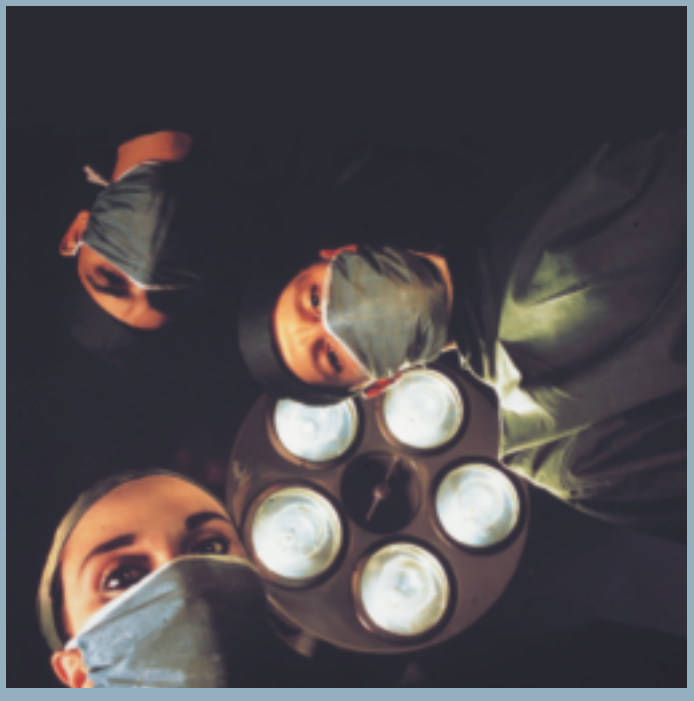
Cancer management

Once cancer is diagnosed, the patient may require medical treatment and specialized care for months, and often years. The principal modes of therapy – surgery, radiotherapy and chemotherapy – may be given alone or in combination. Strong emphasis is now placed on the development of specialized cancer centres in which evidence-based multimodality therapy is applied, subject to evaluation by appropriately designed trials. After successful treatment, specific rehabilitation may be needed.

When cancer treatment is not curative, maintaining the highest possible quality of life is paramount. For many patients, supportive and palliative care are essential and this often involves a range of professional services that extends beyond the discipline of oncology.



SURGICAL ONCOLOGY

SUMMARY

> Surgical oncology is emerging as a specialist discipline; recent advances include more precise identification of the tumour margin, leading to reduced local recurrence.

> New technology has facilitated minimal invasive surgery, laparoscopy and fibreoptic endoscopy.

> The greatly elevated cancer risk in individuals with familial cancer syndromes increasingly raises the prospect of preventive surgery, e.g. mastectomy in carriers of *BRCA1/2* mutations and colectomy in patients with familial adenomatosis coli.

> Surgical management is underpinned by recognition of the whole patient, and not merely focused on tumour excision.

Although surgery for cancer was available for many years prior to the advent of other therapies, the discipline of surgical oncology is not yet recognized in all countries as a speciality. Rather, surgical oncology is a concept which has developed recently, evolving with the emergence of radiotherapy and chemotherapy as separate modalities (*Radiotherapy*, p277 and *Medical oncology*, p281). The surgeon, who in the past was performing solo in the treatment of patients with cancer, has now become part of a team of players working together in a complex programme of multimodal anticancer therapies.

Since a surgical oncologist cannot hope to master the whole field of solid cancers, especially in view of the high technical demands of such surgery, subspecialization in organ-based groupings, such as upper gastrointestinal and colorectal subspecialities, has become necessary. Hyperspecialization into hepato-pancreato-biliary, endocrine and vascular surgery has also developed. Tentative attempts to develop procedure-based subgroupings, with new specializations for surgeons devoted to one type of procedure, such as organ transplantation or video laparoscopy, have generally failed. There is now a tendency to recruit surgeons who focus on one, or a few, organ sites. These specialists bring with them not only basic knowledge of the biology of cancer but the ability to participate in multidisciplinary research and to collaborate with colleagues from other disciplines.

However, with the growing evidence that cancer is rarely an organ-limited disease, both a disease-orientated approach and an organ-orientated approach are necessary to ensure optimal care for the cancer patient. Surgical oncologists have promoted the standardization of surgical practice aiming at the increase of life expectancy. Their participation in multi-centre clinical trials has provided the opportunity to compare clinical results of surgery and outcomes in the treatment of cancer [1,2].

Fig. 6.1 Surgery can cure patients with solid tumours when the tumour is confined to the anatomic site of origin.

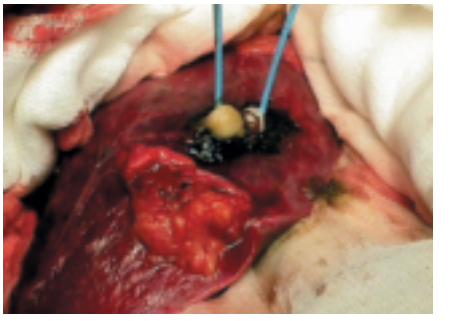


Fig. 6.2 A patient undergoing electrolysis treatment for an unresectable liver tumour. Two platinum electrode catheters deliver a low dose electric current causing local tumour ablation.

Ethical and organizational aspects

Treatment of patients with cancer, of all ages, requires a specific ethical and psychological approach. Most patients move through a state of denial and later acceptance as the diagnosis and treatment of the disease progresses. A decision to perform surgery may be made when the disease has already adversely affected the quality of the patient's life. Cancer is often considered as a mutilating, self-destructive process and surgery is viewed frequently as either a last chance salvage procedure or an additional insult to a ravaged body. Thus, from the patient's perspective, the prospect of surgery is seen as a new burden, but also a chance of cure. Surgeons involved in the care of cancer must help patients to regain their autonomy in decision-making and self-determination. This insight has value as a prelude to obtaining informed consent for surgery and particularly before proposing to a patient that he or she should enter a clinical trial. In practice, patients often have greater confidence in a well-structured and coordinated multidisciplinary team than in a single physician.

The changing relationship between patients and surgeons due to the dissemination of knowledge and to public

awareness of cancer has given rise to new attitudes towards operative risk. Many surgeons involved in the care of cancer patients have had to change their "surgeon-centric" focus to a position of a surgical oncologist committed to an integrated approach to treatment of cancer which merges organ-orientated and disease-orientated specializations. Such surgeons are therefore better placed to face new challenges.

