

## CHAPTER 3

# Diagnosis, staging, treatment intent, and planning

## Chapter contents

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## Early clinical detection

Early detection of cancer is crucial in improving the patient's chances of successful treatment. Early clinical detection means diagnosing the cancer when it is localized and has not developed regional or distant spread to lymph nodes or other tissues.

## Clinical symptoms and signs of cancer

Cancer normally presents with signs or symptoms as a result of changes in normal physiological function. A cancer can cause signs or symptoms either locally at the original site, or once it has spread elsewhere in the body. The local signs and symptoms will depend on where the cancer started. For example, a patient with lung cancer may present with cough, haemoptysis, or breathlessness. If that patient's cancer has spread elsewhere, they may have distant signs and symptoms such as pain from bone metastases or weight and appetite loss related to liver metastases. These non-specific signs and symptoms are often only recognized as having been heralds of malignancy in retrospect.

## Stop and Think

### Difficulties of general practice

Less than 3% of patients who present with rectal bleeding to their GP will have cancer.

## Cancer detection, diagnosis, and staging

Once cancer is suspected, the diagnosis must be confirmed or excluded, usually by obtaining a histological biopsy. If a positive diagnosis is made the extent of the diagnosis must be determined by further investigations.

Establishing that a cancer is present does not provide enough information to start treatment. The temptation to jump to therapeutic decisions must be resisted until an accurate and comprehensive assessment of the patient and their disease has been made. The more that is known about the tumour and the patient, the greater the likelihood that the most effective treatment can be given.

### Key elements in accurate diagnosis and staging

The *histological nature* of the particular tumour is usually determined after fine-needle biopsy, core biopsy, surgical biopsy or excision of a mass.

The *extent of spread of tumour* requires clinical, radiological, biochemical, and sometimes surgical assessment.

### Histological assessment

Expert pathological input is vital in cancer diagnosis and treatment. The pathologist will aim to confirm that a lesion is indeed malignant and also confirm the tissue in which the cancer originated. It is important to know whether the cancer has been fully excised, what the grade is (i.e. whether it appears more or less aggressive,

and any special molecular or biochemical features that may influence treatment.

### Radiological imaging

Marked improvements in non-invasive or minimally invasive imaging techniques have greatly reduced the need for staging surgery. However, laparoscopic assessment of intra-abdominal tumours, such as stomach or ovarian cancer, may detect small peritoneal secondaries and thus radically alter treatment strategies.

An increasing number of medical imaging procedures exist to detect cancer. These include:

- ◆ Plain or contrast radiography
- ◆ Computerized tomography (CT)
- ◆ Radioisotope scanning
- ◆ Ultrasound (US)
- ◆ Magnetic resonance imaging (MRI)
- ◆ Arteriography
- ◆ Positron emission tomography (PET)

MRI and CT techniques are non-invasive techniques that can produce cross-sectional pictures of the body to show the shape, size, and location of a tumour. They are important in staging patients and in assessing response to treatment. The ability to create three-dimensional images also permits better staging and planning for surgery and radiation therapy. Whilst CT is generally preferred to MRI when evaluating the lungs and abdominal cavity, MRI is superior for imaging the mediastinum, liver, and pelvis. Both can be used to examine the brain, but MRI is more sensitive and can also be used to assess the spinal cord.

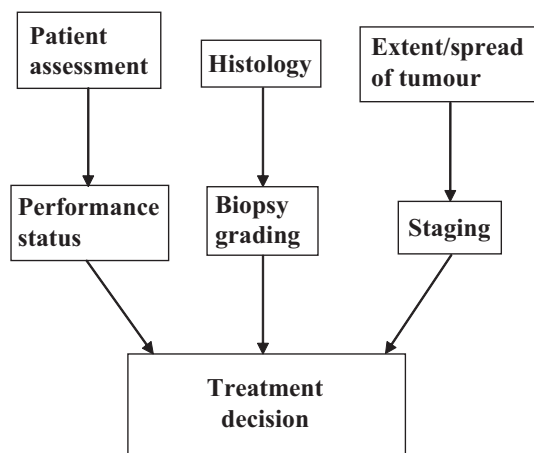


Fig. 3.1 Diagram of process of diagnosis and staging.

