrombosis Clubbing (if present in hands) Skin tethering above the nipple Cushing’s syndrome in a patient with ectopic adrenocorticotrophic hormone (ACTH) production Finger clubbing in lung cancer SVC obstruction in a patient with a mediastinal mass Skeletal survey Focal bone tenderness (pelvis,

spine, long bones) Wrist tenderness (hypertrophic pulmonary osteoarthropathy) Neurological Focal neurological signs Sensory deficit Spinal cord compression Memory deficit Personality change Ascites (ovarian carcinoma)

Supraclavicular Axillary Epitrochlear Inguinal Femoral Popliteal fossa Pre-auricular Parotid Submandibular Submental Posterior cervical Supraclavicular Anterior cervical 3 Examination of the lymph nodes 7 Abdominal examination • Are there scars from previous surgery? • Is the umbilicus everted, suggesting ascites? • Is there a firm nodule at the umbilicus due to ovarian or gastric cancer metastasis, causing a Sister Mary Joseph nodule (p. 1334)? • Is there smooth hepatomegaly – possibly primary liver cancer or heart failure? • Is the liver firm or knobbly, suggesting metastasis? • Is the ascites too tense to demonstrate hepatomegaly? • Are other masses palpable in the abdomen? • Are there signs of obstruction or paralytic ileus with absence of bowel sounds? • Palpate for inguinal nodes (occasionally involved in ovarian cancer) • Percuss for flank dullness and shifting dullness • Perform vaginal and rectal examinations to detect adnexal or rectal masses Examination of the skin Important features of skin lesions that should alert suspicion include: • Asymmetry: irregular shape • Bleeding • Border: not a smooth edge • Colour: uneven, variegated or changing colour • Diameter: > 6 mm in diameter or growing • Itching or pain in a pre-existing mole 5 Superior vena cava obstruction • Venous distension of neck • Elevated but non-pulsatile jugular venous pulse • Venous distension of chest wall • Facial oedema • Cyanosis • Plethora of face • Oedema of arms 5 Pericardial effusion • Tachycardia • Falling blood pressure • Rising jugular venous pressure • Muffled heart sounds • Kussmaul’s sign (p. 544) 6 Malignant pleural effusions Large right pleural effusion Inspection Tachypnoea Palpation ↓Expansion on R Trachea and apex may be moved to L Percussion Stony dull R mid- and lower zones Auscultation Absent breath sounds and diminished or absent vocal resonance R base Crackles above effusion

1. Genome instability and mutation Random genetic mutations occur continuously throughout all cells of the body and very rarely confer a selective advantage on single cells, allowing overgrowth and dominance in local tissue environments. 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 develop DNA repair mechanism failure.
2. Resisting cell death There are three principal mechanisms through which cell death occurs in healthy tissues: apoptosis, autophagy and necrosis. 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 phagocytosed by neighbouring cells. The most important regulator of apoptosis is the TP53 tumour 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. 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. Necrosis This is the premature death of cells and is characterised 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 phagocytosed. Necrotic cell death results in the recruitment of inflammatory immune cells, promotion of angiogenesis, and release of stimulatory factors that increase cellular proliferation Fig. 33.1 The most commonly diagnosed cancers in the UK. (NHL = non-Hodgkin lymphoma) Statistics from Cancer Research UK website (http://info.cancerresearchuk.org). NHL Bladder Prostate Large bowel Lung Breast

Stomach Head and neck Oesophagus Melanoma Pancreas Ovary Leukaemia Kidney Body of uterus Other

Number of new cases (thousands) Male Female Cancer represents a significant economic burden for the global economy and is now the third leading cause of death worldwide. By 2030, it is projected that there will be 26 million new cancer cases and 17 million cancer deaths per year. The developing world is disproportionately affected by cancer and in 2008 developing nations accounted for 56% of new cancer cases and 75% of cancer deaths. These deaths happen in countries with limited or no access to treatment and with low per capita expenditure on health care. The most common solid organ malignancies arise in the lung, breast and gastrointestinal tract (Fig. 33.1), but the most common form worldwide is skin cancer. Cigarette smoking accounts for more than 20% of all global cancer deaths, 80% of lung cancer cases in men and 50% of lung cancer cases in women worldwide, which could be prevented by smoking cessation. Diet and alcohol contribute to a further 30% of cancers, including those of the stomach, colon, oesophagus, breast and liver. Lifestyle modification could reduce these if steps were taken to avoid animal fat and red meat, reduce alcohol, increase fibre, fresh fruit and vegetable intake, and avoid obesity. Infections account for a further 15% of cancers, including those of the cervix, stomach, liver, nasopharynx and bladder, and some of these could be prevented by infection control and vaccination. 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.

that have occurred during DNA replication and thus preventing propagation of these errors to daughter cells. Although the duration of individual phases may vary, depending on cell and tissue type, most adult cells are in a G0 state at any one time. 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 tumour prevention and are referred to as tumour 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. 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 Ras–Raf–mitogen activated protein (MAP) kinase pathway, causing cell proliferation. and tissue invasion, thereby enhancing rather than inhibiting carcinogenesis. 3. Sustaining proliferative signalling 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 signalling 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 signalling pathway components, so that signalling is no longer ligand-dependent. 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). Normal cells grown in culture will stop proliferating and enter a quiescent state called G0 once they become confluent or are deprived of serum or growth factors. 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, utilising 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 Fig. 33.2 The cell cycle and sites of action of chemotherapeutic agents. (CDK = cyclin-dependent kinase; RB = retinoblastoma gene) Quiescent DNA replication G2 Mitosis Terminal differentiation Apoptosis G2 checkpoint for DNA damage DNA replication incomplete Prophase → telophase Nuclear and cellular division Terminal differentiation Apoptosis Further growth or DNA repair S M G1 Cell growth G0 G1 checkpoint for Damaged DNA RB blocks TP53 → CDKs blocked Restriction point (regulated by growth factors) Antimetabolites Mitotic spindle poisons Topoisomerase inhibitors Antibiotics and

alkylating agents (act on entire cycle) Cyclin A CDK2 Cyclin B CDK1 Cyclin D CDK4, 6 Cell growth Cyclin E CDK2

1318 • ONCOLOGY 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. 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. Tumours 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 characterised. During tumour progression, an angiogenic switch is activated and remains on, causing normally quiescent vasculature to sprout new vessels continually that help sustain expanding tumour 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 tumour 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. 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 tumours, 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. Down-regulation of p21 and p27, which can be found in tumours with normal TP53 function, correlates notably with high tumour grade and poor prognosis. 5. Enabling replicative immortality For cancer cells to evolve into macroscopic tumours, they need to acquire the ability for unlimited proliferation. Telomeric DNA sequences, which protect and stabilise 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 specialised polymerase enzyme, adds nucleotides Fig. 33.3 Oncogenesis. The multistep origin of cancer, showing events implicated in cancer initiation, progression, invasion and metastasis. Basal lamina First mutation Inherited or acquired gain of oncogene Loss of tumour suppressor gene Normal epithelium Blood vessel Connective tissue Lymphatic First mutation Initial proliferation Small adenoma Further mutation Further mutation; subset selected for rapid growth Carcinoma Further mutation → invasion or metastasis Blood spread Lymphatic spread Ectopic growth factor production and autostimulation Failed apoptosis (e.g. TP53 mutation) Local invasion through basal lamina ↑ Angiogenesis to support tumour growth (see Fig. 33.4) Breakdown of connective tissue via tumour production of e.g. collagenase tissue metalloproteinases Loss of cell adhesion molecules e.g. E-cadherin

