The biology of cancer

Aim

The aim of this module is to develop knowledge of concepts fundamental to the ability of the Specialist Cancer Nurse to demonstrate competence across all domains of practice.

The module focuses specifically on developing an advanced understanding of the biology of cancer.

Rationale

Cancer is a complex set of diseases that can arise in any cell of the body capable of evading normal regulatory mechanisms. It also typically affects functioning of multiple body systems.

Improvements in understanding of the biology of cancer have resulted in substantial changes in the prevention, detection and treatment of cancer in recent years. To implement appropriately targeted and evidence based interventions at all stages of the cancer journey, Specialist Cancer Nurses (SCNs) require a sound understanding of the biology of cancer and the natural history of this disease.

Key concepts

- Normal cellular growth, proliferation, differentiation and regulatory mechanisms.
- Characteristics of benign and malignant cells.
- Genetic, immunological, and hormonal basis of cancer.
- Processes of invasion and metastases.
- Common classification systems for cancer.
- Common investigations for diagnosing, staging and grading cancer.

Assumed knowledge and related information

Students are expected to understand the fundamentals of:

- human cell structure and function
- cellular components
- the role of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) in protein synthesis.

Objectives

On completion of this supporting resource, you should be able to:

1. Describe the physiological, immunological, hormonal and genetic aspects of cancer.
2. Explain the process of carcinogenesis.
3. Explain the mechanisms of invasion and metastases.
4. Outline the major systems for classifying and staging cancer.
5. Outline common clinical and pathological investigations involved in diagnosing, staging and grading cancer.

Learning activities
At times, you will have learning activities to complete. Click on the learning activities button and a list of questions will pop up. The questions will relate to the content you've just read or the video you've just watched.

Resource links
Resource links are included throughout the resource. These links lead to interesting articles or websites, and are designed to encourage you to explore other available resources.

PDF of EdCaN module: The biology of cancer
You can download a PDF version of the module.

Suggested citation:

Cancer Australia. (2018) EdCaN module: The biology of cancer, version 2.2.

Normal cell proliferation

Cells form the basic structural and functional units of an organism.[1] All cells contain a cell membrane, cytoplasm and nucleus.[1] Situated in the nucleus is the genetic material or deoxyribonucleic acid (DNA), which is the fundamental building block for life. DNA is made up of subunits called genes. Each gene is coded for a specific product such as a protein or enzyme.[2]

Genes are contained in chromosomes and only the genes required are switched on.[2] Some important genes in the context of cellular proliferation include:

- proto-oncogenes: a gene involved in normal cell growth. Mutations (changes) in a proto-oncogene may cause it to become an oncogene, in which it becomes overactive and can cause the growth of cancer cells[3]
- tumour suppressor genes: a type of gene that makes a protein called a tumour suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumour suppressor genes may lead to cancer.[3]

Each tissue and organ in the body is composed of vast populations of cells, totaling more than 10^{14} (100 000 000 000 000). An astonishing 10^{12} (1 000 000 000 000) cells die or are shed in the normal course of each day and must be replaced to sustain life.

The process by which cells grow and divide to replenish lost cells is termed cell proliferation. This is a highly regulated activity in normal, healthy tissue. The synthesis of new cells is balanced against cell loss so that the total number of cells composing all tissues and organs in the body remains essentially unchanged.[4-7]

Cell growth, the replication of genetic material and cell division are all governed by the cell cycle, a highly-ordered series of events that culminates in mitosis (the division of a cell, giving rise to two daughter cells). Progression through the cell cycle depends on successful passage through a number of critical phases, known as checkpoints, which function to ensure the synthesis of fully functioning daughter cells.[6-9]

Learning activities		
Completed	Activities	
☐	1	Define normal cell proliferation and differentiation.
☐	2	Outline the phases of the cell cycle and the cellular activities that occur in each of these phases.
☐	3	Explain the roles of each of the cell cycle control checkpoints.
☐	4	Access nobelprize.org and complete the Control of the Cell Cycle game.