#### Key Facts

##### Spiral CT

A spiral (or helical) CT scan is a new kind of CT. During spiral CT, the X-ray machine rotates continuously around the body, following a spiral path to make cross-sectional pictures of the body. Benefits of spiral CT include:

- ◆ It can be used to make three-dimensional pictures of areas inside the body
- ◆ It may detect small abnormal areas better than conventional CT
- ◆ It is faster, so the test takes less time than conventional CT

## Stop and Think

### CT scan risks

A CT examination has a radiation dose that may be associated with an increase in the possibility of fatal cancer of approximately 1 chance in 2000. This increase in the possibility of a fatal cancer from radiation can be compared to the natural incidence of fatal cancer in the UK population, about 1 chance in 4. In other words, for any one person the risk of radiation-induced cancer is much smaller than the natural risk of cancer. Nevertheless, this small increase in radiation-associated cancer risk for an individual can become a public health concern if large numbers of the population undergo increased numbers of CT screening procedures of uncertain benefit. [http://www.pueblo.gsa.gov/cic\\_text/health/fullbody-ctscan/risks.htm](http://www.pueblo.gsa.gov/cic_text/health/fullbody-ctscan/risks.htm)



**Fig. 3.3** Contrast study

A spot view from a barium enema in another patient with a history of rectal bleeding shows the typical appearance of a cancer involving the descending colon. There is marked concentric narrowing of the bowel lumen with associated shouldering of the edges, giving the typical apple-core appearance of a bowel cancer (arrow).



**Fig. 3.2** Plain radiograph

Frontal chest radiograph of an elderly patient who presented with haemoptysis. The patient was a heavy smoker. The radiograph shows a large shadow (arrows) extending from the right hilum to the periphery of the lung. The mass was biopsied percutaneously by a radiologist and was shown to represent a primary lung cancer.

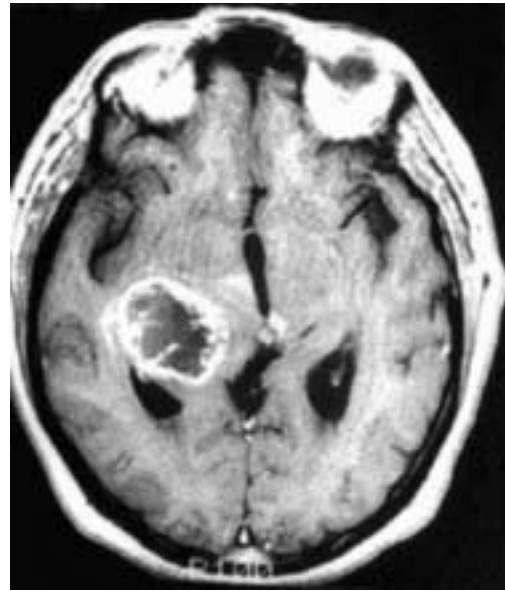


**Fig. 3.4** Ultrasound (US)

Seen in a 51-year-old woman with abdominal distension. US shows bilateral adnexal masses, massive free fluid and seeding along the broad ligament. Laparotomy revealed multiple metastases attached to the abdominal wall.



**Fig. 3.5** Computerized tomography (CT)  
Axial CT scan of a middle-aged man who presented with haematuria. The scans were performed through the level of the kidneys following the injection of intravenous contrast. There is a large mass involving the right kidney. There is marked enhancement of the mass, indicating hypervascularity. The right psoas muscle is directly invaded by the tumour (open arrow). The inferior vena cava is displaced anteriorly by the mass (closed arrow). The mass was confirmed histologically as renal cell carcinoma. The presence of local muscle invasion carries a poor prognosis.



**Fig. 3.7** Magnetic resonance imaging (MRI)  
Glioblastoma multiforme – MRI scan showing tumour in frontal lobe <http://www.sd-neurosurgeon.com/diseases/glioblastoma.html>



**Fig. 3.6** Magnetic resonance imaging (MRI) (normal sagittal view)  
The two major advantages of MRI over other imaging modalities are its lack of ionizing radiation and its ability to view anatomy and pathology in multiple planes. T1-weighted images best demonstrate anatomy. T2-weighted images best demonstrate pathological conditions because most inflammatory and neoplastic processes appear bright in signal as a result of their increased water content.