energy production to glycolysis, even in the presence of oxygen. This has been termed ‘aerobic glycolysis’. Up-regulation 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 amino acids, necessary for the production of new cells. 9. Tumour-promoting inflammation Almost all tumours 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 tumour-associated inflammatory responses promote tumour 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 acellular biochemical cascade systems consisting of pre-formed plasma proteins act in parallel to initiate and propagate the inflammatory response. These include the complement system activated by bacteria, and the coagulation and fibrinolytic systems activated by necrosis, and also in burns and trauma, as well as cancer. Other bioactive molecules, such as growth factors and pro-angiogenic factors, may be released by inflammatory immune cells into the surrounding tumour microenvironment. In particular, the release of reactive 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 organised cell sheets in tissues, and increased expression is recognised as an antagonist of invasion and metastasis. In situ tumours 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 tumour stroma 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 behaviour. Macrophages at the tumour 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 Fig. 33.4 Angiogenesis, invasion and metastasis. A For any cancer to grow beyond 1 mm3, it must evoke a blood supply. B New vessel formation results from the release of angiogenic factors by the tumour cells and loss of inhibition of the endothelial cells. C The loss of cellular adhesion and disruption of the extracellular matrix allow cells to extravasate into the blood stream and metastasise to distant sites. (VEGF= vascular endothelial growth factor) Inhibition Loss of inhibition Viable tumour cell Apoptoptic tumour cell Angiogenic factors VEGF VEGF receptor Tissue factor αvβ3 integrin Plasminogen Coagulation factor Coagulation Fibrinogen Fibrin Cell adhesion Urokinase Urokinase receptor Proteolysis Plasmin A B C

1320 • ONCOLOGY Environmental and genetic determinants of 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 to environmental carcinogens. These are often tumour type-specific but some general principles do apply. 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 (Box 33.1). Smoking is now established beyond all doubt as a major cause of lung cancer, but there are obviously additional predisposing factors since not all smokers develop cancer. Similarly, most carcinomas of the cervix are related to infection with human oxygen species, which are actively mutagenic, will accelerate the genetic evolution of surrounding cancer cells, enhancing growth and contributing to cancer progression. 10. Evading immune destruction The immune system operates as a significant barrier to tumour 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 (see Fig. 4.12, p. 80). Cancers develop and progress when there is loss of recognition by the immune system, lack of susceptibility due to escape from immune cell action and induction of immune dysfunction, often via inflammatory mediators. 33.1 Environmental factors that predispose to cancer Environmental aetiology Processes Diseases Occupational exposure (see ‘Radiation’ below) Dye and rubber manufacturing (aromatic amines) Bladder cancer Asbestos mining, construction work, shipbuilding (asbestos) Lung cancer and mesothelioma Vinyl chloride (PVC) manufacturing Liver angiosarcoma Petroleum industry (benzene) 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 Burkitt’s lymphoma and nasopharyngeal cancer Human papillomavirus Cervical cancer Hepatitis B and C viruses Hepatocellular carcinoma Bacterial infection Helicobacter pylori Gastric MALT lymphomas, gastric cancer Parasitic infection Liver fluke (Opisthorchis sinensis)

Cholangiocarcinoma Schistosoma haematobium Squamous cell bladder cancer Dietary factors Low-roughage/high-fat content diet Colonic cancer High nitrosamine intake Gastric cancer Aflatoxin from contamination of Aspergillus flavus Hepatocellular cancer Radiation UV exposure Basal cell carcinoma Melanoma Non-melanocytic skin cancer Nuclear fallout following explosion (e.g. Hiroshima) Leukaemia Solid tumours, e.g. thyroid Diagnostic exposure (e.g. CT) Cholangiocarcinoma following Thorotrast usage Occupational exposure (e.g. beryllium and strontium mining) Lung cancer Therapeutic radiotherapy Medullary thyroid cancer Sarcoma Inflammatory diseases Ulcerative colitis Colon cancer Hormonal Use of diethylstilbestrol Vaginal cancer Oestrogens Endometrial cancer Breast cancer (CT = computed tomography; MALT = mucosa-associated lymphoid tissue; UV = ultraviolet)

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. 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 (pp. 1314–1315). In order to make a diagnosis and to plan the most appropriate management, information is needed on: • the type of tumour • the extent of disease, as assessed by staging investigations • the patient’s general condition and any comorbidity. papillomavirus (HPV subtypes 16 and 18). For carcinomas of the bowel and breast, there is strong evidence of an environmental component. For example, the risk of breast cancer in women of Far Eastern origin remains relatively low when they first migrate to a country with a Western lifestyle, but rises in subsequent generations to approach that of the resident population of the host country. The precise environmental factor that causes this change is unclear but may include diet (higher intake of saturated fat and/or dairy products), reproductive patterns (later onset of first pregnancy) and lifestyle (increased use of artificial light and shift in diurnal rhythm). Genetic factors A number of inherited cancer syndromes are recognised that account for 5–10% of all cancers (Box 33.2). Their molecular basis is discussed in Chapter 3, but 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 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)

1322 • ONCOLOGY 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. Light microscopy Examination of tumour 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 tumour: • Signet-ring cells favour a gastric primary. • Presence of melanin favours 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 −). Immunohistochemistry Immunohistochemical (IHC) staining for tumour markers can provide useful diagnostic information and can help with treatment decisions. Commonly used examples of IHC in clinical practice include: • Oestrogen (ER) and progesterone (PR) receptors. Positive results indicate that the tumour may be sensitive to hormonal manipulation. • Alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) with or without placental alkaline phosphatase (PLAP). These favour germ-cell tumours. • Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP). These favour prostate cancer. • Carcinoembryonic antigen (CEA), cytokeratin and epithelial membrane antigen (EMA). These favour epithelial carcinomas. • HER2 receptor. Breast cancers that have high levels of expression of HER2 indicate that the tumour 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. Electron microscopy Electron microscopy (EM) can sometimes be of diagnostic value. Examples include the visualisation of melanosomes in amelanotic melanoma and dense core granules in neuro-endocrine tumours. 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 tumours (sarcomas, melanomas, squamous cell cancers) from small round-cell tumours, again due to their ultrastructural differences. Cytogenetic analysis Some tumours demonstrate typical chromosomal changes that help in diagnosis. The utilisation of fluorescent in situ hybridisation (FISH) techniques can be useful in Ewing's sarcoma and peripheral neuro-ectodermal tumours 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). The overall fitness of a patient is often assessed by the Eastern Cooperative Oncology Group (ECOG) performance status scale (Box 33.3). 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 patient. The process of staging determines the extent of the tumour; 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 T (tumour), N (regional lymph nodes), M (metastatic sites) approach of the International Union against Cancer (UICC, Box 33.4). For some tumours, such as colon cancer, the Dukes system (p. 832) is used rather than the UICC classification. Histology 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 Extent of primary tumour* TX Not assessed T0 No tumour Increases in primary tumour size or depth of invasion T1 T2 T3 T4 Increased involvement of nodes* NX Not assessed N0 No nodal involvement N1 Increases in involvement N2/3 Presence of metastases MX Not assessed M0 Not present M1 Present *Exact criteria for size and region of nodal involvement have been defined for each anatomical site. } } 33.4 TNM classification 33.3 Eastern Cooperative Oncology Group (ECOG) performance status scale

Fully active, able to carry on all usual activities without restriction and without the aid of analgesics

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

Ambulatory and capable of all self-care but unable to work. Up and about more than 50% of waking hours

Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

Completely disabled, unable to carry out any self-care and confined totally to bed or chair

metastatic disease or from non-metastatic manifestations due to production of biologically active hormones by the tumour or as the result of an immune response to the tumour. The possible presentations are summarised in Boxes 33.6 and 33.7, and common presenting features discussed below. Although the incidence of cancer increases with patient age, the approach to investigation and management is similar at all ages (Box 33.8). Palpable mass A palpable mass detected by the patient or physician may be the first sign of cancer. Primary tumours of the thyroid, breast, testis and skin are often detected in this way, whereas palpable lymph nodes in the neck, groin or axilla may indicate secondary spread of tumour. Hepatomegaly may be the first sign of primary liver cancer or tumour metastasis, whereas skin cancer may present as an enlarging or changing pigmented lesion. Weight loss and fever Unintentional weight loss is a characteristic feature of advanced cancer, but can have other causes such as thyrotoxicosis, chronic inflammatory disease and chronic infective disorders. Fever can occur in any cancer secondary to infection, but may be a primary feature in Hodgkin and non-Hodgkin lymphoma, leukaemia, renal cancer and liver cancer. The presence of unexplained weight loss or fever warrants investigation to exclude the presence of

occult malignancy. Imaging Imaging plays a critical role in oncology, not only in locating the primary tumour 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. Ultrasound Ultrasound is useful in characterising lesions within the liver, kidney, pancreas and reproductive organs. It can be used for guiding biopsies of tumours in breast and liver. Endoscopic ultrasound is helpful in staging upper gastrointestinal and pancreatic cancers, involving a special endoscope with an ultrasound probe attached. 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 visualise the large bowel if it is prepared (CT colonography), allowing accurate detection of colorectal cancers and adenomas ≥ 10 mm. 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 for the staging of rectal, cervical and prostate cancers. Positron emission tomography Positron emission tomography (PET) visualises metabolic activity of tumour 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 tumour 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. Biochemical markers Many cancers produce substances called tumour 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 tumour 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. Tumour markers in routine use are outlined in Box 33.5. 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 tumour progression, localised 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 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. A B

1324 • ONCOLOGY 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 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 Thromboembolism Thrombosis and disseminated intravascular coagulation (DIC) are common complications in patients with cancer. The prothrombotic state is caused by cancer cells activating the coagulation system via factors such as tissue factor, cancer procoagulant and inflammatory cytokines. The interaction between tumour cells, monocytes/macrophages, platelets and endothelial cells can promote thrombus formation, as part of a host response to the cancer (i.e. acute phase, inflammation, angiogenesis) or via a reduction in the levels of inhibitors of coagulation or impairment

parathyroid hormone-related protein (PTHrP). This can result in a wide variety of presentations, as summarised in Box 33.9. Further details on the presentation and management of ACTH- and vasopressin-producing tumours are given on page 670, and those of FGF23-producing tumours on page 1053. The management of hypercalcaemia associated with malignancy is discussed below. Neurological paraneoplastic syndromes These form a group of conditions associated with cancer that are thought to be due to an immunological response to the tumour that results in damage to the nervous system or muscle. The cancers most commonly implicated are those of the lung (small cell and non-small cell), pancreas, breast, prostate, ovary and lymphoma. • Peripheral neuropathy results from axonal degeneration or demyelination. • Encephalomyelitis can present with diverse symptoms, depending on which region of the brain is involved. Lumbar puncture shows raised protein in the cerebrospinal fluid and a pleocytosis, predominantly that of lymphocytes. In some centres, flow cytometry of the cerebrospinal fluid can be used to detect carcinomatous cells. MRI shows meningeal enhancement, particularly at the level of the brainstem, and anti-Hu antibodies

may be detectable in serum. Encephalomyelitis is due to perivascular inflammation and selective neuronal degeneration. Most cases are caused by small cell lung cancer (75%). • Cerebellar degeneration may be the presenting feature of an underlying malignancy and presents with rapid onset of cerebellar ataxia. Diagnosis is by MRI or CT, which may show cerebellar atrophy. Patients with these neurological paraneoplastic syndromes may be found to have circulating anti-Yo, Tr and Hu antibodies, but these are not completely specific and negative results do not exclude the diagnosis. • Retinopathy is a rare complication of cancer and presents with blurred vision, episodic visual loss and impaired colour vision. If left untreated, it may lead to blindness. The diagnosis should be suspected if the electroretinogram is abnormal and anti-retinal antibodies are detected. • Lambert–Eaton myasthenic syndrome (LEMS) is due to underlying cancer in about 60% of cases. It presents with of fibrinolysis. Furthermore, the prothrombotic tendency can be enhanced by therapy such as surgery, chemotherapy, hormone therapy and radiotherapy, and by in-dwelling access devices (i.e. central venous catheters). In some patients, the thromboembolism is the first presenting feature of the underlying cancer. Ectopic hormone production In some cases, the first presentation of cancer is with a metabolic abnormality due to ectopic production of hormones by tumour cells, including insulin, ACTH, vasopressin (antidiuretic hormone, ADH), fibroblast growth factor (FGF)-23, erythropoietin and 33.8 Cancer in old age • Incidence: around 50% of cancers occur in the 15% of the population aged over 65 years. • Screening: women aged over 65 in the UK are not invited to breast cancer screening but can request it. Uptake is low despite increasing incidence with age. • Presentation: may be later for some cancers. When symptoms are non-specific, patients (and their doctors) may initially attribute them to age alone. • Life expectancy: an 80-year-old woman can expect to live 8 years, so cancer may still shorten life and an active approach remains appropriate. • Prognosis: histology, stage at presentation and observation for a brief period are better guides to outcome than age. • Rate of progression: malignancy may have a more indolent course. This is poorly understood but may be due to reduced effectiveness of angiogenesis with age, inhibiting the development of metastases. • Response to treatment: equivalent to that in younger people – well documented for a range of cancers and for surgery, radiotherapy, chemotherapy and hormonal therapy. • Treatment selection: chronological age is of minor importance compared to comorbid illness and patient choice. Although older patients can be treated effectively and safely, aggressive intervention is not appropriate for all. Symptom control may be all that is possible or desired by the patient. 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)

1326 • ONCOLOGY neuron findings may predominate early on or in cases of nerve root compression. Management Spinal cord compression is a medical emergency and should be treated with analgesia and high-dose glucocorticoid therapy (Box 33.11). Neurosurgical intervention produces superior outcome and survival compared to radiotherapy alone, and should be considered first for all patients. Radiotherapy is used for the remaining patients and selected tumour types when the cancer is likely to be radiosensitive. The prognosis varies considerably, depending on tumour type, but the degree of neurological dysfunction at presentation is the strongest predictor of outcome, irrespective of the underlying diagnosis. Mobility can be preserved in more than 80% of patients who are ambulatory at presentation, but neurological function is seldom regained in patients with established deficits such as paraplegia. Superior vena cava obstruction Superior vena cava obstruction (SVCO) is a common complication of cancer that can occur through extrinsic compression or intravascular blockage. The most common causes of extrinsic compression are lung cancer, lymphoma and metastatic tumours. Patients with cancer can also develop SVCO due to intravascular blockage in association with a central catheter or thromboembolism secondary to the tumour. Clinical features The typical presentation is with oedema of the arms and face, distended neck and arm veins and dusky skin coloration over the chest, arms and face. Collateral vessels may develop over a period of weeks and the flow of blood in the collaterals helps to confirm the diagnosis. Headache secondary to cerebral oedema arising from the backflow pressure may also occur and tends to be aggravated by bending forwards, stooping or lying down. The severity of symptoms is related to the rate of obstruction and the development of a venous collateral circulation. Accordingly, symptoms may develop rapidly or gradually. Clinical features are summarised in Box 33.12. proximal muscle weakness that improves on exercise and is caused by the development of antibodies to presynaptic calcium channels (p. 1143). The diagnosis is made by electromyelogram (EMG), which shows a low-amplitude compound muscle action potential that enhances to near normal following exercise. • Dermatomyositis or polymyositis may be the first presentation of some cancers. Clinical features and management of these conditions are discussed on page 1039. Cutaneous manifestations of cancer Many cancers can present with skin manifestations that are not due to metastases: • Pruritus may be a presenting feature of lymphoma, leukaemia and central nervous system tumours. • Acanthosis nigricans may precede cancers by many years and is particularly associated with gastric cancer. • Vitiligo may be associated with malignant melanoma and is possibly due to an immune response to melanocytes. • Pemphigus may occur in lymphoma, Kaposi’s sarcoma and thymic tumours. • Dermatitis herpetiformis associated with coeliac disease may precede tumour development by many years, and is associated with gastrointestinal lymphoma. The clinical features and management of these skin conditions are discussed in Chapter 29. Emergency complications of cancer Spinal cord compression Spinal cord compression complicates 5% of cancers and is most common in myeloma, prostate, breast and lung cancers that involve bone. Cord compression often results from posterior extension of a vertebral body mass but intrathecal spinal cord metastases can cause similar signs and symptoms. The thoracic region is most commonly affected. Clinical features The earliest sign is back pain, particularly on coughing and lying flat. Subsequently, sensory changes develop in dermatomes below the level of compression and motor weakness distal to the block occurs. Finally, sphincter disturbance, causing urinary retention and bowel incontinence, is observed. Involvement of the lumbar spine may cause conus medullaris or cauda equina compression (Box 33.10). Physical examination reveals findings consistent with an upper motor neuron lesion, but lower motor 33.11 Management of suspected spinal cord compression • Confirm diagnosis with urgent MRI scan • Administer high-dose glucocorticoids: Dexamethasone 16