There is a general trend towards centralizing the care of cancer patients in hospitals where it is possible to muster multidisciplinary teams. Radiation therapy and cytotoxic chemotherapy are often centralized to oncology clinics with oncological surgeons having the opportunity to focus on the surgical part of the treatment. However, since it is unrealistic and undesirable to deprive general surgery of its role in the treatment of cancer patients, it remains essential to improve the knowledge and expertise of general surgeons in oncological practice.

Underlying condition	Associated cancer	Prophylactic treatment
Cryptorchidism	Testicular	Orchidopexy
Familial colon cancer FAP, familial adenomatous polyposis, or HNPCC, hereditary nonpolyposis colorectal cancer	Colon	Colectomy
Ulcerative colitis	Colon	Colectomy
Multiple endocrine neoplasia MEN1, MEN2	Medullary cancer of the thyroid	Thyroidectomy
Familial breast cancer *BRCA1, BRCA2*	Breast	Mastectomy
Familial ovarian cancer *BRCAI*	Ovary	Oophorectomy

Table 6.1 Surgery as a means of cancer prevention. V.T. DeVita et al., (1997) *Cancer: Principles and practice of oncology* © Lippincott, Williams & Wilkins.

Context

Surgery for prevention of cancer

Surgical resection of tumours with severe dysplasia is a strategy for the prevention of cancer (Table 6.1). One striking example is total coloproctectomy in young asymptomatic patients with familial adenomatous polyposis (Fig. 6.4). Another example is total pancreatectomy in a patient with intraductal multifocal papillary mucinous tumour of the pancreas with areas of moderate to severe dysplasia (Fig. 6.5). Liver transplantation for advanced liver cirrhosis, from which small, undetectable hepatocellular carcinomas may develop [3], may be considered a means to prevent liver cancer.

Surgery for cancer cure

Local control of the tumour, which means the total eradication of the primary tumour and disease involving regional lymphatics, is indispensable for obtaining a cure. Surgery is often the most appropriate procedure for obtaining this goal and, from this point of view, remains the cornerstone in treatment [4]. Curative surgery is no longer synonymous, however, with mutilating surgery. The general philosophy of cancer surgery has become more conservative than in the past, as long as such conservation remains compatible with an adequate resection of the tumour. The preoperative assessment, however, is of the utmost importance before subjecting a patient to a potentially hazardous operative procedure.

Conservative surgery in breast cancer is a conspicuous example of how the need for adequate treatment has been reconciled with preservation of the female breast and improved quality of life. Radical mastectomy, although effective, was accompanied by the psychological trauma of breast amputation. This promoted evaluation of more conservative procedures (Table 6.2) and it became apparent that partial mastectomy alone was followed by significant local recurrence rates. Results in the 1980s and 1990s demonstrate that overall and disease-free survival from breast cancer are equivalent for mastectomy and breast-conserving surgery with postoperative radiotherapy for women with early breast cancer [5]. Breast conservation therapy as an alternative to mastectomy is especially important since, as a consequence of mammographic screening, the average size of invasive tumours has decreased while the incidence of non-invasive breast carcinoma has increased.

In the case of stomach cancer, surgery is

Fig. 6.3 The liver of a cirrhotic patient demonstrating multifocal hepatocellular carcinoma.

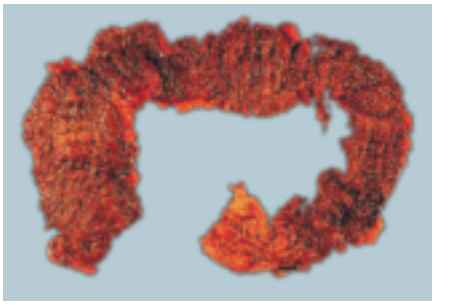


Fig. 6.4 Operative specimen of total coloproctectomy for familial adenomatous polyposis in a 14 year old boy; numerous polyps are evident.

Year	Radical mastectomy (%)	Modified radical mastectomy (%)
1972	47.9	27.7
1976	25.5	51.9
1977	20.9	55.4
1981	3.4	72.3

In a radical mastectomy, all the breast tissue is removed together with the pectoralis minor and major muscles and the axillary contents; the pectoralis major is preserved in the modified procedure. American College of Surgeons, Commission on Cancer, Chicago, 1982.

Table 6.2 Halsted radical mastectomy and modified radical mastectomy in the treatment of breast cancer; use of the less drastic modified procedure has steadily increased.

the only possible curative treatment and results of gastrectomy have improved since 1970 (Table 6.3) [4]. Comparison of five-year survival shows dramatic differences between Japanese and American results (100% for Japan and 50% for the USA for stage I cancer), which may in part due be to differences in classification of stage or in surgical technique. In Japan, extended lymph node dissection is standard procedure and total gastrectomy and dissection of adjacent organs are more commonly performed.

Palliative cancer surgery

Indications for palliative surgery have decreased during the last decades with the increasing emergence of interventional techniques. Endoscopic and radiological technology has enabled significant palliation of disabling symptoms, particularly in the context of lumen-occluding compression by the tumour.

Technological advances

Surgical instrumentation has evolved steadily over the past two decades. Fibre-optic endoscopy, along with other new technologies, has had a significant impact on the development of modern surgery. Laparoscopy (endoscopic examination of the interior of the abdomen) has become a mainstay in the diagnosis of intraperitoneal non-Hodgkin lymphoma and peritoneal carcinomatosis (widespread carcinoma in the abdominal cavity). Combined with ultrasonography, it plays an increasingly important role in the staging of many cancers, such as hepatic and pancreatic tumours [6]. Moreover, new procedures are still being explored in the treatment of cancer. Early results of laparoscopic resection of colonic carcinoma seem to be promising, although the sporadic reports of port site recurrences need further investigation. Peripheral lung metastases can be resected through thoracoscopy by wedge resection. However, more specific data are required to justify adoption of laparoscopic and thoracoscopic procedures as standard operations in the field of cancer. Oncological principles should not be compromised solely to accommodate the technically complex tasks associated with video-endoscopic techniques.