Abnormal cell proliferation

While some cell types, such as those that compose the skin and bone marrow, continue to proliferate throughout life, other types including bone and muscle cells cease active proliferation when a human reaches adulthood. Most normal cells remain in a non-proliferative state unless they are stimulated to divide to replace lost cells. Abnormal regulation of the cell cycle can lead to the over proliferation of cells and an accumulation of abnormal cell numbers. Cancer cells arise from one cell that becomes damaged, and when divided, the damage is passed on to the daughter cell and again to the granddaughter cells and so on. Such uncontrolled, abnormal growth of cells is a defining characteristic of cancer.[7, 10-12]

The total number of cells composing the human body is determined not only by the rate of proliferation of cells but also by the rate of cell loss. Excess cells and those that are aged or have sustained damage that impairs normal functioning are eliminated to prevent accumulation of abnormal numbers of cells. The mechanism for regulating the removal of excess and impaired cells is known as apoptosis. Also referred to as cell suicide or programmed cell death, apoptosis is an orderly process during which internal cellular structures are progressively dismantled, the impaired cell shrinks and finally is rapidly destroyed by immune cells.[6, 8, 13]

Role of key genes TP53 and RB1

A number of key genes, proteins and enzymes that regulate the cell cycle and the process of apoptosis have been identified. The TP53 gene and the regulatory protein it is responsible for producing, p53, together with the RB1 gene and its related protein, pRB, act to inhibit cell proliferation. In addition, the role of a group of proteins (cyclins and enzymes) known as cyclin-dependent kinases (CDKs) that act to stimulate a cell to progress through the cell cycle have also been identified.

It is now understood that mutations of these key genes affect the action of regulating proteins and enzymes and lead to the loss of regulation of cell proliferation that is seen in cancer. Mutations of the TP53 gene are also implicated in disturbances in apoptosis. Cells with mutated TP53 genes evade the apoptosis mechanisms normally responsible for eliminating impaired cells.[4, 6, 7, 10, 13]

DNA mutations may result from:

- artificial sources (pesticides, organic chemicals, alkylating agents)
- naturally occurring sources (plant toxins, viruses)
- radiation.

When cell cycle control checkpoints fail, the following may occur:[2]

- the mistake is quickly fixed
- a mutation results in the production of an abnormal protein or enzyme
- a mutation occurs near or around the proto-oncogene turning on cell division when not required
- a mutation occurs near or around tumour suppressor gene (e.g. the p53 gene that normally inhibits the growth of tumours) resulting in inability to stop uncontrolled cell division.

Learning activities		
Completed	Activities	
☐	1	Access a current text. Identify examples within the following classes of genes and discuss their role in carcinogenesis: • oncogenes • tumour suppressor genes • DNA repair pathway genes.
☐	2	Describe the key differences between the following types of cell proliferation patterns: • anaplasia • dysplasia • hyperplasia • hypertrophy • metaplasia.
☐	3	Access a current text and/or the Research Apoptosis web page[14]. Explain the role of apoptosis in homeostasis and the development of cancer.

What is cancer?

Much has changed in our understanding of cancer since Hippocrates, in around 400BC, described a tumour, most likely of breast tissue, as resembling a crab and named it a 'cancer' (which is Latin for crab). Cancer is not a single disease. It is between 150 and 200 different diseases with a number of common biological properties that identify them as cancer.[5, 15]

Cancer can affect almost any type of cell. Theoretically, therefore, there are as many types of cancer as there are cell types in the human body. Although the location, behaviour and effect of each cancer type may vary, modern advances in biomedical research have identified the biological properties common to all cancer cells that distinguish them from healthy, normal cells. In addition, molecular genetic research has uncovered the role of specific genes and genetic mutations in the transformation of healthy cells to diseased cancer cells.[5, 7, 15-17]

The key biological capabilities that enable the multistep development of cancer include:[18]

- resisting cell death
- avoiding immune destruction
- evading growth suppressors
- deregulating cellular energetics
- sustaining proliferative signaling
- enabling replicative immortality
- genome instability and mutation
- inactivating invasion and metastasis
- tumour-promoting inflammation
- inducing angiogenesis.

Learning activity	
Completed ☐	Activity 1 Review Hallmarks of cancer: the next generation[18] and outline an example of each of the characteristics of cancer cells.

