1.2

Cancer Staging and Classification

There are now believed to be more than 200 different types of cancer, with the potential for the disease to develop in any body organ; this is further complicated by the fact that each organ and tissue is composed of a number of different cell types, each with the potential to develop into a tumour. As you can imagine, the different activities and functions of these ‘normal’ cells directly affects the growth rate, mobility, and lethality of any developing cancer. Consequently, despite the cancer development process being fundamentally similar across different cancer types, vast differences exist in response to treatment, cellular ‘behaviour’ characteristics, and overall disease prognosis.

So, what actually is the difference between a tumour, a cancer, and a malignancy? The answer is contextual, with several of these terms (incorrectly) used interchangeably nowadays. In clinical terms, it is the distinction between benign and malignant which is actually most important, with their use alongside ‘tumour’ to define a particular growth. However, in reality, ‘tumour’ is often used when the term ‘neoplasm’ (which literally means ‘new growth’) would be more appropriate. Presumably for ease more than accuracy we now often use ‘tumour’ as opposed to ‘neoplasm.’ However, whether ‘neoplasm’ or ‘tumour’, they can be either benign or malignant – a difference that is critical and fundamental in interpreting or treating the disease.

1.2.1 Benign Tumour (or neoplasm)

This type of growth is confined to its original location and lacks the ability to invade into surrounding normal tissue, or to dissociate from neighbouring cells and spread to other parts of the body. In general, benign tumours are genetically stable, with very little change in their genotype (genetic composition) over time. Any genetic perturbation within a benign tumour does not provide it with a selective cellular growth advantage over neighbouring cells, with the cells retaining normal growth regulatory mechanisms and defined morphology and functions. As an example, the common skin wart is a benign growth caused by a viral infection, the human papillomavirus (HPV).

The restriction of benign tumours to their site of origin normally means that they can be completely removed via surgery so they are often not life-threatening. However, exceptions do exist, wherein the benign tumour is in an inoperable location and its presence disrupts and retards the normal function of its ‘home tissue’, such as some brain tumours.
1.2.2 Malignant Tumour (or cancer)

Although in the minority of cases benign tumours can be problematic to a person’s health (and so necessitate curative treatment), this very rarely involves the use of medication (commonly termed cancer chemotherapy). However, ‘cancer’ is the complete opposite and commonly requires chemotherapeutic intervention, as described in detail throughout this book.

We will now focus on what cancer actually is, how it differs to a benign tumour, and why we need to administer therapies systemically, rather than just introduce them exclusively to the site of the cancerous tumour.

There are a number of characteristic distinctions between a benign and a cancerous tumour, including cellular differentiation, growth rate, and genetic stability, and the fact that benign tumours histologically resemble their normal tissue of origin. However, the critical and defining difference between a benign tumour and a cancerous tumour is the capability of the latter to invade adjacent tissues and spread to other tissues and organs, a characteristic termed ‘malignancy’. In this context, malignant tumours (malignant neoplasms) are synonymous with cancer, with their ability to move from their origin into neighbouring tissues, and spread and disseminate throughout the body (a process defined as 'metastasis'). This invasive and metastatic capability of malignancy is exactly what makes cancer so dangerous and life-threatening, as once it has spread it can no longer be successfully dealt with by localised treatments and surgery.

In general, benign tumours grow slowly and malignant tumours grow at an accelerated rate, spreading to neighbouring and subsequently distant sites. However, there are several exceptions to this concept, with several benign tumour types growing more rapidly than some cancers because of their resident environment or the presence of endogenous growth-inducing factors etc. Despite these exemptions, it is true to say that most benign tumours develop and expand slowly over the span of months to years.

It is also important to note that not all cancerous tumours are life-threatening or lethal, and some of the most aggressive cancers are also some of the most curable. Similarly, as mentioned previously, benign tumours, although fairly innocent in nature, can in themselves cause lethality as a consequence of their location. Therefore, the risk and fate of both benign and malignant tumours is neither clear-cut nor straightforward.

1.2.3 Tumour Nomenclature and Classification

An important concept when discussing the presence and location of a tumour (and its treatment) is its classification. The descriptive and defining name for a tumour allows us to know where it is, how it associates with the surrounding tissue environment, whether it is predicted to be life-threatening, its likely prognosis, and when and how we treat it.

From a histological and anatomical standpoint, all benign and malignant tumours are composed of two cellular elements: (1) the tumour mass, composed of the neoplastic cells, and (2) the surrounding and supportive host-derived, non-neoplastic cells, comprising stromal support cells, connective tissues, blood vessels, inflammatory cells, and the extracellular protein matrix network. It is now clear that both of these cellular elements are essential for the growth, survival, and support of the tumour, involving a
bi-directional interaction and communication between the tumour and surrounding cells. This realisation was a turning-point in the management of malignant tumours, with a new wave of chemotherapies targeted towards the genetically-stable tumour microenvironment, as opposed to historical chemotherapeutics focused exclusively on the genetically unstable and often drug-resistant malignant tumour mass. This treatment concept is exemplified by several new ‘molecular-targeted’ chemotherapeutics, as discussed later in the book.

The nomenclature of both benign and malignant tumours involves three components:

i) **location** (e.g. brain, breast, lung, prostate),

ii) **type of cell and tissue from which they arose** (e.g. epithelial, mesenchymal), and

iii) **the growth behaviour of the tumour** (e.g. benign or malignant).

The location is easy to define in terms of nomenclature for the majority of tumours (with the exception of metastatic tumours, as described later). Although informative, this alone is insufficient to provide details regarding the type, characteristics, prognosis, and, importantly, the treatment of the particular tumour. These factors rely upon the identification and description of whether the tumour is benign or malignant, the embryonic origin of the tissue from which the tumour has developed, the functional basis of the originating cell type, the level to which the tumour cells resemble their cellular origin (i.e. their degree of cellular differentiation), their cellular growth pattern, and ultimately the microscopic and macroscopic histological features of the tumour. The use of a ‘common language’ when describing and defining tumours is thus essential for comparison, characterisation and classification, for diagnosis and prognosis, and ultimately in identifying the most appropriate treatment options for the particular case.