Over recent years, non-operative ablative techniques have also emerged. These are designed to facilitate local destruction of tumours either by chemical or physical agents, such as arterial chemoembolization, alcohol injection, cryotherapy, radiofrequency ablation, electrolysis (Fig. 6.2) and chemo-hyperthermia [7]. These procedures can be used not only for palliation but also with a curative intent, as an alternative to, or in combination with, surgical resection, according to the stage of the tumour and the general condition of the patient.

Liver transplantation is now considered the best modality of treatment in carefully selected cirrhotic patients with small hepatocellular carcinoma confined to the liver (Fig. 6.3). Although still controversial, this new strategy, which treats both tumour and cirrhosis, is now meeting with increasing success and is becoming more accepted in developed countries. Nevertheless, its application on a large scale remains limited by the persistent shortage of donors and thus of organs available for transplantation. Liver transplantation with living, related donors has become a valuable alternative to reduce the pressure on the significant shortage of cadaveric liver grafts and has been applied to carefully selected patients with a limited range of malignant liver tumours. In Asian countries (particularly Japan and Hong Kong) where transplantation from cadaveric donors is nearly non-existent, this new strategy is progressively being developed by specialized centres.

Period	Resectability (%)	Mortality (%)	5-yr survival (%)
Before 1970	37	15	38
Before 1980	53	13	52
Before 1990	48	5	55

Table 6.3 Survival and mortality following stomach cancer surgery have improved significantly.
A.J.A. Bremers et al. (1999) *Cancer Treatment Reviews*, 25: 333-353.

Role of surgical oncology in multimodality therapy

Surgery remains the primary option for the cure of many cancers. However, on occasions, curative resection is impossible or the prognosis following resection remains unsatisfactory. To combat such

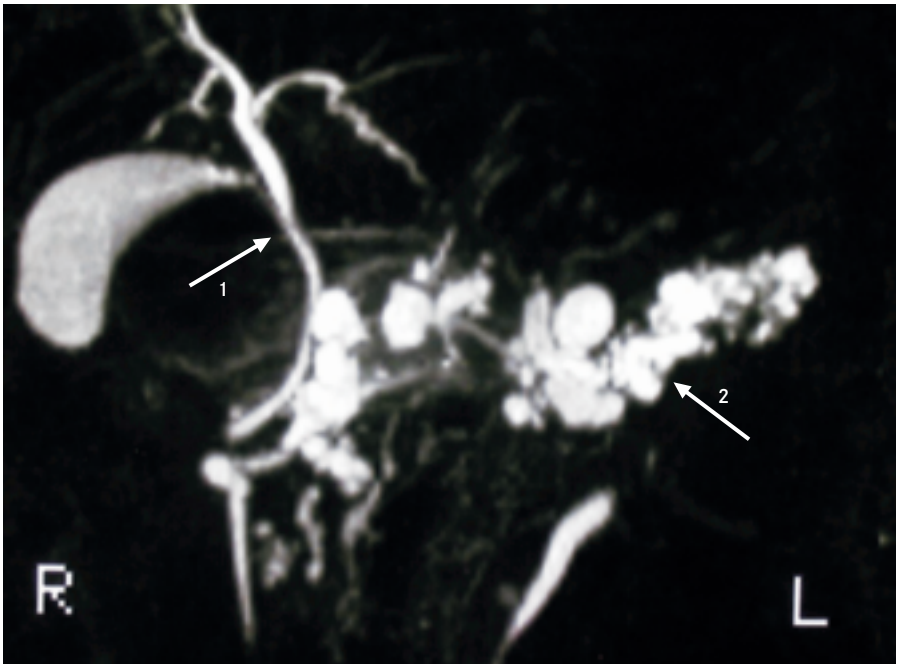


Fig. 6.5 Contrast-enhanced magnetic resonance imaging (MRI) of an intraductal papillary mucinous tumour of the pancreas in an adult patient who was subsequently treated by total pancreatectomy. 1 = common bile duct; 2 = pancreatic duct with multiple dilations caused by the presence of tumour tissue; R = right, L = left.

expectation of poor outcome, adjuvant therapies combining chemotherapy and radiotherapy have been developed and, when added to surgery, may be regarded as an integral part of modern surgical oncology.

Neoadjuvant use of radiotherapy has been developed to help downstage tumours such as rectal carcinoma. Some irresectable tumours may become resectable following such treatment. Similar results can be obtained by chemotherapy in the management of large, awkwardly placed hepatic colorectal metastatic disease, and this can transform certain tumours from irresectable to resectable lesions. Neo-adjuvant therapy may also decrease the rate of regional recurrence after curative resection of aggressive carcinomas, exemplified by pancreatic exocrine adenocarcinoma [8].

The goal of cytoreductive surgery is to remove as much as possible of the tumour mass. Such elimination of large portions of known malignant deposits is referred to as "debulking". Cytoreductive surgery is widely employed as the primary treatment of ovarian cancer, with both five-year survival and median survival better for patients with small residual masses. Some of these findings may, however, be a reflection of patients selected for surgery rather than a treatment-related change in the natural history of disease. Cytoreductive surgery is usually combined with subsequent chemotherapy and radiotherapy. There is increasing use of cytoreductive surgery and intraperitoneal chemotherapy for peritoneal carcinomatosis from ovarian cancer. Recent advances in intraoperative radiotherapy have the potential to offer additional strategies in the management of inaccessible or poorly resected cancers, typified by tumours of the biliary tract. Biliary cholangiocarcinomas can be managed by the placement of intraoperative radiotherapeutic sources as adjuvant treatment following either resection or failed resection.

The future

Typically within more developed countries, there is now a range of fully equipped and staffed specialist cancer hospitals or major centres with specialized cancer units. Despite this infrastructure, in many countries, surgical oncology still remains apart on both a local and national level.

Adoption of new technologies in cancer surgery should be guided by scientific evidence of benefit for the patient and cost-effectiveness in relation to current practice. During the evaluation phase, access to the technology should be restricted to multi-centre controlled clinical trials within a critical academic oncology climate. Such a programme of action will safeguard continuing progress in outcomes of cancer care, while at the same time keeping the economic burden within reasonable and sustainable limits [2].