## Future Possibilities

### Positron emission tomography (PET)

PET will increasingly be used for tumour localization and follow-up. PET scanning uses positron-emitting isotopes of oxygen, nitrogen, carbon, fluorine, and rubidium. Positrons are particles identical to electrons except that they are positively charged. Positrons travel a short distance, giving up kinetic energy by Compton interactions, and finally colliding with a free electron, resulting in total annihilation. It is the photons from the total annihilation of the positron and electron that are detected by PET scanning. A ring of detectors is placed around the area to be imaged which picks up the energy released from the annihilation process. Since each annihilation originates from a specific point in space, an image is generated which contains spatial information.

PET does not offer such high resolution as CT or MRI but provides functional and metabolic information. One of the commonest agents used in PET scanning is 5-FDG (fluorinated deoxyglucose). Because glucose is so avidly taken up by actively dividing cells such as cancer cells, 5-FDG tends to collect in cancer cells, so that tumours are shown as bright spots. PET may therefore help to distinguish benign from malignant lesions and can be helpful in deciding whether a residual mass after cancer therapy represents fibrosis or residual tumour.

## Goals of cancer staging

Clinical decisions regarding the treatment of a particular patient are based upon the histological diagnosis and anatomical extent or stage of the cancer.

The objectives of cancer staging and histological classification are:

- ◆ To allow the clinician to determine the aim of treatment (palliative or curative)
- ◆ To aid the clinician in planning the type of treatment
- ◆ To give some indication of prognosis for the patient
- ◆ To evaluate the efficacy of treatment by repeating investigations following therapy
- ◆ To assist in clinical trials

Staging depends on measuring and defining the extent of the disease.

The tumour stage is a reflection of the tumour burden and is determined by three major criteria which are:

- ◆ **T** - primary tumour
- ◆ **N** - regional lymph node
- ◆ **M** - metastases

The TNM classification defines the primary site as T<sub>1</sub>-T<sub>4</sub> with increasing size of the primary lesion, advancing nodal disease as N<sub>0</sub>-N<sub>3</sub>, and the presence or absence of metastases as M<sub>0</sub> or M<sub>1</sub>. The T, N, and M parameters are combined to define a clinically relevant stage of disease. The exact criteria for staging depend on the individual primary organ sites.

A typical type of stage grouping is the following:

### Stage 1

Clinical examination revealing a tumour confined to the primary organ. This lesion tends to be operable and completely resectable.

### Stage 2

Clinical examination shows evidence of local spread into surrounding tissue and first draining lymph nodes. The lesion is also operable and resectable but there is a higher risk of further spread of the disease.

### Stage 3

Clinical examination reveals an extensive primary tumour with fixation to deeper structures and local invasion. This lesion may not be operable and may require a combination of treatment modalities.

### Stage 4

Evidence of distant metastases beyond the site of origin. The primary site may be surgically inoperable.

## Histopathological staging and classification

Histopathological classification is extremely important in defining the tumour type and for making treatment decisions.

Such classification involves defining the histopathological type, or grade (or degree of differentiation).

Tumours may be classified histopathologically by type, for example:

- ◆ Adenocarcinoma
- ◆ Squamous carcinoma
- ◆ Small cell carcinoma
- ◆ Large cell carcinoma
- ◆ Sarcoma
- ◆ Lymphoma
- ◆ Leukaemia (myeloid and lymphocytic)
- ◆ Glioma
- ◆ Seminoma
- ◆ Teratoma

The degree of differentiation is classified as:

- ◆ Well differentiated
- ◆ Moderately differentiated
- ◆ Poorly differentiated

Tumour grade is classified as:

- ◆ Low grade
- ◆ Intermediate grade
- ◆ High grade

High-grade, poorly differentiated tumours tend to have a poorer outcome than low-grade, well-differentiated tumours.

### Future Possibilities

The particular biochemical, molecular, and genetic characteristics of individual tumours are increasingly important in targeting treatments to a specific tumour.

## Blood tests

Routine blood tests may be helpful. For example, in a patient with cancer, abnormal liver biochemistry tests may indicate the presence of liver metastases while a

raised alkaline phosphatase and serum calcium may reflect bone metastases.

## Tumour markers

Biological markers may also be useful as an adjunct to staging and histological classification of tumours. Tumour markers produced by a cancer, such as carcinoembryonic antigen (CEA), human  $\beta$ -chorionic gonadotrophin ( $\beta$ HCG), alpha-fetoprotein ( $\alpha$ FP), prostate-specific antigen (PSA), and CA-125 may help to define the histopathological classification of tumours. Markers such as epithelial membrane antigen and common leucocyte antigen help differentiate between epithelial and lymphoid malignancies. Some of these markers such as CA-125,  $\beta$ HCG, and  $\alpha$ FP may also be useful in monitoring a tumour's response to treatment.