The classification of tumours, whether benign or malignant, is initially correlated with the embryonic origin from which the cell type derived. In this context, in the early stages of embryonic development there are three defined cellular layers, termed germ layers: the ectoderm, the mesoderm, and the endoderm. Of these germ layers, the ectoderm gives rise to the brain, nervous system, and epidermis (outer layer) of the skin, amongst others; the mesoderm produces supporting tissues, including bone, muscle, and blood; and the endoderm develops into internal organs, such as the pancreas, urinary bladder and liver, and the epithelial linings of the gastrointestinal tract (except the oral and anal cavities) and respiratory tract. Interestingly, the epithelial linings of the urogenital tracts (i.e. ovaries and kidneys) are derived from the mesodermal rather than the endodermal layers. An important point in the context of development is the defined nature and function of these cells originating from the different germ layers, with some specialising (or differentiating) as pancreatic cells capable of secreting hormones, others as nerve cells capable of transmitting an electrical impulse, and others differentiating into specialised acid-secreting cells within the stomach. In all cases, a balance between coordination of cellular division and focused differentiation is essential for these specialisations to be achieved, and the respective organs to develop and function. The importance and relevance of this developmental origin for tumour classification will hopefully become evident in the upcoming parts of this section, and in later chapters when discussing tumour development, malignant and metastatic potential, and response to therapy.

Although both benign and malignant tumours can develop from the same cell type (Figures 1.2.1 and 1.2.2), it is vitally important that the classification and name associated
with these distinct tumour types are clearly articulated (Table 1.2.1). In this context, benign tumours are designated by attaching the suffix –oma to the cell type from which the tumour arises. For instance, a benign tumour arising in mesodermal-derived fibrous connective tissue is termed a fibroma, and a benign tumour of fatty tissue is termed a lipoma (Table 1.2.1). The nomenclature of benign tumours of epithelial origin (endo-dermal and a few mesodermal-derived tissues) is slightly less straightforward, with classification commonly associated with their histology and constituent epithelial cell characteristics, for example glandular, squamous, or transitional epithelium. For
Table 1.2.1 Nomenclature of benign and malignant tumours.

<table>
<thead>
<tr>
<th>Tissue of origin</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumours of connective tissue and mesodermal origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoma</td>
<td>Osteogenic sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ewing’s sarcoma</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Chondroma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Muscle (smooth)</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Muscle (striated)</td>
<td>Rhabdomyoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Adipose cells</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Hemangioma</td>
<td>Hemangiosarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td><strong>Tumours of haematopoietic and lymphoid origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All blood cells</td>
<td></td>
<td>Chronic myelogenous leukaemia</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td>Acute/chronic lymphocytic leukaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myeloma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Hodgkin’s disease</td>
</tr>
<tr>
<td>Granulocytes</td>
<td></td>
<td>Acute myelocytic leukaemia</td>
</tr>
<tr>
<td>Monocytes</td>
<td></td>
<td>Acute monocytic leukaemia</td>
</tr>
<tr>
<td><strong>Tumours of the nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td>Astrocytoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glioblastoma</td>
</tr>
<tr>
<td></td>
<td>Meningioma</td>
<td>Invasive meningioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schwannoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td></td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurofibrosarcoma</td>
</tr>
<tr>
<td><strong>Tumours of epithelial origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratified epithelia*</td>
<td>Papilloma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Epithelial lining of glands*</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Basal cells of skin</td>
<td></td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Skin melanocytes</td>
<td>Nevus</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Kidney epithelium</td>
<td>Renal adenoma</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wilms’ tumour</td>
</tr>
</tbody>
</table>

(Continued)
instance, an **adenoma** is a benign epithelial tumour arising from glandular epithelium (commonly termed a polyp), and a **papilloma** is a benign tumour arising from squamous epithelium on the surface of an organ (e.g. skin, cervix, oral, and pharyngeal tissues). However, there are still exceptions to this simple **-oma** benign nomenclature, such as **melanoma**, which is in fact a highly malignant tumour of the skin, and **neuroblastoma**, a paediatric neuronal cell cancer type (although in the latter case, the suffix is actually **-blastoma**, rather than **-oma**).

Malignant tumours, to a certain extent, follow the principles used for nomenclature of benign tumours, with the clear exception that different suffixes are used (Table 1.2.1). Cancers arising from mesenchymal-derived tissues are termed **sarcomas**, rather than using the benign derivation of **-oma**. For instance, a cancer arising from fatty adipose tissue is termed a **liposarcoma**, whereas a benign tumour in the same tissue would be a **lipoma**. Similarly, a cancer of fibrous connective tissue would be a **fibrosarcoma**, as opposed to the benign **fibroma** (Figure 1.2.1). One clear exception to this rule are cancers arising in the blood and lymphatic system which, although derived from tissues of mesodermal origin and thus theoretically a type of sarcoma, are termed **leukaemia** and **lymphomas**, respectively. For this reason, **sarcomas** are effectively designated as arising in ‘solid’ mesenchymal tissues.

Malignancies developing from epithelial cells, which cover the surface of the body, line internal organs, or constitute the secretory or absorptive function of the majority of organs, are termed **carcinomas**. Since epithelia are derived from all three germ layers, these malignancies cover a spectrum of tissue types and cellular origins. Thus, a malignancy of the liver (derived from endoderm) is a carcinoma, as are those arising in the renal tubular epithelium (mesodermal origin) or the skin (ectodermal origin). An example of the different nomenclature of benign and malignant epithelial tumours is provided in the colon of the gastrointestinal tract, where a benign tumour would be termed a colonic **adenoma** (or colonic polyp) and a malignant tumour would be termed a colonic **carcinoma** (Figure 1.2.2 and Table 1.2.1).

<table>
<thead>
<tr>
<th>Tissue of origin</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Hepatic adenoma</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Transitional epithelium (urinary tract)</td>
<td>Urothelial papilloma</td>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td>Testicular germ cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seminoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td>Ovarian germ cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysgerminoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Germ cell tumour derived from multiple germ cell layers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary, testes, embryonic crest</td>
<td>Dermoid cyst</td>
<td>Immature teratoma</td>
</tr>
<tr>
<td></td>
<td>Mature teratoma</td>
<td>Teratocarcinoma</td>
</tr>
</tbody>
</table>

*Tumours from a range of tissues, derived from all three germ cell layers.*
The specialised nature of epithelial tissues, associated with different epithelial functional morphologies, provides further descriptive classification to carcinomas. Those developing from epithelia of glandular origin are prefixed adeno- (Figure 1.2.2). For instance, a malignant tumour of the glandular secretory tissue of the colon is termed a colonic adenocarcinoma (Figure 1.2.3) and one developed from glandular tissue within the kidney would be termed a renal cell adenocarcinoma. Alternatively, a carcinoma arising from the epithelial cells of a squamous morphology (i.e. skin or oesophagus) is prefixed as being squamous (Figure 1.2.2), such as an oesophageal squamous cell carcinoma.