mg IV stat Dexamethasone 8 mg twice daily orally • Ensure adequate analgesia • Refer for surgical decompression or urgent radiotherapy 33.10 Comparison of features of neurological deficit Clinical feature Spinal cord Conus medullaris Cauda equina Weakness Symmetrical and profound Symmetrical and variable Asymmetrical, may be mild Reflexes Increased (or absent) knee and ankle reflexes with extensor plantar reflex Increased knee reflex, decreased ankle reflex, extensor plantar reflex Decreased knee and ankle reflexes with flexor plantar reflex Sensory loss Symmetrical, sensory level Symmetrical, saddle distribution Asymmetrical, radicular pattern Sphincters Late loss Early loss Often spared Progression Rapid Variable Variable

Patients should initially be treated with intravenous 0.9% saline to improve renal function and increase urinary calcium excretion. This alone often results in clinical improvement. Concurrently, intravenous bisphosphonates should be given to inhibit bone resorption. Calcitonin acts rapidly to increase calcium excretion and to reduce bone resorption, and can be combined with fluid and bisphosphonate therapy for the first 24–48 hours in patients with life-threatening hypercalcaemia. Bisphosphonates will usually reduce the serum calcium levels to normal within 5 days, but, if not, treatment can be repeated. The duration of action is up to 4 weeks and repeated therapy can be given at 3–4-weekly intervals in the outpatient department. Hypercalcaemia is frequently a sign of tumour progression and the patient requires further investigation to establish disease status and review of the anti-cancer treatment strategy. Neutropenic fever Neutropenia is a common complication of malignancy. It is usually secondary to chemotherapy but may occur with radiotherapy if large amounts of bone marrow are irradiated; it may also be a component of pancytopenia due to malignant infiltration of the bone marrow. Neutropenic fever is defined as a pyrexia of 38°C for over 1 hour in a patient with a neutrophil count of $< 0.5 \times 109/L$ or $< 1.0 \times 109/L$ if the nadir is anticipated to drop to $< 0.5 \times 109/L$ in the next 24 hours. The risk of sepsis is related to the severity and duration of neutropenia and the presence of other risk factors, such as intravenous cannulae or bladder catheters. Neutropenic fever is an emergency in cancer patients as, if left untreated, it can result in sepsis with a high mortality rate. Clinical features The typical presentation is with high fever, and affected patients are often non-specifically unwell. Examination is usually unhelpful in defining a primary source of the infection. Hypotension is an adverse prognostic feature and may progress to systemic circulatory shutdown and organ failure. Investigations and management An infection screen should be performed to include blood cultures (both peripheral and from central lines), urine culture, chest X-ray, and swabs for culture (throat, central line, wound). High-dose intravenous antibiotics should then be commenced, pending the results of cultures. The standard approach is to commence empirical antibiotics according to local hospital policies agreed with microbiologists and based on the local antibiotic resistance patterns observed. First-line empirical therapy is either monotherapy with piperacillin–tazobactam or meropenem, or with the addition of gentamicin. Metronidazole may be added if anaerobic infection is suspected, and teicoplanin where Gram-positive infection is suspected (e.g. in patients with central lines). Antibiotics should be adjusted according to culture results, although these are often negative. If there is no response after 36–48 hours, antibiotics should be reviewed with microbiological advice, and antifungal cover should be considered Investigations and management The investigation of choice is a CT scan of the thorax to confirm the diagnosis and distinguish between extra- and intravascular causes. A biopsy should be obtained when the tumour type is unknown because tumour type has a major influence on treatment. CT of the head may be

indicated if cerebral oedema is suspected. Tumours that are exquisitely sensitive to chemotherapy, such as germ cell tumours and lymphoma, can be treated with chemotherapy alone, but for most other tumours mediastinal radiotherapy is required. This relieves symptoms within 2 weeks in 50–90% of patients. In many centres, stenting is now increasingly favoured over radiotherapy, as it produces rapid results and can be repeated with reasonable effectiveness. This technique is particularly useful when dealing with tumours that are relatively chemo- or radio-resistant, such as non-small cell lung cancer or carcinoma of unknown primary. Where possible, these measures should be followed by treatment of the primary tumour, as long-term outcome is strongly dependent on the prognosis of the underlying cancer. Hypercalcaemia Hypercalcaemia is the most common metabolic disorder in patients with cancer and has a prevalence of up to 20% in cancer patients. The incidence is highest in myeloma and breast cancer (approximately 40%), intermediate in non-small cell lung cancer, and uncommon in colon, prostate and small cell lung carcinomas. It is most commonly due to over-production of PTHrP (80%), which binds to the PTH receptor and elevates serum calcium by stimulating osteoclastic bone resorption and increasing renal tubular reabsorption of calcium. Direct invasion of bone by metastases accounts for around 20% of cases while other mechanisms, such as ectopic PTH secretion, are rare. Clinical features The symptoms of hypercalcaemia are often non-specific and may mimic those of the underlying malignancy. They include drowsiness, delirium, nausea and vomiting, constipation, polyuria, polydipsia and dehydration. Investigations and management The diagnosis is made by measuring serum total calcium and adjusting for albumin. It is especially important to correct for albumin in cancer because hypoalbuminaemia is common and total calcium values under-estimate the level of ionised calcium. The principles of management are outlined in Box 33.13. *Percentage of patients affected. 33.12 Common symptoms and physical findings in superior vena cava obstruction* Symptoms • Dyspnoea (63%) • Facial swelling and head fullness (50%) • Cough (24%) • Arm swelling (18%) • Chest pain (15%) • Dysphagia (9%) Physical findings • Venous distension of neck (66%) • Venous distension of chest wall (54%) • Facial oedema (46%) • Cyanosis (20%) • Plethora of face (19%) • Oedema of arms (14%) 33.13 Medical management of severe hypercalcaemia • IV 0.9% saline 2–4 L/day • Zoledronic acid 4 mg IV or pamidronate 60–90 mg IV • For patients with severe, symptomatic hypercalcaemia that is refractory to zoledronic acid, denosumab (initial dose 60 mg SC, with repeat dosing based on response) is an alternative option