Carcinogenesis

The process by which normal, healthy cells transform into cancer cells is termed carcinogenesis or oncogenesis. The development of a malignant tumour in otherwise healthy tissue is the result of a complex series of events beginning with a single cell that has acquired malignant properties through cellular DNA damage.

Errors in the DNA sequence interrupt the genetic codes that govern the structure and function of the affected cell. The survival and proliferation of a cell with DNA damage, dividing to give rise to two daughter cells, each then capable of dividing, eventually results in a population of clones with similar genetic errors and malignant properties.[7, 16, 19]

Before malignant cells can cause symptoms or be detected, successive generations of daughter cells must divide and double the size of the clonal population approximately 30 times. At this point, the tumour will likely measure one cubic centimetre, weigh about one gram and comprise one billion cells.[5, 7]

Most current theories of carcinogenesis characterise it as a multi-step process involving initiation, growth, promotion, conversion, propagation, invasion and metastasis.[7, 9, 13]

Carcinogens

Carcinogens are defined as agents capable of initiating the development of malignant tumours by inducing cellular genetic changes. The transformation of a normal cell to a malignant cell is thought to be due to successive and cumulative exposures to carcinogens and other factors over the course of decades. Most human cancers result from exposure to environmental (or exogenous) carcinogens. Other carcinogens that cause malignant transformation include a broad group of factors from within the body, termed endogenous factors.[6, 19]

Learning activities	
Completed	Activities
☐	1 Access a current text and/or the Cancerquest website[20], and: • Summarise the three stage model of carcinogenesis. • List two examples each of exogenous and endogenous carcinogens. • Provide an explanation of how the carcinogens identified in the previous activity act to initiate the development of a malignant tumour.

Genetics and cancer

The transformation of normal, healthy cells into diseased cancer cells is directly attributable to genetic damage causing DNA abnormalities that alter cell growth, proliferation and survival.[6, 8, 9] These abnormal genetic changes are termed mutations and may take the form of any of a number of alterations in the DNA sequence of a cell. Mutations may include point mutation, deletion, translocation, and inversion. The eventual impact of a mutation depends on where in the genetic sequence the error occurs.

Increasingly, research is identifying the specific genes and the mutations of the genes that are implicated in the transformation of a normal cell into a cancer cell. The key role played by two groups of cancer genes, proto-oncogenes and tumour suppressor genes, in the malignant transformation of cells is now evident.[6, 7, 9] Examples of such mutations include the up regulation of HER2 in breast cancer, the BCR-ABL translocation in chronic myeloid leukaemia, epidermal growth factor receptor in lung cancer, and C-KIT mutations in gastrointestinal stromal tumours.[21]

Genetic mutations that lead to the malignant transformation of cells and the development of cancer may be acquired or hereditary. Genetic damage resulting from exposure to carcinogens, whether exogenous or endogenous, is classified acquired mutation. Inherited abnormal alterations in the genetic sequence that predispose individuals to cancer are known as hereditary mutations.[6, 8]

Learning activities	
Completed	Activities
☐	1 Outline the key differences between the impact of hereditary and acquired genetic mutations in the development of cancer.
☐	2 Differentiate point mutations from translocations.
	3 Summarise the role of proto-oncogenes and tumour suppressor genes and compare this to the role that their mutated counterparts play in the development of cancer.
	4 Define the following genetic terms: • Penetrance. • Expressivity. • Anticipation. • Pleiotropism.
	6 Identify how the following genes contribute to the development of specific cancers and impact on a person's cancer journey: • BRCA 1/2 • C-KIT.
	7 In the case of chronic myeloid leukaemia, identify the location of the mutation that results in the formation of an abnormal receptor and the resultant progression of disease.
	8 Access the website for the Centre for Genetics Education[22] and outline the information, resources and supportive care the SCN may provide for the person who is concerned they have a family history of cancer.

Hormones and cancer

Hormones are naturally occurring substances secreted by specialised cells and circulated throughout the body in the blood. Hormones act by binding to receptors on the surface of and influencing the metabolism or behaviour of cells. The normal growth and development of a range of tissues throughout the human body occurs under the influence of hormones.