This further sub-classification and additional descriptive nomenclature of carcinomas is important as it can further aid prognosis and guide optimal treatment for the particular cancer. For example, cancers of the lung (discussed in Section 3.4) can be divided into four major types, which are dependent upon the histology and morphology of the cancer cells: non-small cell lung cancers (NSCLCs, including adenocarcinomas, squamous cell carcinomas, and large cell carcinomas) and small cell lung cancers (SCLCs, small cell carcinomas). These sub-classified types of lung cancer grow and expand at

![Figure 1.2.3](image)

**Figure 1.2.3** Colonic adenocarcinoma. (a) Surgically resected caecum, indicating a tumour (white mass) around two-thirds of the colonic circumference. The tumour was diagnosed histopathologically as a moderately differentiated adenocarcinoma: (b) low magnification; (c) high magnification. This malignant tumour had invaded from the epithelial layer of the caecum through the underlying muscle tissue.
varying rates, demonstrate different metastatic potentials, and respond differently to chemotherapy. Although all classified as carcinoma, clear differences exist between these pathological sub-divisions of lung cancer [1]. For instance, NSCLCs account for approximately 85% of all lung cancers, and as a class are relatively insensitive to chemotherapy. Conversely, SCLCs (which are believed to derive from neuroendocrine cells within the lung) are often more rapidly growing and widely metastatic than NSCLCs, but are normally more responsive to chemotherapy (well, initially, at least). However, the high prevalence of early metastasis in SCLCs often leads to a poor prognosis, despite the favourable response to chemotherapy.

Although fairly straightforward and relatively defined, there are several exceptions to this ‘standardised’ nomenclature for describing benign and malignant tumours. As briefly mentioned above, malignancies of the haematopoietic and lymph systems are named leukaemias and lymphomas rather than the conventional sarcoma nomenclature based on their mesenchymal origin. Additionally, this family of malignancies is further sub-classified depending upon the specific cell type involved (Table 1.2.1).

Other tumour types in which the nomenclature is inconsistent and could be misleading include melanoma, mesothelioma, seminoma, and tumours described with the suffix -blastoma, all of which are malignancies. Melanomas are highly aggressive and invasive skin malignancies developing from melanocytes within the skin (see Section 3.9), mesotheliomas are malignancies of the pulmonary mesothelium commonly associated with previous industrial exposure to asbestos, and seminomas are malignancies within the testes (see Section 3.10). The suffix -blastoma is associated with many paediatric tumour types and those resembling embryonic tissues, with examples being neuroblastoma (paediatric neuronal malignancy) and retinoblastoma (paediatric cancer of the retina in the eye) (Table 1.2.1). There are also several individual tumour types named after the individual who discovered or identified them, such as Hodgkin (and non-Hodgkin) lymphoma (types of lymphoma), Ewing’s sarcoma (paediatric cancer of the bone), Kaposi’s sarcoma (malignancy of blood vessels), and Wilm’s tumour (type of renal malignancy) (Table 1.2.1).

Another intriguing tumour type with an inconsistent nomenclature and pathology are teratomas. These tumours arise from totipotential germ cells (i.e. primitive cells that have the ability to become any specialised cell type they choose) and are a mixed tumour type with potential derivations from all germ layers, being associated with ovarian and testicular tissues. Occasionally teratomas can also present at extragonadal (outside testes or ovaries) sites in children, located along the embryogenic midline path such as chest, abdomen, pelvis or lower back (sacrococcygeal) areas. Since teratomas are composed of germ cells, with their inherent ability to differentiate into any of the cell types found in the human body, they can present as a complex mixture of mature and immature cell types and tissues. Consequently, it is not uncommon for teratomas to contain epithelial tissue, muscle, nerve tissue, and even eyes, hair, and bone. It is thus no surprise that these tumours can be scientifically very interesting, but yet also daunting. The difficulty in terms of nomenclature is that teratomas can be either benign or malignant, despite the apparent benign terminology. Whereas benign teratomas (often termed dermoid cysts) are composed of mature ‘differentiated’ cells, malignant teratomas are largely composed of immature and ‘undifferentiated’ cells with potential for motility and subsequent metastatic potential.
The importance of tumour nomenclature, which in principle is simple, but in practice not straightforward, is that it provides information regarding the nature, identity, pathogenesis, and categorisation of the neoplasm and subsequently the potential prognosis and treatment options.

1.2.4 Cellular Differentiation and Tumour Grade

The degree of cellular differentiation (i.e. morphological and functional similarity to corresponding ‘normal’ cells) within the tumour mass is an important criterion for understanding tumour pathogenesis and metastatic potential, and in helping to decide the most appropriate treatment options. In benign tumours the cells are well differentiated, closely resembling normal cell morphology and histology, and functional activities. The high degree of differentiation associates with a low level of cell division and close resemblance to that of the normal tissue. For example, a chondroma is composed of mature cartilage capable of synthesising a cartilaginous matrix, reinforcing the existence of morphological similarity, a normal functional phenotype, and a high level of cellular differentiation.

In contrast, malignant cells within the tumour mass demonstrate various levels of differentiation, ranging from well differentiated to undifferentiated (i.e. anaplastic and stem-cell like). As an example, colorectal carcinomas may present histologically with a glandular morphology, indicating the presence of a well-differentiated malignant tumour. Alternatively, the malignant mass may be composed of cells with no clear morphological similarity to normal colorectal cells, lacking polarity and orientation, and weak (if any) functional activity, indicating a poorly differentiated or undifferentiated cancer. Between these two extremes are tumours classified as moderately or poorly differentiated.

The rate of growth of malignant tumours is often inversely correlated to the level of differentiation, with poorly differentiated tumours growing at a much greater rate than well-differentiated tumours. It is, however, important to be aware that there is huge variability in growth rates between tumours, irrespective of the level of differentiation or similarities in tumour pathologies. Simply speaking, all tumours enlarge over time, and it is the rate of this growth which discriminates between them, with benign and well-differentiated tumours towards one side of the spectrum and poorly differentiated aggressive tumours towards the other. As we will learn later, this is strongly linked to the degree of genomic abnormalities present and the number of ‘cancer hallmarks’ which are affected. In this context, the fact that malignancies take several years to develop into clinically evident tumours reinforces the concept of the multistep process of tumourigenesis and accumulation of several genetic dysfunctions [2,3]. This is true even in the case of acute paediatric malignancies, which begin to accumulate the underlying genetic aberrations during foetal development, before presenting as a cancer during the early years of life [4].