 efficacy of these interventions has not been proven adequately in a randomised trial setting. Patients with brain metastases as the only manifestation of an undetected primary tumour have a more favourable prognosis, with an overall median survival of 13.4 months. Tumour type also influences prognosis; breast cancer patients have a better prognosis than those with other types of cancer, and those with colorectal cancer tend to have a poorer prognosis. 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 tumour-associated oedema, 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. 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. Liver metastases Metastatic cancer in the liver can represent the sole or lifelimiting component of disease for many with colorectal cancer, ocular melanoma, neuro-endocrine tumours (NETs) and, less commonly, other tumour 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 chemoembolisation or radiofrequency ablation, can also be used, provided the number (liposomal amphotericin B). Granulocyte–colony-stimulating factor (G–CSF) is not routinely used for all patients with neutropenia and guidelines for use have been established. Other supportive therapy, including intravenous fluids, inotrope therapy, ventilation or haemofiltration, may be required. Tumour lysis syndrome The acute destruction of a large number of cells can be associated with metabolic sequelae and is called tumour lysis syndrome. It is usually related to bulky, chemosensitive disease, including lymphoma, leukaemia and germ cell tumours. More rarely, it can occur spontaneously. Clinical features Cellular destruction results in the release of potassium, phosphate, nucleic acids and purines that can cause transient hypocalcaemia, hyperphosphataemia, hyperuricaemia and hyperkalaemia. This can lead to acute impairment of renal function and the precipitation of uric acid crystals in the renal tubular system. These can manifest with symptoms associated with multiple underlying electrolyte abnormalities, including fatigue, nausea, vomiting, cardiac arrhythmia, heart failure, syncope, tetany, seizures and sudden death. Investigations and management Serum biochemistry should be monitored regularly for 48–72 hours after treatment in patients at risk. Elevated serum potassium may be the earliest biochemical marker but pre-treatment serum lactate dehydrogenase (LDH) correlates with tumour bulk and may indicate increased risk. Good hydration and urine output should be maintained throughout treatment administration. Prophylaxis with allopurinol should be considered and recombinant urate oxidase (rasburicase) can be used to reduce uric acid levels when other treatments fail. Adequate hydration is vital, as it has a dilution effect on the extracellular fluid, improving electrolyte imbalance, and increases circulating volume, improving filtration in the kidneys. In high-risk patients, hydration should be commenced 24 hours before the start of treatment. If normal treatment methods fail to correct the problems, haemodialysis should be considered at an early stage to prevent progression to irreversibility. 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. 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. Tumours that typically metastasise to the brain are shown in Box 33.14. Most involve the brain parenchyma but can also affect the cranial nerves, the blood vessels and other intracranial structures. In cases of solitary metastasis to the brain, the use of surgery and adjuvant radiotherapy has been shown to increase survival. Practices vary, however, for patients with more advanced brain metastases. In these cases, median survival without treatment is approximately 1 month. Glucocorticoids can increase survival to 2–3 months and wholebrain radiotherapy improves survival to 3–6 months, but the true 33.14 Primary tumour sites that metastasise to the brain Primary tumour Patients (%) Lung

Breast

Melanoma

Colon

Other known primary

Unknown primary

or pleuritic in nature. Diagnosis and management of ascites are discussed on page 863. 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 (Box 33.15). Those who present with malignant pleural effusion as the initial manifestation of breast cancer, small cell lung cancer, germ cell tumours 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 pleurodesis, pleurectomy and pleuroperitoneal shunt. Ideally, pleurodesis should be attempted once effusions recur after initial drainage. Therapeutics in oncology Anti-cancer therapy may be either curative or palliative, and this distinction influences the approach to management of individual patients. The goal of treatment should be recorded in the medical notes. • Palliative chemotherapy is the most common treatment and is primarily used to treat patients with metastatic disease. The goal is an improvement in symptoms with a focus on improving quality of life, and any survival increments are secondary. As a result, the treatment should be well tolerated and should aim to minimise adverse effects. • Adjuvant chemotherapy is given after an initial intervention that is designed to cyto-reduce the tumour bulk and remove all macroscopic disease. Chemotherapy is then given with the intention of eradicating the micrometastatic disease that remains. The focus is on achieving an improvement in disease-free and overall survival. and size of metastases remain small. If these are not feasible, symptoms may respond to systemic chemotherapy. 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 tumours that commonly metastasise to bone include those of the kidney and thyroid. Bone metastases are an increasing management problem in other tumour 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 (see above). 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 tumour types associated with fracture include the kidney (11%), lung (8%), thyroid (5%), lymphoma (5%) and prostate (3%). Investigations and management 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 falsenegative 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 tumours may look very similar to metastases on X-ray. The main goals of management are: • pain relief • preservation and restoration of function • skeletal stabilisation • local tumour control (e.g. relief of tumour 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 therapy or systemic radionuclides (strontium treatment), can also be useful for these patients. In some settings (e.g. breast carcinoma), chemotherapy may be used in the management of bony metastases. 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 dyspnoea, cough or chest discomfort, which can be dull 33.15 How to aspirate a malignant pleural effusion • Ask the patient to sit up and lean forwards slightly. • Identify a suitable site for aspiration. Typically, this should be in the mid-scapular line, below the top of the fluid level and above the diaphragm. • Confirm that the site is below the fluid level by reviewing the chest X-ray and percussing the chest. • Infiltrate the skin and the intercostal space immediately above the rib below with 1% lidocaine. • As you advance the needle, aspirate at each step prior to injecting the local anaesthetic. • On reaching the pleural cavity, you should be able to aspirate pleural fluid; when you do, note the depth of the needle. • Insert a thoracentesis needle into the pleural space by advancing it along the same track as was used for the local anaesthetic and connect it to a three-way tap and container to collect the fluid. • Drain the pleural effusion, to a maximum of 1.5 L. If the effusion is larger than this, repeat the procedure on further occasions as necessary. • Consider using ultrasound-guided placement of a drainage catheter if the effusion proves difficult to drain. • Permanent drains can be useful for some patients with recurrent effusions where pleurodesis is not possible.

1330 • ONCOLOGY Combination therapy 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. An increase in effectiveness can be achieved by changing the approach to treatment. In some cases this will increase toxicity too, but it can change the nature of the toxicity and such developments are evaluated in clinical trials. • Low-dose therapy is the standard approach and most palliative chemotherapy is given in this manner. The next cycle is started once bone marrow function has recovered sufficiently to start the treatment (neutrophils > 1.0 × 109/L and platelets > 100 × 109/L). • High-dose therapy uses a higher individual drug dose to achieve a higher cell kill but results in more bone marrow toxicity. This can be minimised by using G–CSF. This approach allows more drug to be delivered within the same schedule of administration, but the total received dose can be less than the intended dose due to