TELEMEDICINE

The prospects for telemedicine in cancer treatment primarily involve information distribution for quality assurance and sharing of medical technology resources. The Internet provides a powerful platform for information and knowledge distribution worldwide. Routine use of telemedicine is currently limited to developed countries. The impact of telemedicine in developing countries remains limited since Internet access is often restricted. In developed countries, sharing of medical technology resources among health care institutions is likely to increase markedly with the development of advanced Internet-based services. These may include remote diagnosis, telemedical services such as remote image processing (including 3D or virtual reality for diagnosis or training), remote therapy planning (e.g. in radiation therapy) and expert system counterchecks (e.g. to monitor treatment courses) which may improve treatment outcome at affordable costs.

Today, with modern network capacities no longer limiting electronic medical data transfer, the management of huge quantities of information and quality assurance are the major challenges in advanced medical informatics. Although much effort has been directed towards the development of electronic patient records, no truly authoritative standard has thus far evolved (European Committee for Standar- dization, Technical Committee for Health Informatics, http://www.centc251.org/).

In developed countries, most hospitals rely on electronic data processing as the means of delivering services. Individual medical departments often employ their own digital information systems. In most instances, these applications will have been implemented over many years without reference to sharing, and communication, even within the hospital information system, may not be practicable due to proprietary communication standards. In effect, within a single health care institution, relevant patient information is distributed in numerous information systems without proper exchange capabilities. Attempts have been made to utilize Web technology to create integration platforms, with HL 7 as the communication standard (Health Level 7, http:// www.HL7.org). However, disadvantages apply with respect to data handling, security and speed of performance. An alternative, as integration middleware, may be CORBA (Object Management Group, http://www.omg.org/) but commercial applications still have to prove their value in clinical routine.

Only broad distribution of electronic infrastructures in health care will allow the integration of beneficial telemedical services into medical practice. In developed countries, the evolution of electronic patient records promises extensive advantages in terms of quality assurance and cost-effectiveness of patient treatment. In developing countries, ubiquitous access to Internet information sources will help tremendously in the distribution of medical standards and knowledge (Ricke J and Bartelink H, *Eur J Cancer* 36, 827-834, 2000; Wootton R ed., *European telemedicine* 1998/99. Kensington publications, London 1999).

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WEBSITES

Society of Surgical Oncology (USA):
http://www.surgonc.org

European Society for Surgical Oncology:
http://www.esso-surgeonline.be/

World Federation of Surgical Oncology Society:
http://www.wfsos.com/

On-line Medical Dictionary (CancerWeb):
http://cancerweb.ncl.ac.uk/omd/

RADIOTHERAPY

SUMMARY

> Radiotherapy is fundamental to the optimal management of cancer patients; its efficacy is affected by technical (the nature and delivery of the beam) and biological factors (tumour susceptibility modulated by hypoxia and drugs).

> Provision of radiotherapy services is central to national cancer control strategies, requiring long-term planning and appropriate assessment of health care resources.

> Without recourse to sophisticated technology, effective radiotherapy for many cancers can be comprehensively provided at moderate cost.

It is estimated that 50% of all patients who are diagnosed with cancer in the world would currently benefit at some stage of their illness from radiotherapy. This could be either as part of radical therapy with curative intent or as palliation for pain or other symptoms. The delivery of radiotherapy requires long-term planning in the construction of facilities as well as specialized doctors, physicists and technicians [1]. In many parts of the world facilities are very poor, even though upgrading is well within many health service budgets. The increasing reliability of modern equipment together with the reducing costs of the associated sophisticated computer planning facilities should result in considerable global improvement over the next decade.

Radiobiology

Radiotherapy is defined as the use of ionizing radiation for the treatment of malignant disease. Modern high energy X-ray machines deliver radiation which is up to one hundred times more penetrating than the X-rays used for diagnosis and can be delivered using tight beams to well defined areas in the body. This allows for the treatment of deep-seated tumours with minimal radiation being delivered to surrounding normal tissue. Although the majority of treatments given in this way use X- or gamma rays, ionizing radiation can also be given by electron beam accelerators or particle accelerators.

The biological basis for the therapeutic effect of radiation has been examined extensively in both cell culture and animal tumours. Although there are correlations from the laboratory, most clinical radiotherapy regimens are based on experience rather than biological modelling. There is considerable heterogeneity between tumours which defies rigid prediction.

Cell survival curves after the administration of different doses of radiation have been used to explore the best way to enhance selectivity between normal and malignant cells. Radiation causes profound DNA damage which is then repaired in most cells (*Carcinogen activation and DNA repair*, p89). The amount of damage depends on the type of radiation used and is increased in the presence of oxygen. Many tumours are hypoxic, simply because they have outgrown their blood supply (*Invasion and metastasis*, p119) and this renders such tumours more resistant to radiation damage. Different techniques to overcome this problem, such as the use of hyperbaric oxygen, hypoxic cell sensitizers and neutron radiation, have had only limited success. It is

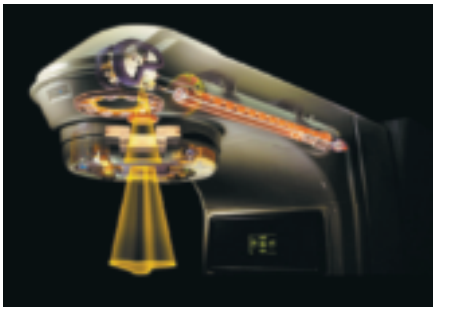

Fig. 6.6 Schematic drawing of the inside of a linear accelerator, indicating the wave-guide in which electrons are accelerated before hitting a target. ©Varian Medical Systems.

Fig. 6.7 A patient being prepared for treatment on a modern linear accelerator. © Varian Medical Systems.

Equipment	Energy	50% depth dose (depth at which electron beam ionization is 50%)	Approximate machine cost (million US$)
Orthovoltage	50-250 KeV	4 cm	0.2
Cobalt	1.25 MeV	9 cm	0.6
Linear accelerator	4-20 MeV	15 cm	1.0
Particle accelerator	4-20 MeV	5-20 cm	20 - 50

Table 6.4 Characteristics of radiotherapy equipment.

likely that as more is understood about the molecular genetics of cancer, the effects of radiation will be more accurately predictable. This will allow for more tailored and appropriate radiation schedules and doses, with better efficacy and less toxicity.