In a similar manner to processes occurring during embryonic development, malignant tumours, despite their limitless replicative potential, are known to contain specialised ‘stem’ cells, with the capacity for self-renewal. Although the cancer stem cell is fundamentally different to the embryonic stem cell, the underpinning concept and role is essentially the same. The source of these cancer stem cells is still under debate, being either derived from normal tissue stem cells or from dedifferentiation of ‘mature’ cells [3,5,6]. A higher proportion of these neoplastic stem cells within a tumour is believed to
correlate with a poorer prognosis [3,5,6]. The essential nature of stem cells for cancer development and persistence therefore dictates that successful cancer management is dependent upon elimination of this cell population. Unfortunately, cancer stem cells are known to be resistant to conventional chemotherapy as a consequence of their low rate of cell division and inherent protective resistance to drug therapy [4–6]. Therefore, from a therapeutic perspective, future emphasis needs to be focused on eliminating these cells to successfully destroy the root of the cancer.

Related to perturbations in cellular differentiation and pleomorphism is the loss of cellular uniformity and appropriate orientation, a state termed dysplasia (Figure 1.2.4). This is principally associated with epithelial cells, with the dysplastic cells exhibiting extensive pleomorphism and disproportionate and irregular cell division throughout the tissue. In many cases, cell proliferation (identified via the presence of mitotic cells) is evident in unexpected areas, such as in all layers of stratified epithelia or apical surfaces of glandular tissues. When dysplasia is present across the entire depth of the epithelial layer, a condition called carcinoma-in-situ can develop (see Section 3.1 for breast cancer, where we talk about ductal carcinoma in situ [DCIS] and lobular carcinoma in situ [LCIS]). This is considered a pre-invasive stage of cancer, although it is not a malignancy in its own right. This is supported by the regression of tissues demonstrating moderate dysplasia, wherein the entire thickness of epithelia is not affected. However, carcinoma-in-situ, despite not being life threatening, commonly requires therapeutic intervention based on the elevated likelihood of progression towards an invasive carcinoma.

**Table 1.2.2** Histopathological grading of malignant tumours.

<table>
<thead>
<tr>
<th>Tumour grade</th>
<th>Degree of anaplasia</th>
<th>Histological appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade unknown (GX)</td>
<td>Grade cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>Grade 1 (G1)</td>
<td>Well differentiated</td>
<td>Closely resemble normal parental cells</td>
</tr>
<tr>
<td>Grade 2 (G2)</td>
<td>Moderately differentiated</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (G3)</td>
<td>Poorly differentiated</td>
<td></td>
</tr>
<tr>
<td>Grade 4 (G4)</td>
<td>Undifferentiated</td>
<td>Highly anaplastic, cell of origin unclear</td>
</tr>
</tbody>
</table>

*Figure 1.2.4* Cervical squamous dysplasia. Whereas the epithelium is normal and stratified on the left of the image, from the centre across to the right the cells are dysplastic, with a disorderly pleomorphic appearance and abnormally large nuclei. The dysplastic process involves the full thickness of the epithelium, but the basement membrane remains intact. (Courtesy of Ed Uthman from Houston, TX, USA under the Creative Commons Attribution 2.0 generic licence.)
Clinical identification and communication of the degree of anaplasia and/or differentiation is an important central histopathological concept, essential for the clinical prediction of tumour prognosis, pathogenesis, metastatic potential, and therapeutic options. The tumour grade is assigned by an experienced pathologist and is recorded as one of four grades (Table 1.2.2 and Figure 1.2.5). There are few exemptions to this system, which may also use an alternative or additional system, such as the bone and soft tissue sarcomas, which commonly state ‘high’ or ‘low’ grade, and the prostate, which is commonly also classified using the Gleason scoring system (see Section 3.8).

**Figure 1.2.5** Microscopic view of transitional cell carcinomas of the urinary bladder, indicating different levels of cellular differentiation and tumour grade. Increased pleomorphism and increased nuclear-to-cytoplasmic ratio is visible with increasing grade and decreasing differentiated status.
1.2.5 Tumour Invasion and Metastasis

The defining feature of malignancy is the ability of cells to invade and metastasize (disseminate) to other areas of the body, rather than remaining confined to their site of origin. These are fundamental hallmarks of cancer, as described in the later parts of this section. A benign neoplasm (and to a certain extent carcinoma-in-situ) will, in theory, grow until cell–cell contact or physical barriers restrict its continued expansion, as they do not have the capacity to infiltrate or invade into neighbouring tissues. These benign growths will slowly expand, but remain demarcated from their host tissue. This localised behaviour thus allows feasible surgical resection of these growths.

Conversely, malignant cells are not ‘contact-inhibited’ and the resultant tumour will progressively invade and penetrate the surrounding tissue. Once invasion into adjacent tissues has occurred, surgical resection becomes progressively more difficult because of the greater complexity associated with removing all the cancerous cells (Figure 1.2.6). Consequently, the removal of a wide margin of surrounding normal tissue is required when excising a malignant tumour. Although this is clearly practical for certain tumour sites and locations, such as colorectal cancers, it is particularly difficult for others whereby the surrounding tissue is either minimal or precious, such as in the case of brain tumours. This resected margin is clinically important, as it permits the assessment of whether the tumour mass was fully removed.

The initial step in the progression from carcinoma-in-situ or a localised malignancy is invasion of the tumour cells through the basement membrane (on which epithelia reside) into the underlying connective tissue. These cells continue to grow and the tumour mass expands, invading further into the host tissue. For instance, a colon adenocarcinoma will originate in the epithelial mucosa (lining the colonic lumen), invade through the basement membrane into the underlying submucosa (connective tissue), into the surrounding musculature, and then eventually through the external surface of the colon and into adjacent organs (e.g. urinary bladder, small intestine, pancreas) or peritoneum.