Excessive hormonal stimulation of cell proliferation increases the risk of mutation and subsequent proliferation of clones of mutated cells. Hormones are therefore capable of acting as powerful carcinogens, and are considered a 'complete carcinogen' because of their ability to both initiate and promote the development of cancers.[4, 6, 7, 19]

Hormones have been implicated in the genesis of breast, prostate, uterine, ovarian, testicular, thyroid and bone cancers. Increased exposure to the hormones oestrogen and progesterone in females has been demonstrated to increase the risk of breast cancer. The early onset of menstruation, late first pregnancy, obesity, late menopause and the use of oral contraceptives all increase the exposure of breast tissue to oestrogen, stimulating increased proliferation. Similarly, the male sex hormone testosterone has been implicated in the development of prostate cancer.[6, 7, 19, 23]

Learning activity	
Completed	Activity
☐	1 Access a current text and summarise the role of hormones in the development of the following cancers: • Ovarian. • Thyroid. • Prostate.

The immune system and cancer

The immune system has several functions such as defense against foreign organisms, homeostasis, and the destruction of damaged cells and surveillance.[24, 25]

There are two types of immune responses: innate or non-specific immunity and adaptive or specific immunity. Cytokines are naturally occurring proteins produced by cells of the immune system (such as lymphocytes and macrophages) that coordinate and initiate effector defense functions.[26]

Cytokines

Cytokines include the interleukins, interferons, colony stimulating factors and tumour necrosis factor. Cytokines can be defined by the following properties:[26]

- they mediate and regulate the immune defense functions by acting as messengers between the various immune cells
- they usually function over short distances and their half-life is brief
- they are produced by a variety of cells types, and can act on diverse cell targets within the immune system and on organs such as the liver
- their actions are both overlapping and contradictory in that they can both stimulate and inhibit growth. They can act directly or indirectly on a cell causing a cytokine cascade.

Immune system response

An important function in the defense against cancer is surveillance and identification of foreign or 'non-self' substances.[24] Foreign antigens may be exogenous microbes or endogenous altered or virally transformed cells.[26]

The immune system, which recognises foreign micro-organisms as 'non-self' and mounts a response to destroy these disease-causing agents, plays a similar role in protecting the body from malignancy. The damaged DNA in cancer cells frequently directs the mutated cell to produce abnormal proteins known as tumour antigens. These abnormal tumour proteins mark cancer cells as 'non-self'. The immune system likely encounters and eliminates cancer cells on a daily basis. However, it is apparent that cancer cells possess mechanisms that allow them to escape the immune responses that ordinarily prevent the development of malignant tumours.[4, 7, 11, 27, 28]

When the immune system loses its function of surveillance, tumour cells have the ability to form a tumour. Tumour cells that evade detection can be explained by the following proposed mechanisms:[29]

- down regulation of major histocompatibility class (MHC) I expression - allowing antigen to go unrecognised
- lack of co-stimulatory signals needed for antigen presentation - loss or alteration of the MHC molecule
- tumour secretion of immunosuppressive products inhibiting the body's immune response
- tumour being immunogenic by expression of one or more antigens
- antigen modulation - where the antigen either enters the cell or leaves it, completely limiting the ability of the immune system to recognise the tumour cell as 'non-self'
- tumours do not give off inflammatory warning signals.

Learning activities		
Completed	Activities	
☐	1	Access a current text and identify the role of the following cells in the immune response to cancer: • T-lymphocytes. • B-lymphocytes. • Natural killer (NK) cells. • Macrophages.
☐	2	Describe the ways in which cancer cells evade the immune response.
☐	3	Explain the differences between innate immunity and adaptive immunity.
☐	4	Outline the role of cytokines in the immune system.
☐	5	Outline your evidence based response to a man's question of how his acute leukaemia developed.