limitations of non-haematological toxicity. • Dose-dense therapy involves fractionating the intended dose of drug and administering each fraction on a more frequent basis (often weekly). Each individual dose produces less toxicity but the anti-cancer effect is related to the accumulative dose over time. Such an approach can overcome drug resistance, produce a greater cell kill and, in some cases, produce a response with weekly administration when the 3-weekly schedule demonstrates a lack of response or even disease progression. • Alternating therapy involves giving different drugs in an alternating manner. This is most commonly used with haematological malignancies and is designed to treat different subpopulations of cancer cells where individual clones of cells might be resistant to one or more of the agents. Adverse effects Most cytotoxics have a narrow therapeutic window or index and can have significant adverse effects, as shown in Figure 33.6. Considerable supportive therapy is often required to enable patients to tolerate therapy and achieve benefit. Nausea and vomiting are common, but with modern antiemetics, regimens such as the combination of dexamethasone and highly selective 5-hydroxytryptamine (5-HT3, serotonin) receptor antagonists like ondansetron, most patients now receive chemotherapy without any significant problems. Myelosuppression is common to almost all cytotoxics and this not only limits the dose of drug but also can cause life-threatening complications. The risk of neutropenia can be reduced with the use of specific growth factors that accelerate the repopulation of myeloid precursor cells. The most commonly employed is G–CSF, which is widely used in conjunction with chemotherapy regimens that induce a high rate of neutropenia. More recently, it has been used to ‘accelerate’ the administration of chemotherapy, enabling standard doses to be given at shorter intervals where the rate-limiting factor has been the time taken for the peripheral neutrophil count to recover. Accelerated chemotherapy regimens have now been demonstrated to offer therapeutic advantages in small cell lung cancer, lymphoma and possibly breast cancer. • Neoadjuvant chemotherapy or primary medical therapy is where chemotherapy is administered first before a planned cyto-reductive procedure. This can result in a reduced requirement for surgery, increase the likelihood of successful debulking, reduce the duration of hospitalisation and improve the fitness of the patient prior to interval debulking. This approach has the same goals as adjuvant treatment but creates an opportunity for translational research to measure responses to treatment and correlate with subsequent specimens removed at the time of surgery. • Chemoprevention is the use of pharmacological agents to prevent cancer developing in patients identified as being at particular risk. The agents used therefore aim to modify risk and, as such, should not have significant adverse effects. Surgical treatment Surgery has a pivotal role in the management of cancer. There are three main situations in which it is necessary. 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. Excision The main curative management of most solid cancers is surgical excision. In early, localised cases of colorectal, breast and lung cancer, cure rates are high with surgery. There is increasing evidence that outcome is related to surgical expertise, and most multidisciplinary teams include surgeons experienced in the management of a particular cancer. There are some cancers for which surgery is one of two or more options for primary management, and the role of the multidisciplinary team is to recommend appropriate treatment for a specific patient. Examples include prostate and transitional cell carcinoma of the bladder, in which radiotherapy and surgery may be equally effective. Palliation 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. 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.

of normal and tumour tissue. In addition, techniques such as conformal radiotherapy, in which shaped rather than conventional square or rectangular beams are used, allow much more precise targeting of therapy to the tumour, and reduce the volume of normal tissue irradiated by up to 40% compared to non-conformal techniques. Biological differences between normal and tumour tissues are used to obtain therapeutic gain. Fundamental to this is fractionation, which entails delivering the radiation as a number of small doses on a daily basis. This allows normal cells to recover from radiation damage but recovery occurs to a lesser degree in malignant cells. Fractionation regimens vary, but radical treatments given with curative intent are usually delivered in 20–30 fractions given daily on 5 days a week, over 4–6 weeks. Radiotherapy can be extremely useful for the alleviation of symptoms, and for palliative treatments such as this a smaller number of fractions (1–5) is usually adequate. 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. Normal tissue also varies in its radiosensitivity, the central nervous system, small bowel and lung being among the most sensitive. The side-effects of radiotherapy (see Fig. 33.6) depend on the normal tissues treated, their radiosensitivity and the dose delivered. 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. Three methods are usually employed: • Teletherapy: application from a distance by a linear accelerator. • Brachytherapy: direct application of a radioactive source on to or into a tumour. This allows the delivery of a very high, localised dose of radiation and is integral to the management of localised cancers of the head and neck, and cancer of the cervix and endometrium. • Intravenous injection of a radioisotope: such as 131iodine for cancer of the thyroid and 89strontium for the treatment of bone metastases from prostate cancer. 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. This is possible with modern imaging techniques such as CT and MRI, which allow better visualisation Fig. 33.6 Adverse effects of chemotherapy and radiotherapy. Acute effects are shown in pink and late effects in blue. Alopecia Hair follicles Mucositis Oral mucosa Mucositis Oesophagus Fibrosis Lung Heart Upper GI tract Nausea and vomiting Breast tissue Bowel Mucositis, diarrhoea Small bowel Skin Sensory neuropathy Neural tissue Kidneys Renal impairment Fertility Thrombocytopenia Bone marrow Any organs Children Alopecia Mucositis Mucositis Cough

↑ Risk breast cancer Nausea, diarrhoea Premature gonadal failure Increased risk of malignancy Reduced growth Xerostomia Strictures ↑ Risk ischaemic heart disease Fibrosis Fibrosis and perforation Erythema and desquamation Telangiectasia, thinning of the skin Neutropenia, anaemia ↓ Haemoglobin, platelet count Neutropenia Arrhythmias Heart failure Motor neuropathy Nerve deafness Amenorrhoea Premature gonadal failure Chemotherapy (often drug-specific) Radiotherapy Erythema

1332 • ONCOLOGY Biological therapies 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. Some examples are discussed below, but in the years to come many more such agents will come into clinical use, with the potential to revolutionise our approach to some cancers. 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. 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 chemotherapy is less effective. 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. 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. Evaluation of treatment The evaluation of treatment includes an assessment of overall survival duration, response to treatment, remission rate, diseasefree survival and response duration, quality of life and treatment toxicity. Uniform criteria have been established to measure these, including the response evaluation criteria in solid tumours (RECIST, Box 33.16) and common toxicity criteria. This allows clinicians to inform patients accurately about the prognosis, effectiveness and toxicity of chemotherapy and empowers patients to take an active role in treatment decisions. Late toxicity of therapy The late toxicities of treatment for cancer are particularly important for patients where the multimodality therapy is given with curative Adverse effects An acute inflammatory reaction commonly occurs towards the end of most radical treatments and is localised to the area treated. For example, skin reactions are common with breast or chest wall radiotherapy, and proctitis and cystitis with treatment to the bladder or prostate. These acute reactions settle over a period of a few weeks after treatment, assuming normal tissue tolerance has not been exceeded. Late effects of radiotherapy develop 6 weeks or more after treatment and occur in 5–10% of patients. Examples include brachial nerve damage and subcutaneous fibrosis after breast cancer treatment, and shrinkage and fibrosis of the bladder after treatment for bladder cancer. There is a risk of inducing cancer after radiotherapy, which varies depending on the site treated and on whether the patient

has had other treatment such as chemotherapy. 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, but there is no convincing evidence that it is an effective therapy following potentially curative surgery. Progestogens are active in the treatment of endometrial and breast cancer. In the metastatic setting, progestogen use (e.g. megestrol acetate) is associated with response rates of 20–40% in endometrial cancer. In breast cancer, progestogens are used in patients whose disease has progressed with conventional anti-oestrogen therapy. Their exact mechanism in this setting is not fully understood. Immunotherapy A profound stimulus to the patient’s immune system can sometimes alter the natural history of a malignancy, and the discovery of interferons was the impetus for much research. Although solid tumours show little benefit, interferons are active in melanoma and lymphoma, and there is evidence that they are beneficial as adjuvants (after surgery and chemotherapy, respectively) to delay recurrence. Whether interferon-induced stimulation of the immune system is capable of eradicating microscopic disease remains unproven. More powerful immune responses can be achieved with potent agents like IL-2 but the accompanying systemic toxicity is a problem still to be overcome. The most striking example of successful immunotherapy is that with rituximab, an antibody against the common B-cell antigen CD20. It increases complete response rates and improves survival in diffuse large cell non-Hodgkin lymphoma when combined with chemotherapy, and is effective in palliating advanced follicular non-Hodgkin lymphoma (p. 965).