Figure 1.2.6 Metastatic tumours in the liver. A cross-section of liver containing several pale tumour deposits, originating from primary pancreatic adenocarcinoma.
A major outcome of local invasion is that the tumour cells have access to the vasculature and lymphatic systems, the vessels of which are located in the submucosa and subsequent tissue layers, which in turn permits their ‘escape’ from their locality and passage to other parts of the body. The lymphatic system is the body’s ‘drainage’ system, through which fluid from tissues re-enters the circulatory system. This involves lymphatic fluids (drainage from tissues) progressing through a number of lymph nodes (resident site for lymphocytes, to fight infections), initially local, and then distant, to the originating organ. Lymphatic spread, common with carcinomas, involves tumour cells entering lymphatic vessels and ‘draining’ into local lymph nodes, followed by further spread to regional and distal lymph nodes and other organs. The pattern of lymph node spread is heavily dependent upon the locality of the tumour and the natural drainage routes from that respective tissue or organ. For instance, lung cancers generally metastasise first to the regional bronchial lymph nodes (‘apex’ of each bronchial lobe), then the tracheobronchial lymph nodes, and ultimately the hilar lymph node (site at which bronchial tubes enter the lungs). From there the tumour cells progress to the regional lymph node, termed a ‘sentinel lymph node’ (identified via injection of a tracker dye near the primary tumour), and then potentially to other lymphatic sites within the body, or into the circulatory system. Since the lymphatic system is a common site for cancer metastasis, with tumour cells depositing and transiting through lymph nodes, the degree to which a tumour has spread is commonly assessed by histopathologically determining the presence and extent of tumour cells within lymph nodes, both locally and regionally (and, via imaging techniques, distant lymphatic nodes).

In addition to lymphatic drainage and subsequent metastasis through this route, cancer cells can also metastasise via the circulatory system (haematogenous spread). This route is favoured for sarcomas, but is also evident for some carcinomas. In this case, tumour cells invade (intravasate) the blood vessels and thus the circulation, consequently allowing the tumour cells to transfer to any site in the body. The tumour cells then arrest in the capillary bed of the new tissue, penetrate the capillary endothelium (extravasate), survive attack by the natural immunological defence systems (phagocytic and natural killer cells) associated with exit of materials from the blood, and then invade this new host tissue. In the vast majority of cases, tumour cells preferentially enter the venous system, draining the site of the malignancy (primarily because of the reduced blood pressure, increased vessel thickness, and subsequent restrictive factors). Tumour cells are then trapped in the next capillary bed network, with the liver and lungs being the most frequently involved secondary sites because of portal venous system drainage into the liver and high blood flow to the lungs. Alternatively, tumour cells can spread by invading a natural body cavity and the seeding of this site. For instance, nervous system malignancies, such as medulloblastoma, can enter the cerebrospinal fluid and re-implant on meningeal surfaces of the brain and spinal cord. In addition, ovarian carcinomas often spread via this route, whereby they ‘exit’ the ovary into the peritoneal cavity and disseminate throughout this cavity, causing growths to appear and ascites to form. Interestingly, in this situation the secondary cancers implant throughout the abdominal cavity but do not routinely invade into other tissues and organs therein.

Although the local anatomy is an important driver for metastatic spread, it does not fully account for systemic metastatic dissemination of many tumours. Certain tumours characteristically spread to specific structures, whilst others do not, for example sarcomas commonly spread to the lungs, prostate and breast cancers to the bone, and lung
carcinomas to the brain. In contrast, despite being highly vascularised, skeletal muscle is a rare site for tumour metastasis. The basis for this ‘unexpected’ tissue-specific spread is not largely dependent upon gravity or direct tissue drainage (as exemplified by lung cancer metastasis to the brain), but rather a concept termed the ‘seed and soil’ theory [7]. The principle of this theory is that the new ‘host’ tissue must have a permissive environment for tumour growth, including an appropriate extracellular matrix, growth factors, and supportive cellular network. The attraction of the tumour cells to a permissive and receptive tissue involves cancer cells harnessing chemoattractant systems normally utilized for directed chemotaxis (movement) of leukocytes and other inflammatory cell types. This is supported by the high-level expression of specific chemokine receptors on cancer cells, complementary to the high levels of the receptor ligands at the preferential metastatic site. However, the precise route and site of metastasis cannot be predicted with any form of cancer. Frustratingly, the capacity for invasion, dissemination and colonisation of secondary tissues varies with different classes of tumour, different patients, and even more so with the heterogeneous nature of cells within the tumour itself.

It is important to be cognisant that escape of a cancer cell from the primary tumour into a body cavity, the circulatory, or lymphatic system is only the initial step in metastatic spread. The tumour will encounter formidable barriers to metastasis, with the vast majority of cells making it to the circulation being eliminated. It is estimated that less than one in 10,000 tumour cells will successfully establish as a metastatic growth. However, the concept of dormancy or prolonged survival of micrometastatic deposits without progression, whereby the cells are awaiting either a suitable growth environment or ‘trigger’ for re-initiating growth is a factor that should be remembered in this context.

1.2.6 Clinical Staging of Cancer

In the preceding sections tumour nomenclature and tumour grading were discussed, both key contributors to identifying and managing tumours (and consequently improving patient survival and quality of life). To reiterate, we use specific naming criteria to discriminate benign from malignant, provide information regarding the origin and likely behaviour of the tumour, and additionally use a numerical system to attribute the level of tumour ‘aggressiveness’ or ‘grade.’ Of course the object of all of these descriptive factors is to identify the patients for which a particular treatment approach should be adopted, and to provide prognostic indicators of survival and likelihood of cure.

Despite knowing the type and classification of the tumour, and the extent of cellular differentiation within the tumour, the third important strand of critical significance for prognostic prediction and identifying the best treatment plan is the tumour stage. By this we mean the extent of the disease at presentation, or the degree to which the cancer has progressed, invaded or metastasized. In addition to representing the growth rate and invasive activity of the tumour, tumour stage also indirectly reflects the tumour–host tissue relationships, which have prognostic and therapeutic implications.

Categorisation of tumours into stages arose from the fact that survival rates were higher for localised neoplasms relative to those in which the tumour had extended
beyond its originating tissue or organ [8]. Using this primitive two-group system, tumours were often referred to as early or late cases, suggestive of a time-dependent regular progression for cancer. This evolved into systems wherein anatomical and histological factors became the basis for staging, commonly based on pre-surgical radiographic examination (e.g. magnetic resonance imaging [MRI], X-ray, or computed tomography [CT]), evaluation during surgical resection, and post-surgical pathological assessment. There have been several systems of staging used over the years in this respect, often utilised for specific types of tumour or neoplasm. However, the description of the same aspects of tumour progression and severity in different ways led to significant confusion and complications, with a lack of non-standardisation between hospitals, geographical regions, and subsequently patients. There are now two unified methods of staging generally accepted for use: the American Joint Committee (AJC) system [9] and the TNM system developed by the International Union Against Cancer [8] (although close agreement now exists between these two systems) [8,9].