Equipment

Radiotherapy equipment is complex and varied [2]. The penetrating power of a radiotherapy beam is defined in terms of its energy and is measured in electron volts (eV). The simplest type of equipment is a low energy orthovoltage machine that basically represents an enhanced diagnostic X-ray machine. It can produce a beam of up to 250KeV. The problem in using a standard X-ray tube to produce a beam of higher energy is the heat generated at the target site (the site at which X-rays are generated by electron bombardment). Even with elaborate water cooling systems, target degradation occurs rapidly at higher voltages. Although the penetration of such low voltage beams is only 1-4 cm, they are effective at treating superficial cancers of the skin and for palliating bone metastases. The application of multiple orthovoltage fields was used to treat deep tumours in the past, but severe skin reactions and the large volume of normal tissue irradiated posed severe problems.

Isotope-based radiotherapy using gamma ray-emitting sources produces beams with a higher energy. Initially radium was the source used, but this was superseded by cobalt. Cobalt machines produce an energy of 1.25 MeV and are very reliable.

Tumour	Total Dose (Gy)	Duration of treatment (weeks)	No. of fractions (dose (Gy) per fraction)
Prostate cancer	64	6	32 (2)
Glioblastoma	60	6	30 (2)
Oesophageal cancer	60	6	30 (2)
Laryngeal cancer	60	6	30 (2)
Pituitary tumour	50	5	25 (2)
Lung cancer	50	4	20 (2.5)
Hodgkin disease	40	4	20 (2)
Bone metastases	8	1	1 (8)

Table 6.5 Radiotherapy treatment appropriate to particular cancers.

The cobalt source is housed in a lead box with a shutter, which is opened electrically. The only mechanical failure to be addressed involves malfunction of the shutter mechanism. However there are problems with radiological protection as the sources need to be changed every five years because of radioactive decay. There have also been several bizarre incidents in developing countries where stolen cobalt heads have been sold for scrap metal resulting in highly radioactive home and office furniture.

Linear accelerators (Fig. 6.7) are now the "gold standard" for radiotherapy provision. Electrons are accelerated down a linear wave-guide of about a metre in length and then hit a target where their kinetic energy is transferred into X-rays. Such machines can reliably produce beams of up to 20MeV energy. These beams pass directly through the skin surface causing little or no skin reaction. In order to deliver maximal quantities of radiation to deep tumours while keeping normal tissue dose low it is necessary to use more than one beam. The amount of energy given up by each beam diminishes as it penetrates. With modern equipment and computer planning facilities, excellent dose distribution can usually be achieved in most parts of the body using three fields. The characteristics of the radiation produced and the approximate equipment costs are shown in Table 6.4.

The process by which the volume to be irradiated is identified by the radiotherapist is called "planning". Information is taken from clinical examination, plain X-rays, computed tomography (CT) and magnetic resonance imaging (MRI) scans and used to identify the target high dose volume. A simulator (a diagnostic apparatus with the same characteristics as a treatment machine) is used to check the anatomical relationships. In many situations, computed tomography planning systems allow direct marking of the volume on a computed tomography scan.

For small volume, very accurate fields, such as those used for laryngeal or pituitary tumours, some form of patient immobilization shell is required. This is a thin perspex mask made to fit each patient

individually and onto which marks for the entry and exit points have been made. In this way, the set-up is reproduced identically each day with no inaccuracy caused by slight shifts in the patient's position or changes in skin shape or contour due to weight loss that may occur during treatment. Radical radiotherapy is usually fractionated into small daily doses given five days a week. This allows a lethal dose to be given to the tumour, whilst the normal tissues have time to recover and repair the DNA damage caused by radiation.

The relative merit of cobalt machines as compared to linear accelerators is often debated. In the past there have been concerns regarding capital cost, reliability and clinical need for linear accelerator technology in the developing world [3]. Recent technical advances in beam collimation, conformal therapy, modular design and the ability to construct national and indeed international computer networks now favour linear accelerators as the workhorse for radiotherapy provision in developed countries. Although there are some who still consider cobalt effective [4], most organizations, including the UK's Royal College of Radiologists, consider linear accelerators to be the way forward [5].

Dosimetry

Radiation can be measured in several ways. In the early days, techniques such as film blackening, skin erythema and measuring changes in chemicals contained in pastilles placed on the skin, gave an approximate indication of dose. In 1937 the "Roentgen" was defined, reflecting the energy of the beam measured in an ionization chamber. This did not, however, reflect absorbed dose in a target volume in a patient. The "Rad" was the first unit of absorbed dose, with 1 rad representing the absorption of 100 ergs of energy per gram of tissue. The current unit using the S.I. system (International System of Units) is the Gray (Gy) which is the equivalent of 100 rads. Most fractionation schemes are expressed in centi-Gray (cGy), which is the same as 1 rad.

Different types of radiation – X-rays of different energy, neutrons and particles – have different biological effects on tissue even though the same dose may be given. This has to be taken into account in radiation safety calculations. For radiological protection the "Sievert" is used. This is calculated from the absorbed dose in cGy multiplied by a quality factor Q, which is 1.0 for most X-rays, 10 for neutrons and 20 for alpha particles.

In prescribing radiation, the timing, fractionation and volume to be treated are all interdependent. Many radical radiotherapy plans use a dose of approximately 60 Gy given in 30 daily fractions of 2Gy each day, Monday to Friday, over six weeks. Palliative treatments may be given with much larger fractions over a short period of time, using a lower total dose. For control of bone pain, a single large fraction of 8 Gy may be used. When the size of each fraction is increased the amount of normal tissue damage also rises because of the reduced time for the normal repair processes to work. Therefore the biological effects of giving the same total dose over a short period of time are much greater than giving it over a longer period of time. Various complex formulae have been developed to relate time dose and fraction size. The radiotherapist chooses a dose based on the type of tumour, whether treatment is radical or palliative and the volume and type of normal tissue included (Table 6.5).