Distinguishing benign and malignant growth

The terms 'tumour' and 'neoplasm' are often used interchangeably to describe an abnormal mass of tissue that results from excessive cell proliferation. The term tumour has its origins in the Latin word *tumere*, meaning 'to swell' and is used to describe an abnormal mass of tissue with no useful bodily function. Neoplasm comes from the Ancient Greek neo (new) and plasma (formation) and refers to the pathological formation and growth of abnormal tissue. Both of these terms may be used to describe and classify either a benign or a malignant growth.[7]

Benign growths

A benign growth does not usually threaten life unless it interferes with vital structures, tissues or organs. Benign growths are generally composed of masses of cells that closely resemble the normal cells composing the tissue in which they are found. Benign tumours perform no useful bodily function and treatment or removal is usually curative.[10, 11]

Malignant growths

A malignant growth is composed of cells of atypical structure and function when compared to the healthy cells surrounding them. A malignant tumour, reflecting the Latin origin of the term *malignans*, meaning to be wicked or to act maliciously, is capable of invading other tissues and, if untreated, usually results in death. Thus, cancer is a malignant disease and the masses of abnormal cells that form a cancer may be termed a malignant tumour or malignant neoplasm.[10, 11]

Learning activities	
Completed	Activities
☐	1 Access a current text and construct a table that compares and contrasts the characteristics of benign and malignant tumours.
☐	2 Develop an evidence based response for a person affected by benign brain tumour who asks the following two questions: • Do I have cancer? • Seeing as the tumour is not malignant does that mean I will be ok?

Tumour nomenclature

With the exclusion of hair, teeth and nails, almost any group of cells in the body might become a site for cancer. In order to distinguish cancers, tumours are classified according to the tissue in which they develop.[4, 10, 30]

The human body is composed of two major classes of tissue: parenchymal or epithelial tissues and mesenchymal tissues, comprising connective tissues, muscle and blood vessel. Benign tumours of most tissues are usually simply designated the suffix -oma. Malignant tumours of the parenchyma are designated the term carcinoma, while malignant tumours of mesenchymal tissues are designated the term sarcoma.[4, 7, 10]

Learning activity	
Completed ☐	Activity 1 Access the NCI Cancer as a Disease[31] module and/or a current text and identify the terminology for benign and malignant tumours associated with the following cell types: • smooth muscle • liver • nerve sheath • Schwann cells • glandular • colon • blood vessel • lung • bile duct • striated muscle • bone.

Invasion and metastasis

A key feature that distinguishes cancer cells from all other cells is the capability to spread throughout the body by two related mechanisms: invasion and metastasis.

Invasion

Invasion refers to the direct extension and penetration by cancer cells into neighbouring tissues. The proliferation of transformed cells and the progressive increase in tumour size eventually leads to a breach in the barriers between tissues, leading to tumour extension into adjacent tissue. Local invasion is also the first stage in the process that leads to the development of secondary tumours or metastases.[4, 7, 10]

Metastasis

Metastasis, from the Greek *methistanai*, meaning to move to another place, describes the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through these systems and invade normal tissues elsewhere in the body. This process proceeds in an orderly and predictable manner, sometimes termed the 'metastatic cascade'.[4, 7, 10]

The ability of cancer cells to migrate from a primary site of disease is attributed to the mutation of genes that regulate the production of proteins that normally tether cells to their surrounding tissues. Decreased synthesis by cancer cells of a number of substances that bind them to neighbouring cells, together with the abnormal synthesis of enzymes capable of degrading the bonds between cells and tissues, allow cancer cells to escape the primary tumour site.[4, 7, 10]

Angiogenesis

Angiogenesis has a role in tumour growth, invasiveness and metastasis.[32, 33] Tumour angiogenesis refers to the growth of new vessels which develop following stimulation of endothelial cells within existing vascular networks near the tumour, providing a blood supply for that tumour.[33] A balance of stimulators and inhibitors tightly control angiogenesis under normal circumstances.[2, 26] One specific and potent promoter of angiogenesis is vascular endothelial growth factor (VEGF).[26]

Vascular endothelial growth factor (VEGF)

VEGF is a cytokine which exerts its effects on vascular endothelial cells promoting the formation of new blood vessels and is critical to both normal and tumour angiogenesis:[26, 34] VEGF is over-expressed in a variety of solid tumours and certain hematologic malignancies. VEGF action involves:[26]

- binding to and activating two structurally related membrane receptor tyrosine kinases (TKs)
- switching on of multiple signaling pathways
- stimulating the growth, survival, and proliferation of vascular endothelial cells
- promoting tumour growth and contributing to tumour invasion and metastasis.