As we shall see in detail in Section 3, the staging or extent of the disease is described in terms of three parameters: the size and local invasiveness of the primary tumour, the extent of lymph node involvement, and the presence of distant metastatic tumour deposits. Using the AJC method, cancers are categorised as stages 0 to IV depending upon the size of primary tumours, coupled to the pattern of spread to the lymph nodes and presence or absence of metastases [9]. This system is commonly applied as a generic comparator for treatment modalities, as indicated in specific cancer types in Section 3. The more common TNM staging system is often more precise, while remaining simplistic, defining the tumour in terms of [8]:

- **T** the extent, size, and local invasiveness of the primary tumour
- **N** the absence or presence and extent of regional lymph node metastasis
- **M** the absence or presence of distant metastasis.

Through the addition of numbers against these three components, the extent of the malignant disease is indicated: T0, T1, T2, T3, and T4 describing the increasing size and extent of local invasiveness of the primary tumour; N0, N1, N2, and N3 indicating progressively advancing involvement of lymph nodes; and M0 and M1 signifying the absence or presence of distant metastases, respectively.

In terms of T-staging, prognosis in several cancer types simplistically relates to the size of the primary tumour. In others, however, the prognosis is not just a factor of tumour size but rather the depth of invasion (e.g. colorectal, non-small-cell lung cancer, and urinary bladder cancer). In melanoma, the depth of tumour involvement is believed to be a better prognostic indicator than other factors.

The N-staging also has major implications for prognosis, with the classification of N3 node involvement indicating a poorer prognosis than that of N1. Additionally, N-stage designation is also indicative of the probability of haematogenous or lymphatic spread. In many cases, the N stage is a strong indicative marker of tumour aggressiveness, metastatic potential, and ultimately patient survival.

Whereas in the TNM system, T and N are highly informative of stage of disease progression, it is the presence of metastasis (i.e. M1 classification) which represents the worst-case scenario, for both prognosis and treatment, being beyond the scope of localised therapy, necessitating systemic chemotherapy, and associating with poor survival rates. However, despite being unquestionable that M1 cancers relate to
significantly reduced patient survival, it is important to consider that many tumours reported as M0 (i.e. absence of observable metastatic deposits) may actually have micrometastases, it is just that they are below the level of detection or not yet found. Although it may be difficult to comprehend, and can often be stated as unacceptable (or potentially unethical) by patients and their families, clinicians will often evaluate the ‘conventional’ sites for metastasis of the particular tumour type, and will not spend extensive time searching for the existence of micrometastatic deposits. It is not that the clinician does not care about metastases, and nor is this a cost-saving exercise, rather it reflects the fact that, unless the metastasis reveals itself or causes a physiological dysfunction, it is actually difficult to detect or even know it is there. In this context, searching for the existence of small metastatic deposits in all patients (which in the majority of cases will not be there) would be analogous to tracking down the hypothetical needle in a haystack, and would be associated with the use of extensive diagnostic resources, and increased patient anxiety and stress. However, significant advances are constantly being made in imaging and diagnostic capabilities through improvements in sensitivity, the combination of different methodologies (e.g. PET/CT, as described below), and the ability to undertake full body scanning, resulting in accelerated and earlier detection of these micrometastases. It is also worth remembering that the development of these micrometastatic deposits necessitates increased invasiveness of the primary tumour (i.e. T2–T4) and commonly lymph node positivity (i.e. N1–N3). Therefore, since T and N staging directly inform clinical prognosis, metastatic potential, and the type and severity of therapy, these ‘micrometastases’ are often encompassed and ‘captured’ within the diagnostic framework and consequent treatment options.

There are, however, drawbacks to the use of the TNM system for certain cancer types, such as lymphoma, wherein the disease is diffuse, and leukaemia, where there is no focal growth or localised invasion. In a few other cancer types, despite TNM being widely accepted, additional staging systems are often used, such as Duke’s staging for colorectal cancers (although this is often based on pathologist preference and favouritism more than anything else), as described in later chapters. Another system is the FIGO (Federation International of Gynaecological Oncologists) system used for several gynaecological tumour types, although clear comparators are made with the TNM system (see Section 3.6).

In effect the TNM system (and the vast majority of alternative schemes) is an indicative notation for communicating the extent and putative prognosis of a malignant tumour across the clinical care team. However, there are slight differences within the scheme that often cause confusion or are misinterpreted, the most common being the clinical versus pathological classification of the tumour. A clinical (pre-treatment) staging is initially provided, which is designated as cTNM (or often just TNM), based upon factors noted during physical examination, imaging, surgical exploration, and other clinical analyses. Following resection and histopathological evaluation, the staging is reported as pTNM (indicating input from a pathologist). This latter classification requires evaluation of the resected (or biopsied) tumour to identify the highest pT category, histological analysis of the surgically removed lymph nodes to attribute the highest pN classification, and pathological assessment of distant metastases (pM) by microscopic examinations. The pTNM classification subsequently guides therapeutic options and allows prognostic estimations.
In the majority of cases, the use of the TNM staging system and supplementary schemes invariably alters and informs the management of the particular clinical case. For instance, surgical interventions and localised therapies (i.e. radiotherapy) would not be a primary option for high-stage, lymph-node positive disseminated cancer (e.g. T4, N3, M1). In this particular case, where the patient has detectable metastatic disease (M1), the disease is unlikely to be curable and thus prolongation of the life expectancy through the appropriate use of systemic chemotherapy would be the most appropriate treatment regimen. These factors are addressed for specific cancer types in Section 3.

### 1.2.6.1 Imaging Methodologies for Identification and Staging of Cancers

There are many techniques and technologies now used to assist and derive the diagnosis and staging of cancers, with significant advances in imaging technologies and their precision over the past few decades. There are now several different modalities available in this regard, categorised as either anatomical or functional imaging approaches. Within this book it is not possible to explain all of these methodologies in great detail, so the following section provides an overview of the common techniques and their utility in terms of diagnosis and treatment selection.

At first presentation of a patient with suspected cancer, investigations including clinical biochemical analyses (e.g. blood counts, liver enzymes tests, renal function) and physical palpation are often performed. Depending upon the location and suspected origin of the cancer, these tests may be supplemented with other tests, such as chest X-rays or urine analyses. For instance, a positive chest X-ray would support the presence of primary tumours in the lung, lymph node enlargement, or potentially metastatic deposits from other cancers elsewhere in the body. A positive response would thus lead to further in-depth investigations and clinical imaging to confirm diagnosis and enrich the degree of precision for staging of the tumour [10].