The total amount of radiation tolerated by different parts of the body varies enormously. There are several tissues in the body that have a poor capacity to repair following exposure to radiation. The most sensitive are the lens of the eye, the spinal cord, lung, kidney and small intestine. Depending on the patient's general condition and expectation of cure, it is often necessary to construct elaborate plans to avoid these structures. More recently, conformal plans which correspond precisely to the shape of the tumour have become widely available (Fig. 6.8). Such plans reduce normal tissue toxicity and allow the actual tumour dose to be escalated, increas-

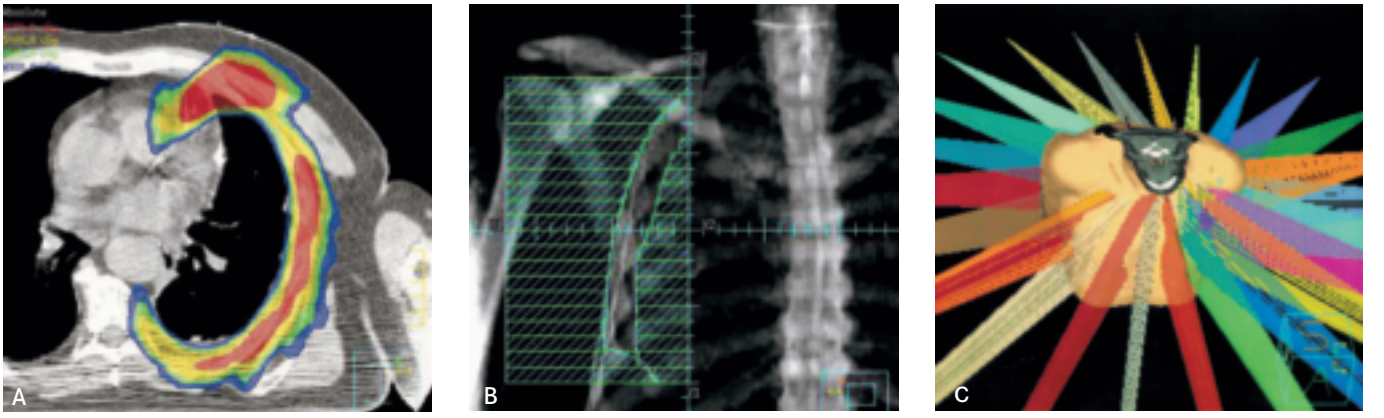

Fig. 6.8 Conformal radiotherapy to a pleural mesothelioma. **A** The calculated dose distribution in the axial or transverse view. **B** An example of one Beam's Eye View (BEV). The BEV at this particular gantry angle has a crescent shape that conforms to the target volume. **C** Different Beam's Eye Views (BEVs) that are delivered in one conformal X-ray arc field. ©Varian Medical Systems

CANCER EDUCATION IN MEDICAL COURSES

The Edinburgh Declaration of 1988 (World Conference on Medical Education, *Lancet* 2:464, 1988) aimed to change the character of medical education so that "it truly reflects the defined needs of the society in which it is situated". The total burden of cancer on the global community and the health care professions is increasing. These realities are prompting increased efforts in cancer control, and medical student cancer education must be an integral part of this effort. The International Union Against Cancer (UICC) monograph (Robinson E et al., *Cancer Education for undergraduate medical students : curricula from around the world*, UICC, Geneva 1994) describes global concerns about the status of medical student education about cancer, and provides a series of model curricula.

The continued orientation of most medical student curricula around traditional department-discipline areas rather than community or patient needs inhibits the development of clinical service-based integrated teaching. It also inhibits the incorporation of new knowledge about cancer biology and epidemiology and improved cancer treatments into medical student education. Medical educators stress the importance of medical students' experience as a major determinant of lifetime approaches to cancer. Initial perspectives may not be greatly affected by postgraduate training. For many doctors, their only formal cancer education is that gained as a medical student, partly because cancer management and control does not fall squarely on any of the individual postgraduate educational bodies. It is clearly important that medical students should be appropriately educated about cancer. The joint UICC/WHO statement (Undergraduate education in cancer, UICC/WHO Workshop, Geneva, 1981), to the effect that "in most countries there is a significant gap between the actual cure rates of various cancers and the maximum cure rates obtaining through utilizing current available knowledge", is sobering. An important first step in the reform of medical student cancer education is the appointment of a cancer education committee or co-ordinator in all medical schools. A reorganization of the existing syllabus with the introduction of problem-based learning relating to cancer biology, cancer prevention, diagnosis, treatment and symptom control, would rectify many of the deficiencies identified in surveys of medical student cancer education.

ing the chance of tumour eradication, provided no metastases are present.

Brachytherapy

This literally means "short distance treatment" and is used to describe techniques where radioactive sources are placed directly through or in contact with a tumour. Such systems for the treatment of cervical cancer are very effective. This cancer is common in many parts of the developing world and, if better education could result in earlier presentation, more women would be curable by this relatively low-tech procedure. Basically rods of caesium or other isotope are placed directly into the uterus with further radioactive material inserted into the vaginal vault. In this way a pear-shaped deposition of high intensity radiation is delivered over a two- to three-day period. More sophisticated after-loading systems are available in which the isotope, in the form of cobalt or iridium beads, is inserted into guides by a hydraulic system. This reduces unwanted exposure of staff and relatives to radiation.

Iridium 191 wires are flexible and can be inserted directly into tumours of the tongue, buccal mucosa, anus and breast. This gives a very high dose of radiation precisely to the tumour. The wires remain in position for three to five days and the results are often as good as found with more expensive external radiotherapy systems.

Side effects of radiotherapy

Most patients tolerate radiotherapy relatively well. Problems arise from the intrinsic sensitivity of normal tissue inevitably included in the treatment volume. Mucous membranes became oedematous and painful, skin reaction leads in extreme cases to ulceration and scarring. Abdominal radiation causes enteritis and diarrhoea. The general acute effects of radiation include radiation sickness and general debility. Good nursing care with drugs to control sickness, headaches, diarrhoea and oedema can effectively control most problems. The delivery of high quality radiotherapy requires teamwork between a range of professionals to maximize its benefits and reduce the severity of its side effects.

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http://www.cancerbacup.org.uk/info/radiotherapy.htm

MEDICAL ONCOLOGY

SUMMARY

- The efficacy of chemotherapy varies markedly depending upon the malignancy. Some, such as testicular seminoma, leukaemias and malignant lymphomas are highly responsive, while minimal response tumours include those of the brain (glioblastoma), lung and pancreas.
- WHO has identified a list of essential anticancer drugs.
- Drugs are typically used in combination, based on and progressively improved by randomized trials.
- Inherent or induced drug resistance limits efficacy.
- Most currently-used drugs inhibit DNA synthesis and/or cell division, inducing apoptosis. Drugs that target tumour-specific signalling pathways, including the tryrosine kinase inhibitor Gleevec for stromal tumours and acute myeloid leukaemia, are being developed.
- New approaches include gene therapy and novel strategies for immunotherapy, but clinical results thus far are largely disappointing.