Tyrosine kinases (TK)

Tumour growth and progression is further reliant on the activity of specific cell membrane receptors which control signaling pathways within the cell. Cell signaling or 'signal transduction' involves the communication process where messages or signals from outside the cell are transferred to the nucleus inside the cell.[26] Tyrosine kinases (TK) are a subgroup of growth receptors involved in the signal transduction process.[26] Because TKs are regulators of the signal transduction process, they play a role in cellular processes such as proliferation, migration, metabolism, differentiation and survival.[26] Several important growth factors and other TKs have been identified:[26]

- EGFR family
- platelet derived growth factor receptor (PDGF)
- BCR-ABL
- KIT
- vascular endothelial growth factor (VEGF)
- transforming growth factor (TGF)
- fibroblast growth factor (FGF).

Learning activities		
Completed	Activities	
☐	1	Access a current text and map the stages of the metastatic cascade, explaining the events in the development of metastases.
☐	3	Distinguish between the different members of the EGFRs family.
☐	4	Apart from EGFR components of the TKs involved in signal transduction, list two other TK receptors and the specific cancer they are expressed in.
☐	5	Distinguish between the different members of the VEGF receptors, including the receptor which leads to the development of anti-angiogenic agents in cancer therapy.

Cancer signs and symptoms

The average time between when the initial genetic and cellular changes leading to the development of a cancer occur and the emergence of symptoms related to a tumour is estimated to be as long as 15 to 20 years. During this pre-clinical phase of the development of a cancer, the primary tumour doubles in size as many as 30 times, until it begins to invade and destroy local tissues and organs. It is at this time that clinical symptoms of the tumour become apparent, caused by impairment of the function of normal tissues.[35]

As treatment can be more effective when cancer is found early, Cancer Council Australia recommends that individuals get to know their own body and to keep an eye out for any unusual changes such as:[36]

- lumpiness or a thickened area in breasts, any changes in the shape or colour of your breasts, unusual nipple discharge, a nipple that turns inwards (if it hasn't always been that way) or any unusual pain
- a lump in the neck, armpit or anywhere else in the body
- sores or ulcers that don't heal
- coughs or hoarseness that won't go away or coughing up blood
- changes in toilet habits that last more than two weeks; blood in a bowel motion
- new moles or skin spots, or ones that have changed shape, size or colour, or that bleed
- unusual vaginal discharge or bleeding
- unexplained weight loss.

The detection of preclinical signs of some cancers, such as breast, colorectal and cervical cancers, has given rise to highly effective screening programs that reduce the morbidity and mortality associated with these diseases. More often, however, the presence of worrisome signs and symptoms prompts a visit to a health care professional, in turn leading to diagnosis of a cancer.[37-39]

Learning activities		
Completed	Activities	
☐	1	Access a current text, Cancer Council Australia[40] and/or the American Cancer Society[41] and describe the significance of each of the bodily changes associated with cancer.
☐	2	Identify current Australian health initiatives and resources to educate the community and individuals about the signs of cancer.
☐	3	As an SCN, describe how you can promote the early detection of cancer.

Diagnosing cancer

The initial evaluation of a person presenting with symptoms suggestive of cancer begins with an assessment of the presenting symptoms, personal and family medical history, risk factors for cancer and a thorough physical examination.

This history and physical examination might suggest an initial diagnosis. However, most often, laboratory tests are performed to confirm the clinician's initial working diagnosis and assist in the evaluation of the impact of a cancer on major organ function. Laboratory studies may include analysis for tumour markers which are helpful in the diagnosis and evaluation of the progress of some cancer types.