For the vast majority of imaging techniques, these investigations are time-consuming, expensive, and require highly skilled technical and analytical staff, but their use often helps increase confidence in diagnosis and cancer staging, or to address specific questions related to treatment options.

**Ultrasound investigations** rely upon differences in echo patterns obtained from tissues when interrogated with ultrasonic sound waves. These echoes are produced in response to changes in densities of tissues, unless the tissue under investigation is shielded by bone or gas. Consequently, this technique is mainly used for analyses of soft tissues [11] or the abdomen, especially liver metastases [12]. The advantages of this technique are its cheap, non-invasive nature and flexibility, allowing evaluation of tissue from many different angles; an example is provided in Figure 1.2.7.

**Computed tomography (CT)**, sometimes also called a computerised axial tomography (CAT) scan, is now probably the most common anatomical imaging technique used in the diagnostic evaluation of cancers. This imaging modality is more sensitive than ultrasound, albeit more expensive, but provides a greater level of anatomical diagnostic detail [11]. CT imaging exploits differences in X-ray attenuation between tissue types, with the presence of a tumour identified by organ distortion, enlargement, or alteration of the density. This scanning technique functions to produce a series of cross-sectional images from different angles through the area investigated, generating three-dimensional images from a series of two-dimensional scans, thus allowing the analysis of
anatomical structures at varying depths within the body and in different geometric planes (examples are provided in Figures 1.2.8 and 1.2.9). In many cases, imaging accuracy is further improved through the use of intravenous contrast reagents [10,13]. In terms of tumour classification and staging, CT is of use in defining the T stage (degree of tissue invasion of primary tumour), and dissemination of tumours both regionally

Figure 1.2.7 Identification by ultrasound imaging of hepatic metastases of an ovarian carcinoma (identified by the arrow). Source: Reproduced with kind permission of Dr. Geertsma.

Figure 1.2.8 CT scan (axial cross-section) through the thorax. A large adenocarcinoma tumour mass is located in the periphery of the left lung. (Image provided by Yale Rosen under the Creative Commons Attribution-Sharealike Licence 2.0 via Wikimedia Commons.)
(lymph nodes; \( N \) staging) and to distant sites such as the liver (\( M \) staging). In this context, CT imaging has significant advantages over conventional X-ray imaging because of its inherently high contrast capability and subsequent ability to distinguish even extremely small differences in tissue density (e.g. subpleural malignant deposits). However, since CT images are enriched by the adipose tissue of organs, clarity and reliability of anatomical detail is reduced via loss of these fat planes. Furthermore, CT scans are of limited value in the tracking of a primary tumour following the detection of distant metastases.

CT imaging has particular strengths, relative to other anatomical imaging modalities, for assessing tumour spread in the thorax [14]. In cancers of the lung, this technique has significant advantages over chest X-rays in the diagnosis of advanced cancers through detection of smaller tumours [15] and nodal staging through the ability to evaluate the involvement of the hilar lymph nodes (the site at which bronchial tubes enter the lungs) and regional lymph nodes [16]. Similarly, CT is the primary modality utilised for the diagnosis and staging of asbestos-related mesothelioma and pleural malignancies, including the extent of lymph node positivity and degree of extrathoracic spread [17].

In addition to tumours of the thorax, CT imaging also has applicability for diagnosis of cancers in the abdominal cavity [18–20]. In particular, it has significant value in the diagnosis of colorectal tumours and is currently the most common modality for the evaluation of treatment response in advanced colorectal cancer [19,21,22]. The use of dynamic contrast-enhanced CT (DCE-CT), involving the introduction of contrast agents and utilisation of CT imaging as a tool for measuring tumour blood flow via perfusion CT, has also shown validity for the assessment of treatment options, and in monitoring subsequent responses to both targeted and loco-regional therapeutic approaches for several cancer types located in the thorax or abdominal cavities [21–24].

It is important to note, however, that the interpretation of CT scans can be difficult, leading to the possibility of both false positive and false negative results. For instance, in

![Figure 1.2.9 CT scan through the upper abdomen. Characteristic appearance of metastatic deposits on a contrast-enhanced axial CT scan. Deposits appear as negative defects against the normally enhanced liver. (Image provided by James Heilman under the Creative Commons Attribution-Sharealike Licence 3.0 via Wikimedia Commons.)](image)
the case of colorectal malignancies a false negative may arise for a lymph-node positive cancer in which the lymph node appears within normal size limitations, and a false positive may arise as a consequence of natural variations in colonic topography.

*Magnetic resonance imaging (MRI)* creates anatomical images based on differential tissue relaxation times after radiofrequency excitation [10,25,26]. MRI detects and processes the signals generated when hydrogen atoms (abundant in water and fat molecules within tissues) placed in a strong magnetic field are excited by a resonant magnetic excitation pulse, emitting a nuclear magnetic resonance signal. The differences in this signal between tissues and tumours results in an image of the investigated anatomical being created, with inherent differences in contrast between tissues (Figure 1.2.10) [26]. Thus MRI, which is non-radioactive, is fundamentally different to CT, which exploits differences in X-ray radiation attenuation between tissues to produce anatomical representations of the investigated body area [10].

MRI is a very versatile technique, with high spatial resolution and good soft tissue contrast. Relative to conventional CT, MRI has the capability to simultaneously report anatomical and functional information in cancer diagnosis, offering the opportunity to evaluate tumour pathophysiology and heterogeneity, and to provide increased confidence in tumour staging and identification of viable treatment options. Improvements in MRI include the ability to use different pulse sequences to highlight different tissues [25,26], variations in the MRI process and analysis (e.g. diffusion weighted MRI;
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DW-MRI) [25–27] and the incorporation of specific contrast agents into the procedure [25,26]. The DW-MRI technique relies upon the diffusion of water within the tissue, with tumours demonstrating a higher DW-MRI signal relative to other tissues because of the high cellularity and limited extracellular spaces within tumour tissue [25–27]. The incorporation of exogenous contrast agents, either simple paramagnetic metal ion–ligand complexes or superparamagnetic particles, has allowed further refinements and greater sensitivity, and the expansion of imaging capabilities to this imaging technique, including dynamic susceptibility contrast MRI (DSC-MRI) and dynamic contrast-enhanced MRI (DCE-MRI). The DSC-MRI technique is generally restricted to the clinical evaluation of perfusion in brain tumours, whereas DCE-MRI involves imaging before, during, and after administration of the contrast agent. In both cases, the dynamic data allows evaluation of tissue kinetics and consequent physiological activities [25–27]. In addition to diagnostic versatility, dynamic MRI approaches and contrast agents are also now important in the assessment of therapeutic response because of perturbations in tissue permeability, tumour perfusion, and changes to blood volumes and flow [25–27].