## Principles of cancer treatment

The major principle governing the initial approach to treatment for a cancer patient is to define the goals of clinical management. For those patients with curable disease, the goal is to cure the patient using proven single or combined modality treatments. However, if the cancer is not curable, the goals of treatment are to improve the quality of the patient's life and prolong life (with good quality).

Treatment principles are based upon:

- ◆ The preferences of the patient
- ◆ The biological behaviour of the cancer
- ◆ The mortality and morbidity of the therapeutic procedure
- ◆ The efficacy of the therapeutic procedure under consideration

- ◆ The performance status (general level of fitness) of the patient

In the treatment of cancer it is important to realize that standard treatments for cancer patients are based upon large clinical studies that have shown improved disease-free and overall survival. The most commonly chosen parameters to measure survival and benefit of treatment are 5-year disease-free and overall survival rates.

- ◆ Patients with localized cancers are often curable
- ◆ Patients presenting with positive lymph nodes tend to have poorer prognosis but can be cured
- ◆ Patients with distant metastases are rarely cured but in some cases may survive for 5 years with multimodality treatments. Exceptions to this graver prognosis include childhood cancers, haematological malignancies, and germ cell tumours

**TABLE 3.1** Eastern Co-operative Oncology Group (ECOG) Performance Status Scale

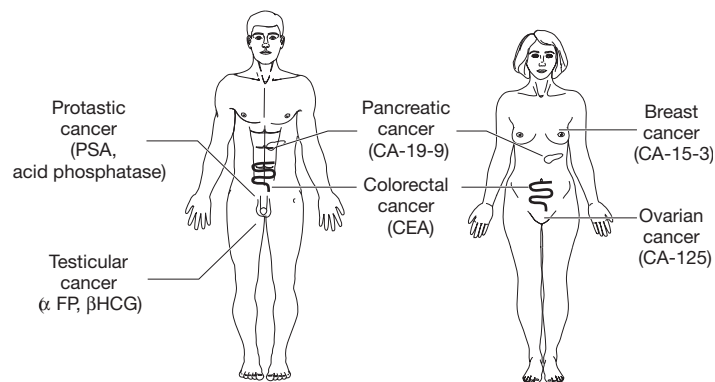
|  |   |
|--|---|
| Fully active; able to carry on all activities without restriction  | 0 |
| Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature | 1 |
| Ambulatory and capable of all self-care; confined to bed or chair 50% of waking hours                                | 2 |
| Capable of only limited self-care; confined to bed or chair 50% or more of waking hours                              | 3 |
| Completely disabled; cannot carry on any self-care; totally confined to bed or chair                                 | 4 |

### Key Fact

#### Performance Status Scale

Patients who have a performance status score greater than two usually do not tolerate intensive oncological treatments.

**Fig. 3.8** Tumour markers used in the diagnosis and evaluation of cancer (PSA, prostate-specific antigen; CEA, carcinoembryonic antigen;  $\alpha$ FP, alpha-fetoprotein;  $\beta$ HCG,  $\beta$ -chorionic gonadotrophin).



## Stop and Think

### Communicating difficult information

Before commencing any treatment it is important that the patient, their relatives, and carers are aware of the goals and limitations of treatment.

It is not unusual, after what the consultant feels to have been a very full and frank discussion outlining these goals, for a patient to ask a much more junior member of the team to clarify what has been said. This may be because they do not wish to admit not understanding what was being discussed. Alternatively, they may feel able to ask more questions from a member of the team whom they find more approachable. Frequently the shock of the diagnosis prevents patients from taking in what is being said.

It is also possible, particularly if the outlook is not good, that patients will question different members of the team hoping to find a more optimistic prognosis. Clearly it is not in the patient's interest to hear conflicting opinions about their prognosis and this should be avoided.

Later, they may seek information from the internet which can be misleading. Openness regarding realistic treatment outcomes is also important in maintaining staff morale. While the death of a patient is often difficult, particularly for the nurses who are most closely involved in their care, this is especially so if unrealistic expectations of treatment have been fostered.

## The goals of oncology treatment

### Stop and Think

#### Adjusting to different treatment goals

For patients and carers who have been through radical or adjuvant therapy the switch to palliative treatment can be difficult to understand.