The next stage in the diagnostic process generally involves the use of diagnostic imaging techniques to locate the primary tumour and, if indicated, determine the extent of any metastatic disease. Following the localisation of the primary and/or secondary disease sites, the definitive step in establishing a diagnosis is the collection of a tumour tissue sample for pathological analysis. Tissue biopsy for pathological analysis is essential in determining the characteristics of a tumour that will guide decisions about how it should best be treated.[37, 38, 42]

Learning activities		
Completed		Activities
☐	1	Access a current text or relevant literature. For the following tumour markers, summarise the associated malignancies, normal ranges, and implications of the marker for cancer detection and monitoring: • prostate-specific antigen (PSA) • CA-125 • alpha-fetoprotein (AFP).
☐	2	Access a current text and summarise the indications, adverse effects and nursing implications for the following methods of obtaining biopsy tissue samples for the purpose of making a cancer diagnosis: • fine-needle aspiration • core needle biopsy • excisional biopsy • incisional biopsy • endoscopic biopsy.
☐	3	For the following imaging techniques, discuss the indications and their role in cancer diagnosis and preparation required for the procedure: • magnetic resonance imaging (MRI) • positron emission tomography (PET) • x-ray • bone scan • mammogram.
☐	4	Select one cancer type and describe the likely pathway for a person who may have a suspected diagnosis of this cancer type, from symptom presentation to commencement of treatment.

Cancer grading and staging

After a diagnosis of cancer has been made, the person undergoes a series of investigations to determine the characteristics of the tumour tissue and the extent of spread of disease in the body. This process, known as disease staging, is generally commenced before treatment begins.

The information gathered from staging investigations is used to classify a tumour and, based on accumulated evidence on the clinical behaviour of other tumours with similar characteristics, guides treatment planning and estimations of disease prognosis.[37, 38]

Histopathological review

Histopathological review, the microscopic examination of tumour tissue, allows the identification of a number of properties that will enable assessment of a tumour's aggressiveness. The amount of necrosis, inflammation, haemorrhage, cellular genetic changes and the degree mitotic activity within a tumour tissue specimen are some of the properties examined in the laboratory. These histopathological characteristics are used to categorise a tumour into a grade, ranging from well-differentiated (grade 1), through moderately (grade 2) and poorly differentiated (grade 3) to undifferentiated (grade 4). In general, higher grade tumours are more aggressive and carry a worse prognosis than lower grade malignancies.[37, 38, 42]

Anatomical extent

In addition to classifying a cancer on the basis of histopathological characteristics, it is also usual to classify a malignancy on the basis of the anatomical extent of disease. Once again, extensive observation of the clinical behaviour of cancers allows prediction of the natural history of growth and progression of a cancer.

Information gathered from tests conducted during the process of cancer diagnosis, often referred to as staging investigations, can be used to compare a newly diagnosed cancer to similar cases and make predictions about the potential outcomes of treatment. In general, the greater the anatomical extent of the cancer, the more limited the successful treatment options and the poorer the prognosis becomes.[30, 38]

The tumour-node-metastasis (TNM) staging system

One of the most commonly used staging systems for solid tumours such a breast, lung and colon cancers, is the tumour-node-metastasis or TNM system. The TNM system, used internationally, is regularly reviewed to incorporate changing knowledge about the behaviour of tumours. The system assesses and classifies three properties:

- the extent of the primary tumour (T)
- the presence and extent of lymph node involvement (N)
- the presence of metastases (M).

Numerical values are assigned to various levels within each of the three categories, reflecting increasing extent of disease. The summing of the numerical values for each of the three categories allows the tumour to be classified into one of four stages, numbering stage I through

to stage IV. High stage disease (stage III or IV) reflects greater anatomical extent and is correlated with poorer prognosis.

There are also a number of other staging systems, devised by the interest groups of oncology clinicians that are used together with or instead of the TNM system. Each of these systems defines the clinical aspects of particular cancers that correlate with favourable and unfavourable outcomes and are used to guide treatment decisions.[30, 37, 38]

Learning activities		
Completed	Activities	
☐	1	Access a current text and/or the National Cancer Institute web site – Tumor Grade[43] and prepare a brief explanation of the term high grade tumour for a person affected by cancer.
☐	2	Access a current text or website (such as cancer.gov[44]) and compare the methods of staging lung and breast cancers.
☐	3	Access the How Is Cervical Cancer Staged?[45] and / or the Cervical Cancer: Stages[46] webpage and compare the FIGO and TNM systems of staging cervical cancer.

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