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). The survival for breast cancer by stage is outlined in Box 33.18. Pathogenesis 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. Clinical features 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. Less common presentations include inflammatory carcinoma with diffuse induration of the skin of the intent, the patient is young and more patients are living longer. This can cause considerable morbidity: for example, radiotherapy can retard bone and cartilage growth, impair intellect and

cognitive function, and cause dysfunction of the hypothalamus, pituitary and thyroid glands. Late consequences of chemotherapy include heart failure due to cardiotoxicity, pulmonary fibrosis, nephrotoxicity and neurotoxicity. Premature gonadal failure can result from chemotherapy or radiotherapy and leave a patient subfertile. Patients should be made aware of this before treatment is initiated, as it may be possible to store sperm for male patients before treatment starts; this should always be offered, if practical. Egg or embryo banking after in vitro fertilisation may be an option for young women. Sterility develops at higher radiotherapy doses but erectile dysfunction is seen in patients receiving high radiotherapy doses to the pelvis, as in prostate cancer. Additional social or psychological support may be required. Infertility and pubertal delay are potential late effects of therapy in children, especially boys. Second malignancies may be induced by cancer treatment and occur at greatest frequency following chemoradiation. Secondary acute leukaemia (mostly AML) can occur 1–2 years after treatment with topoisomerase II inhibitors, or 2–5 years after treatment with alkylating agents. The most common second malignancy within a radiation field is osteosarcoma but others include soft tissue sarcoma and leukaemia. Specific cancers The diagnosis and management of cancers are discussed in more detail elsewhere in the book (Box 33.17). Here we discuss the pathogenesis, clinical features, investigation and management of common tumours that are not covered elsewhere. 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 33.16 Response evaluation criteria in solid tumours (RECIST) Response Criteria Complete response (CR) Disappearance of all target lesions Partial response (PR) At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD Progressive disease (PD) At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started and at least 5 mm increase or the appearance of one or more new lesions Stable disease (SD) Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started 33.17 Specific cancers covered in other chapters Bladder cancer p. 435 Colorectal cancer p. 827 Familial cancer syndromes p. 56 Gastric cancer p. 803 Hepatocellular carcinoma p. 890 Leukaemia p. 954 Lung cancer p. 598 Lymphoma p. 961 Mesothelioma p. 618 Myeloma p. 966 Oesophageal cancer p. 796 Pancreatic cancer p. 842 Prostate cancer p. 438 Renal cancer p. 434 Seminoma p. 439 Skin cancer p. 1229 Teratoma p. 439 Thyroid cancer p. 649 33.18 Five-year survival rates for breast cancer by stage Tumour stage Stage definition 5-year survival (%) I Tumour < 2 cm, no lymph nodes

II Tumour 2–5 cm and/or mobile axillary lymph nodes

III Chest wall or skin fixation and/or fixed axillary lymph nodes

IV Metastasis

 Pathogenesis Genetic and environmental factors play a role. The risk of ovarian cancer is increased in patients with BRCA1 or BRCA2 mutations, and Lynch type II families (a subtype of hereditary non-polyposis colon cancer, HNPCC) have ovarian, endometrial, colorectal and gastric tumours due to mutations of mismatch repair enzymes. Advanced age, nulliparity,

ovarian stimulation and Caucasian descent all increase the risk of ovarian cancer, while suppressed ovulation appears to protect, so pregnancy, prolonged breastfeeding and the contraceptive pill have all been shown to reduce the risk of ovarian cancer. Investigations Initial workup for patients with suspected ovarian cancer includes imaging in the form of ultrasound and CT. Serum levels of the tumour marker CA-125 are often measured. Surgery plays a key role in the diagnosis, staging and treatment of ovarian cancer, and in early cases, palpation of viscera, peritoneal washings and biopsies are generally performed to define disease extent. Management In early disease, surgery followed by adjuvant chemotherapy with carboplatin, or carboplatin plus paclitaxel, is the treatment of choice. Surgery should include removal of the tumour along with total abdominal hysterectomy, bilateral salpingooophorectomy, and omentectomy. Even in advanced disease, surgery is undertaken to debulk the tumour and is followed by adjuvant chemotherapy, typically using carboplatin and paclitaxel. Bevacizumab is indicated for patients with highgrade tumours that are suboptimally debulked or those with a more aggressive biological pattern. Monitoring for relapse is achieved through a combination of serum CA-125 and clinical examination with CT imaging for those with suspected relapse. Second-line chemotherapy is aimed at improving symptoms and should not be used for CA-125 elevation only in the absence of symptoms. Treatments can include further platinum/paclitaxel in combination, liposomal doxorubicin or topotecan. These regimens are associated with a response rate of 10–40%. The best responses are observed in patients with a treatment-free interval of more than 12 months. Endometrial cancer Endometrial cancer accounts for 4% of all female malignancies, producing a 1 in 73 lifetime risk. The majority of patients are post-menopausal, with a peak incidence at 50–60 years of age. Mortality from endometrial cancer is currently falling. The most common presentation is with post-menopausal bleeding, which often results in detection of the disease before distant spread has occurred. Pathogenesis Oestrogen plays an important role in the pathogenesis of endometrial cancer, and factors that increase the duration of oestrogen exposure, such as nulliparity, early menarche, late menopause and unopposed HRT, increase the risk. Endometrial cancer is 10 times more common in obese women and this is thought to be due to elevated levels of oestrogens. Investigations The diagnosis is confirmed by endometrial biopsy. breast, and this confers an adverse prognosis. Around 40% of patients will have axillary nodal disease, with likelihood correlating with increasing size of the primary tumour. 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 receive an LHRH analogue. Aromatase inhibitors also have benefit in this setting but are still under investigation. 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. Ovarian cancer Ovarian cancer is the most common gynaecological tumour in Western countries. Most ovarian cancers are epithelial in origin (90%), and up to 7% of women with ovarian cancer have a positive family history. Patients often present late in ovarian cancer with vague abdominal discomfort, low back pain, bloating, altered bowel habit and weight loss. Occasionally, peritoneal deposits are palpable as an omental ‘cake’ and nodules in the umbilicus (Sister Mary Joseph nodules).

where oropharyngeal cancers are concerned. The rising incidence of oropharyngeal cancers, especially in the developed world, is thought to be secondary to HPV infection. Presentation depends on the location of the primary tumour and the extent of disease. For example, early laryngeal cancers may present with hoarseness, while more extensive local disease may present with pain due to invasion of local structures or with a lump in the neck. Patients who present late often have pulmonary symptoms, as this is the most common site of distant metastases (Box 33.19). Pathogenesis The tumours are strongly associated with a history of smoking and excess alcohol intake, but other recognised risk factors include Epstein–Barr virus for nasopharyngeal cancer and HPV infection for oropharyngeal tumours. Investigations Careful inspection of the primary site is required as part of the staging process, and most patients will require endoscopic evaluation and examination under anaesthesia. Tissue biopsies should be taken from the most accessible site. CT of the primary site and the thorax is the investigation of choice for visualising the tumour, while MRI may be useful in certain cases. Management Generally speaking, the majority of patients with early or locally advanced disease are treated with curative intent. In localised disease where there is no involvement of the lymph nodes, long-term remission can be achieved in up to 90% of patients with surgery or radiotherapy. The choice of surgery versus radiotherapy often depends on patient preference, as surgical treatment can be mutilating with an adverse cosmetic outcome. Patients with lymph node involvement or metastasis are treated with a combination of surgery and radiotherapy (often with chemotherapy as a radiosensitising agent – proven agents include cisplatin or cetuximab), and this produces long-term remission in approximately 60–70% of patients. Recurrent or metastatic tumour may be palliated with further surgery or radiotherapy to aid local control, and systemic chemotherapy has a response rate of around 20–30%. Second malignancies are common (3% Management Surgery is the treatment of choice and is used for staging. A hysterectomy and bilateral salpingo-oophorectomy are performed with peritoneal cytology and, in some cases, lymph node dissection. Where the tumour extends