Perhaps some of the 'bad press' which oncological care has received has been the result of patients and relatives feeling that they were being given so-called 'curative' treatments beyond the point when any cure was possible.

In particular, patients and carers can be puzzled about the change in emphasis with fewer investigations compared with the treatment phase. It is not easy to adapt to such a change in emphasis with the priority shifting to symptomatic management, and patients can feel that they have been 'abandoned'.

## Radical treatment

Radical oncological interventions are curative in intent. They may involve surgery, radiotherapy, chemotherapy, or a combination of these modalities.

Because the potential benefits of treatment are great, a relatively high incidence of toxicity is more acceptable.

Providing patients with good symptom control and emotional support throughout radical treatment is important. They need to be encouraged to complete what is often a very demanding treatment course to benefit maximally. Without such encouragement patients may miss the only opportunity they have of cure.

Increasingly there is an appreciation that such treatments may be associated with long-term side effects. Clearly, in this potentially curable group, care must be taken to minimize the potential for cumulative dose toxicities such as cardiotoxicity caused by anthracyclines.

## Adjuvant treatment

Many patients experience tumour relapse months or years after apparently curative surgery for their primary cancer. This is believed to be the result of the presence of micrometastatic disease that is not clinically apparent at the time of the primary treatment.

Anticancer treatment given after surgery when micrometastatic disease is suspected improves long-term survival for patients with some types of cancer such as breast and colon cancer.

This is true for tumours where chemotherapy would not be curative in the metastatic setting and is presumably related to the increased chemosensitivity associated with microscopic volumes of disease.

The absolute gains in survival from adjuvant therapy are generally modest but real. Adjuvant chemotherapy in premenopausal women with breast cancer for example is associated with an approximately 30% relative improvement in 10-year survival. At present there are few predictive factors to identify those patients most likely to benefit from adjuvant therapy. The decision to proceed is often based on the statistical likelihood of relapse, with those at highest risk generally benefiting most.

Because the majority of patients will not benefit from adjuvant therapies, such treatments should have manageable acute toxicities and a low incidence of long-term complications.

## Palliative treatment

Palliative treatment is indicated when cure is not possible but where treatments may improve cancer-related symptoms and can delay progression of disease or prolong survival. In many cases improvement of symptoms is accompanied by tumour shrinkage that is detectable clinically or by radiological methods such as CT scan or MRI. Increasingly, however, it is recognized that there may be a palliative benefit even in the absence of major tumour shrinkage.

As an important object of therapy is to maintain or improve quality of life, such treatments should be well tolerated with a low incidence of acute side effects. Long-term toxicities are generally not relevant.

Patients presenting with advanced ovarian cancer, for example, usually have incurable disease. However, the tumour is often chemosensitive and lengthy remissions are often seen following primary chemotherapy. In such patients a relatively high incidence of acute toxicity may be acceptable, with efforts being focused on managing chemotherapy-related symptoms. Conversely, a patient presenting with relapsed ovarian cancer following first-line chemotherapy has a low expectation of benefit from further chemotherapy. Consequently only a low incidence of acute toxicity is acceptable with second-line chemotherapy, from which expectation of benefit is very limited.

## Clinical trials

Clinical research is necessary to improve outcome for patients with cancer. The link between the laboratory

### Stop and Think

#### What does palliative mean?

The word *palliative* is used to mean different things to different people.

Palliative treatment from an oncologist will usually involve the use of oncological treatments aimed at prolonging survival and maintaining quality of life in patients who can no longer be offered curative treatment.

Palliative treatment from a palliative medicine specialist will focus on reducing disease-related symptoms (physical, emotional, and spiritual) in patients towards the end of their disease.

Palliative care may be understood by patients as meaning end of life care, whereas those receiving palliative radiotherapy or chemotherapy may survive for several years.

### Test Yourself

Studies show that there are consistently improved outcomes for patients enrolled in clinical trials compared with patients who are not enrolled. Why might this be?

and the clinic is developing and increasingly patients are being recruited into trials.

There are three main types of clinical trial: Phase I, Phase II, and Phase III.

### Phase I

#### Aims

- ◆ To establish the human toxicity of a new drug through delivering carefully selected increasing doses to patients
- ◆ To establish a safe dose at which to start further trials with the drug
- ◆ To evaluate the body's handling of the drug by pharmacokinetic studies

#### Eligible patients

Patients typically have progressive disease despite standard oncological therapy or tumours for which no standard therapy exists.