CHEMOTHERAPY

The use of chemotherapy to treat cancer began in 1943 following the observation of leukopenia (reduction in number of leukocytes) in military personnel exposed to mustard gas after an explosion of a battleship in Bari harbour. This alkylating agent was adapted for intravenous use and produced dramatic but short-lived responses in patients with lymphoma and leukaemia. Other agents, such as the folic acid and pyrimidine inhibitors, followed and the armamentarium rapidly grew. It was recognized that drug resistance developed when single agents were used, so combination chemotherapy became standard. During the 1950s and 1960s, major strides were made in the treatment of leukaemias, lymphomas and choriocarcinomas with many patients being completely cured. New drugs were discovered following extensive screening programmes – the vinca alkaloids from the periwinkle, the anthracyclines from fungi and platinum drugs from experiments on the effects of electric currents on bacterial growth. The 1970s and 1980s brought effective drug combinations for testicular cancer and many childhood malignancies. Thus chemotherapy is now given in the setting of paediatric malignancy, germ cell tumours *(Cancers of the male reproductive tract,* p208*)* and some types of lymphoma (*Lymphoma*, p237) with curative intent. Chemotherapy may be administered prior to surgery (neoadjuvant) to facilitate resection and prevent metastasis or after surgical debulking (adjuvant) to reduce the risk of distant relapse. Adjuvant chemotherapy for breast and colon cancer was proven to be beneficial in large-scale randomized trials followed by sophisticated meta-analyses [1]. The value of chemotherapy in improving the quality of life of patients, by palliating symptoms and pain, even in the absence of survival advantage, is evident.

New drugs have been launched and new combinations put together. However, many challenges remain (Table 6.6). Despite many new agents becoming available, often at great cost, the gains in terms of cure rates have been small. Fashions for high dose chemotherapy with

Fig. 6.9 Chemotherapeutic drugs for injection may be available as ampoules (as shown) or ready-prepared in a syringe.

High complete response High cure	High complete response Low cure	Low complete response Low cure
Hodgkin disease	Acute myeloid leukaemia	Non small cell lung cancer
Acute lymphoblastic leukaemia	Breast cancer	Colon cancer
Testicular cancer	Ovarian cancer	Stomach cancer
Choriocarcinoma	Small cell lung cancer	Prostate cancer
Childhood cancer	Sarcoma	Pancreatic cancer
Burkitt lymphoma	Myeloma	Glioblastoma

Table 6.6 Chemotherapy for advanced cancer: the current situation.

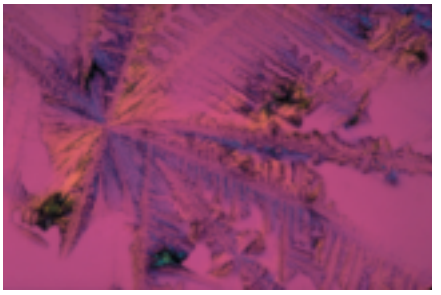

Fig. 6.10 Crystals of cisplatin: more than 90% of patients with advanced germ cell tumours are curable since the introduction of cisplatin-based chemotherapy.

bone marrow transplantation, the use of marrow support factors, biological therapies such as monoclonal antibodies or cytokines, have resulted in little overall gain but considerable expense. The driving force for medical oncology comes from the USA, which spends 60% of the world's cancer drug budget but has only 4% of its population (Fig. 6.11). Huge cultural differences exist in the use of chemotherapy, with USA-trained physicians following aggressive regimens for patients who in other countries would simply be offered palliative care. This has created a tremendous dilemma for those responsible for health care budgets. For example, the use of paclitaxel in patients with metastatic breast cancer will prolong survival by six months at a cost of US$12,000. In many countries this would far exceed the total health care consumption throughout a cancer patient's life. Yet the pressure to use expensive patented drugs is enormous. Conferences, travel and educational events sponsored by the drug industry rarely give a real perspective on the effective prioritization of cancer care for poorer countries.

The biological basis

In respect of their molecular structure, drugs currently used in cancer chemotherapy represent an enormous range of structural diversity. Anticancer drugs may be characterized as being toxic to, and hence able to cause the death of, dividing cells. Many agents for which a mechanism or mechanisms of action is relatively clear interfere with biological processes necessary for cell division, specifically including the synthesis of DNA or RNA (Fig. 6.12). Antimetabolites limit synthesis of nucleic acid precursors. In this way methotrexate inhibits dihydrofolate reductase, thereby limiting synthesis of reduced folate, which is necessary for production of purines and pyrimidines. Similar agents include 5-fluorouracil and cytarabine. After synthesis, the macromolecular processing of DNA is dependent upon topoisomerases and these enzymes are specifically inhibited by a number of classes of drugs, including anthracyclines (doxorubicin, daunorubicin and epirubicin), epipodophyllotoxins (etoposide and teniposide) and the camptothecins (irinotecan and topotecan). Some drugs cause structural damage to mature DNA, as exemplified by alkylating agents (cyclophosphamide, chloroambucil and procarbazine) and platinum derivatives (cisplatin and carboplatin). Functioning of the mitotic spindle is variously affected by vinca alkaloids (vincristine and vinblastine) and the taxanes (paclitaxel and related compounds). Hormonal agents such as tamoxifen affect proliferation of hormonally responsive cells and are thus effective in breast cancer. Otherwise, pharmacological mechanisms such as those summarized above often fail to account for the marked differences in responsiveness of particular tumour types to the various agents, and for which no mechanistic insight may be available.

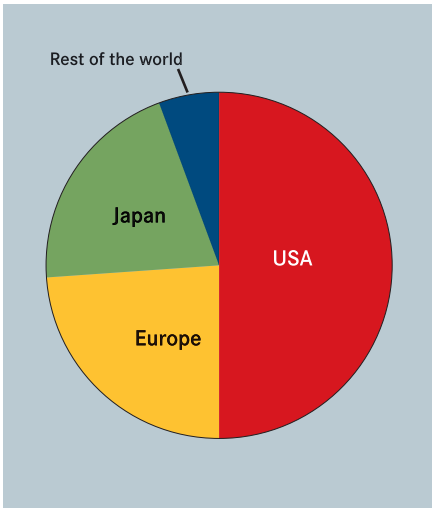

Fig. 6.11 The global cancer drug market.