beyond the inner 50% of the myometrium or involves the cervix and local lymph nodes, or there is lymphovascular space invasion, adjuvant pelvic radiotherapy is recommended. Chemotherapy is used as adjuvant therapy and hormonal therapy and chemotherapy are used to palliate symptoms in recurrent disease. Cervical cancer This is the second most common gynaecological tumour worldwide and the leading cause of death from gynaecological cancer. The incidence is decreasing in developed countries but continues to rise in developing nations. The most common presentation is with an abnormal smear test, but with locally advanced disease the presentation is with vaginal bleeding, discomfort, discharge or symptoms attributable to involvement of adjacent structures, such as bladder, or rectal or pelvic wall. Occasionally, patients present with distant metastases to bone and lung. Pathogenesis There is a strong association between cervical cancer and sexual activity that includes sex at a young age and multiple sexual partners. Infection with HPV has an important causal role, and this has underpinned the introduction of programmes to immunise teenagers against HPV in an effort to prevent the later development of cervical cancer (p. 342). Investigations Diagnosis is made by smear or cone biopsy. Further examination may require cystoscopy and flexible sigmoidoscopy if there are symptoms referable to the bladder, colon or rectum. In contrast to other gynaecological malignancies, cervical cancer is a clinically staged disease, although MRI is often used to characterise the primary tumour. A routine chest X-ray should be obtained to help rule out pulmonary metastasis. CT of the abdomen and pelvis is performed to look for metastasis in the liver and lymph nodes, and to exclude hydronephrosis and hydroureter. Management This depends on the stage of disease. Pre-malignant disease can be treated with laser ablation or diathermy, whereas in microinvasive disease a large loop excision of the transformation zone (LLETZ) or a simple hysterectomy is employed. Invasive but localised disease requires radical surgery, while chemotherapy and radiotherapy, including brachytherapy, may be given as primary treatment, especially in patients with adverse prognostic features such as bulky or locally advanced disease, or lymph node or parametrium invasion. In metastatic disease, cisplatin-based chemotherapy may be beneficial in improving symptoms but does not increase survival significantly. Head and neck tumours Head and neck cancers are typically squamous tumours that arise in the nasopharynx, hypopharynx and larynx. They are most common in elderly males but now occur with increasing frequency in a younger cohort, as well as in women, especially 33.19 Common presenting features by location in head and neck cancer Hypopharynx • Dysphagia • Odynophagia • Referred otalgia • Enlarged lymph nodes Mouth • Non-healing ulcers • Ipsilateral otalgia Nasal cavity and sinuses • Discharge (bloody) or obstruction Nasopharynx • Nasal discharge or obstruction • Conduction deafness • Atypical facial pain • Diplopia • Hoarse voice • Horner’s syndrome Oropharynx • Dysphagia • Pain • Otalgia Salivary gland • Painless swelling • Facial nerve palsy

 radiotherapy and surgical palliation can all be helpful. Some patients remain free of cancer for some years after resection of a single metastasis of an adenocarcinoma of unknown primary, justifying this approach in selected patients. In those with no obvious primary, systemic chemotherapy may achieve some reduction in tumour burden and alleviation of symptoms, but long-term survival is rare. Multidisciplinary teams The multidisciplinary team (MDT) is well established in oncology and meets on a regular basis to discuss patient progress and provide a forum for patient-centred, interdisciplinary communication to coordinate care and decision-making. It is a platform on which individual clinicians can discuss complex cases or situations and draw on the collective experience of the team membership to decide on the best approach for an individual patient. This can be particularly important when discussing patients with a rare condition or in a rare situation. Specific roles of the MDT include: • planning the diagnostic

and staging procedures • deciding on the appropriate primary treatment modality (most commonly surgery but the use of neoadjuvant chemotherapy before interval surgery is increasing) • arranging review by the oncology team to plan assessment of the patient prior to systemic therapy or radiotherapy • discussing additional support requirements for the individual patient, such as physiotherapy; psychological support; symptom control; nutritional care or rehabilitation in the post-operative period • ensuring access to accurate information on treatment, prognosis, side-effects and other related matters, such as stoma care • planning surveillance strategies • ensuring the appropriate transition from treatment with curative intent to that of palliation of symptoms • promoting recruitment into clinical trials • agreeing on operational policies to deliver high-quality care to patients • planning and reviewing audit data to ensure the delivery of quality care to patients by the team. Further information Books and journal articles Cassidy J, Bissett D, Spence RAJ, et al. Oxford handbook of oncology, 4th edn. Oxford: Oxford University Press; 2015. Dark GG. Oncology at a glance. Chichester: Wiley–Blackwell; 2013. Hanahan D, Weinberg RA. The hallmarks of cancer: the next generation. Cell 2011; 144:646–674. Tobias J, Hochhauser D. Cancer and its management, 7th edn. Chichester: Wiley–Blackwell; 2014. Websites cancer.org American Cancer Society: clinical practice guidelines. ctep.cancer.gov/reporting/ctc.html Common toxicity criteria. info.cancerresearchuk.org/cancerstats/ A wide range of cancer statistics that can be sorted by type or geographical location. per year) following successful treatment for primary disease, and all patients should be encouraged to give up smoking and drinking alcohol to lower their risk. Carcinoma of unknown origin Some patients are found to have evidence of metastatic disease at their initial presentation, prior to diagnosis of a primary site. In many cases, a subsequent biopsy reveals adenocarcinoma but the primary site is not always clear. Investigations In this situation, there is a temptation to investigate the patient endlessly in order to determine the original primary site. There is a compromise, however, between exhaustive investigation and obtaining sufficient information to plan appropriate management. For all patients, histological examination of an accessible site of metastasis is required. The architecture of the tissue can assist the pathologist in determining the likely primary site, and therefore it is better to perform a biopsy rather than fine needle aspiration. The greater volume of tissue permits the use of immunohistochemistry. Extensive imaging to search for the primary is rarely indicated; a careful history to identify symptoms and risk factors (including familial) will often permit a judicious choice of imaging and other diagnostic tests, reserving additional tests for specific patients (Box 33.20). Management Management of the patient will depend on that person’s circumstances, as well as on the site(s) involved and the likely primary sites. The overriding principle is to ensure that a curable diagnosis has been excluded. For example, lung metastases from a testicular teratoma do not preclude cure; nor do one or two liver metastases from a colorectal cancer. Early discussion with an oncologist within a multidisciplinary team is essential and avoids unnecessary investigation; for example, a single hCG-based pregnancy test in a young man with lung metastases might confirm the presence of a teratoma and allow rapid administration of potentially curative chemotherapy. Treatment should not necessarily wait for a definitive diagnosis; appropriate analgesia, *Offer when clinically appropriate. 33.20 Initial diagnostic tests in patients presenting with carcinoma of unknown primary* • Detailed history and examination, including breast, nodal areas, skin, genital, rectal and pelvic regions • Full blood count, urea and electrolytes, renal function, liver function tests, calcium, urinalysis, lactate dehydrogenase • Chest X-ray • Myeloma screen (if lytic bone lesions) • CT scan of chest, abdomen and pelvis • Symptom-directed upper and lower gastrointestinal endoscopy • Tumour markers: prostate-specific antigen (PSA) in men, cancer antigen 125 (CA-125) in women with peritoneal malignancy or ascites, α-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) • Testicular ultrasound (if clinical features suggest germ cell tumour) • Histological

examination of biopsy, with immunohistochemistry if required

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