Small numbers of patients are used, i.e. 10–20. These patients must be aware that the primary objective of the studies is to assess tolerability and side effects. There is little expectation of benefit for themselves, with a response rate of approximately 5%.

Patients may have a range of tumour types but must have a good performance status. They also need to be highly motivated, since involvement often requires frequent visits to the hospital and additional investigations. Tissue biopsies and functional imaging studies may be used to demonstrate that the drug hits its intended molecular target.

### Phase II

#### Aims

- ◆ To establish the activity (usually tumour shrinkage) of the drug against a particular tumour type

#### Eligible patients

Patients have a specific tumour, usually with progressive disease despite standard chemotherapy or for whom no standard therapy exists.

They usually require a good performance status and motivation.

Patients are closely monitored with toxicity and response assessments but not as intensively as those in Phase I studies.

Moderate numbers of patients are often required (50–200).

### Phase III

#### Aim

- ◆ To compare the new treatment with conventional therapy

#### Eligible patients

Patients for whom a standard therapy exists. (New drugs may also be compared with 'best supportive care' where no standard therapy exists.)

Large numbers of patients (hundreds or thousands) are often required to demonstrate clear benefit.

Important and common end points include overall survival (in adjuvant studies) and disease-free survival (in non-curative studies). Increasingly, more clinically relevant end points such as improvements in pain, performance status, weight gain, and quality of life are being used in Phase III trials of agents in the palliative setting or secondary end points. However, patients require less intensive monitoring than in early trials.

#### End points

In any clinical trial it is vital to have defined the end points by which the trial will be judged at the outset. End points can be primary, relating to the central question of the trial, or secondary, relating to other outcomes such as side effects.

#### Survival

Survival is the ideal end point, but may require long follow-up, and the effect of the trial treatment may be obscured by subsequent therapy.

#### Disease-free survival

In the adjuvant disease-free survival is the length of time after initial setting treatment until recurrence of cancer. Time to progression is the time from treatment to progression of the cancer in patients with metastatic disease.

### Test Yourself

Would you enter a Phase I clinical trial?

#### Key Facts

The commonest end points used in clinical trials include:

- ◆ Survival
- ◆ Disease-free survival
- ◆ Time to progression
- ◆ Response
- ◆ Toxicity
- ◆ Quality of life

#### Response

Response is a very useful end point in trials looking at new agents and their potential efficacy. There are clear definitions of response. One is the RECIST criteria based on the longest diameter of target lesion.

- ◆ Complete response – complete disappearance of all detectable disease for at least 1 month
- ◆ Partial response –  $\geq 30\%$  reduction in measurable disease for at least 1 month
- ◆ Stable disease – neither sufficient reduction to qualify as a PR nor sufficient increase to qualify as progressive disease (PD)
- ◆ Progressive disease –  $\geq 20\%$  increase in size of measurable disease during the treatment period

Before the commencement of the trial, clear measurement parameters will need to be defined, and it would be best if the measurement were carried out by independent observers.

#### Toxicity

These measures are crucial to ensure that the benefits of treatment clearly outweigh both short-term and long-term side effects. Assessment may be carried out using blood investigations as well as by scoring the severity of anticipated symptoms.

#### Quality of life

Quality of life measures look at the global impact of the trial treatment on the patient's life including side effects and psychological effects of the treatment.

Common examples used are the EORTC QLQ-C30 (European Organization for Research on Treatment of Cancer Quality of Life Questionnaire) and FACT (Functional Assessment of Cancer Treatment).

### Chapter summary

- ◆ The early signs of cancer are often easier to see retrospectively than at their first appearance
- ◆ Cancer diagnosis and staging must be carried out in a systematic and thorough manner
- ◆ Improved imaging techniques have reduced the need for many major diagnostic surgical interventions
- ◆ Staging involves histological classification and defining the extent of the disease
- ◆ Goals of treatment need to be clarified
- ◆ Radical treatment aims at cure and thus makes a high incidence of treatment toxicity acceptable
- ◆ Adjuvant treatment, usually chemotherapy given after surgery, aims to improve long-term survival
- ◆ Palliative treatment is aimed at prolonging survival and improving cancer-related symptoms when cure is no longer possible
- ◆ Clinical trials play a vital role in establishing whether a new treatment is safe and effective
- ◆ Before commencing any trial it is important to have determined clear end points and to stipulate how these end points will be measured