Tumour identification and diagnosis using MRI has significant applicability in a vast number of soft tissue solid cancers, especially sarcomas and brain tumours (Figure 1.2.11) [19,26,27]. In recent years, the scope of MRI has expanded to include the evaluation of the whole body in paediatric cancer patients, primarily because of its radiation-free nature and advanced ability to simultaneously provide functional tumour information [28].

The major drawback to MRI is the relatively long acquisition time and invariably lower sensitivity compared to other techniques [10,25]. However, the sensitivity, quality,
and acquisition times continue to improve through new approaches and technological innovations such as parallel imaging and as higher field strengths are developed and introduced [25,26].

**Positron emission tomography (PET)** is a non-invasive imaging modality which produces a three-dimensional image of functional processes in the body, rather than anatomical structure [10,29]. This technique provides functional or metabolic assessment of cancer through detection of tracers labelled by positron emitters. PET thus provides information regarding tumour physiology and biochemical activity, which aids and supports tumour staging, rather than defining it in its own right [10,29].

Mechanistically, a probe comprising a metabolically active molecule incorporating a $\gamma$-ray emitting radioisotope is introduced into the patient and its uptake and metabolism monitored. The most common probe used in the clinic is 18-fluorodeoxyglucose (FDG-PET), the uptake of which indicates glucose metabolism (and thus the enhanced glycolysis associated with malignancy), enabling differentiation between malignant and benign tissue [29,30]. There are now an increasing number of probes for a range of tumour molecular characteristics, such as the use of $^{18}$F-fluoromisonidazole for the measurement of tumour hypoxia, with several others targeted against a range of tumour characteristics and specific tumour biomarkers to supplement and advance diagnostic imaging [30,31].

Despite the numerous advantages provided by PET in relation to tumour ‘activity’, its limited spatial resolution and inability to provide detailed morphological information means that it alone is insufficient to support tumour staging.

**Multimodal imaging strategies.** Despite morphological imaging techniques, such as CT and MRI, providing significant anatomical tumour detail, they are limited in regards to physiological and molecular information. Conversely, whereas functional imaging approaches, including PET, provide a depth of information regarding physiological activity they provide very little detail relating to tumour morphology. Consequently, anatomical and functional imaging strategies are now commonly combined to provide the greatest level of information to aid clinical diagnosis and improve staging of cancers, creating modalities such as PET/CT and PET/MRI [10,17,19,26]. One clear advantage of these combinations is that changes in functional activity, such as increased glucose metabolism, are associated with more aggressive, invasive and poorly differentiated cancers and the need for higher intensity therapy. Similarly, functional and metabolic changes within a tumour are detectable prior to any physical morphological alterations, permitting earlier cancer staging at diagnosis.

PET/CT is now considered the standard of care for cancer through the combined provision of precise CT anatomical information complementary to the metabolic and physiological activity provided by PET, with applicability for staging a number of cancer types. In particular, PET/CT has been shown to be effective in imaging of cancers of the lung, breast, head and neck, oesophagus, colon and rectum, with its validity in several other types also suggested. The additional accuracy of PET/CT has been reported to improve non-invasive staging in a wide range of cancers in comparison to PET or CT alone [29,30,32]. For example, tumour staging with PET/CT in lung cancer identifies a greater number of patients with mediastinal and distant metastatic disease relative to CT or MRI alone [29]. Additionally, because PET/CT can be used to image the whole body, and thus help identify distant metastases, this technology has significant impact upon both tumour staging and choice of treatment, which theoretically could include a change from surgical to chemotherapeutic intervention.
Figure 1.2.12 PET/MRI imaging of metastatic colon cancer. Top, transaxial MRI indicating two low signal masses in the liver; middle, contrast-enhanced (gadoxetate disodium) transaxial MRI image indicating enhancement of the liver masses, consistent with metastatic colon cancer; bottom, PET/MRI image indicating high-intensity FDG activity, confirming the presence of malignant deposits. The specificity of the methodology is shown by the detection of a mass by MRI (red circle, top image) with lack of PET-detectable metabolic activity (red circle, lower image). Mass identified as a benign haemorrhagic cyst. (Image obtained from Matthews et al. [35] under the Creative Commons Attribution License.)
PET/MRI is a more recently adopted modality than PET/CT, showing significant promise in terms of diagnosis, staging, and identification of the most appropriate treatment regimen in cancer (Figure 1.2.12). As discussed previously, the use of MRI is advantageous over CT due to a lack of ionising radiation, improved soft-tissue contrast, and the diversity of options regarding image acquisition and morphological assessments (e.g. DCE-MRI, DW-MRI etc.) [25–27]. Although previously problematic due to technological issues, the advent of combined and integrated PET/MRI systems led to a revolution in this particular technology [33,34].

Although still in its relative infancy, the increased soft-tissue contrast offered by PET/MRI imaging is predicted to prove beneficial in the staging of many cancer types, including those located within the pelvic area (e.g. gynaecological and prostate cancers), brain, head and neck, musculoskeletal system, and in the staging of hepatic metastatic deposits [33,36]. In lung cancer no significant advantage for the use of PET/MRI over PET/CT has yet been reported for thoracic staging of the disease. However, detection of metastases (and thus designation of the M stage) is suggested to be marginally superior for whole-body PET/MRI in lung cancer, with increased confidence for tumour staging for organs such as the brain and liver [33]. In contrast, it is unlikely PET/MRI will prove superior to PET/CT for detection of pulmonary metastases. With regards to cancer of the colon and rectum, PET/MRI is expected to be more sensitive and accurate for detection of metastatic liver disease and accurate non-invasive staging of the malignancy. Based on the fact that the evaluation of primary rectal cancer is a particular strength of MRI, the initial staging and presence of tumour-positive lymph nodes in this disease is predicted to be superior with PET/MRI compared to PET/CT or other modalities [33]. However, the greatest advantage for PET/MRI is the diagnosis and staging of cancers in children and adolescents, through the greatly reduced radioactive exposure of this methodology relative to those involving CT imaging [33,37]. Despite significant promise, the ultimate barrier to the use of PET/MRI relative to the commonly used PET/CT as a clinical approach may be the cost justification of the equipment and complexity of the imaging approach therein.

References

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