Cytotoxic drugs evoke drug resistance. Tumours (relative to normal tissue) may be inherently resistant or acquire resistance as a consequence of treatment. Such resistance may be anticipated to include drugs of similar structure, but often extends to multiple classes of structurally unrelated agents (Box: *Resistance to cancer chemotherapy*, p285). The phenomenon has been extensively studied experimentally, by selection of cell populations able to proliferate in the presence of a high drug concentration. While relevant processes have been revealed, including production of the multidrug resistant protein 1 (which mediates drug transport out of cells), the extent to which these processes limit patient responses is still being determined.

Delivery

Increasingly, chemotherapy can be given entirely in a day care or outpatient setting. This reduces costs and is preferred by most patients and their families. Prior to initiation, the goal of therapy must be realistically defined. Prognostic factors such as the stage of the disease, the sites of metastases, the general medical condition of the patient, the willingness to accept any likely toxicity and the availability of the necessary facilities to treat complications must all be considered. It is essential to carefully document the degree of involvement at key sites so that the response to drugs can be measured. Although a particular tumour may be curable in some circumstances, not all patients with that tumour type will be cured. The risk-benefit concept needs to be discussed beforehand. Increasingly, cancer patients are being given more information about their disease and the options available. An honest appraisal of cost-effectiveness is vital in countries where the full cost of drugs is paid for by the patient. Cancer chemotherapy requires access to laboratory facilities to monitor at least blood counts, liver and renal function and tumour markers. Nurse-led chemotherapy suites are very effective and liked by patients. Clear protocols must be in place and adapted to local circumstances.

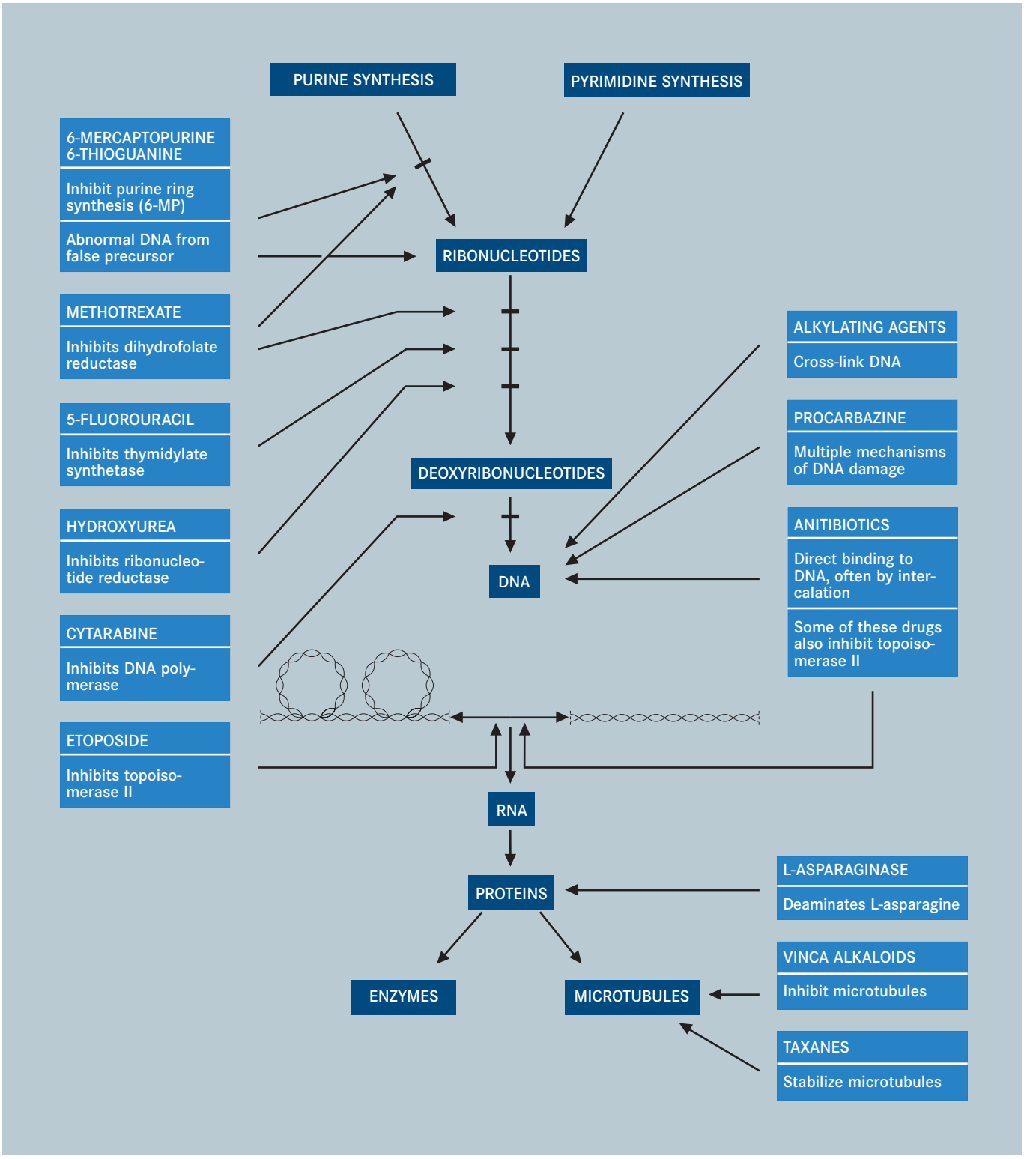

Fig. 6.12 Summary of the mechanisms and sites of action of selected cancer chemotherapeutic drugs.

Responsiveness (in decreasing order of efficacy)	Cancer
Category 1	Germ cell, leukaemias, lymphomas, choriocarcinoma
Category 2	Breast, colorectal, ovarian, osteosarcoma, Ewing's sarcomas, Wilms tumour
Category 3	Lung, bladder, prostate, stomach, cervical
Category 4	Head and neck
Category 5	Liver, melanoma, pancreatic, brain, renal, thyroid

Table 6.7 Categorization of cancer by effectiveness of chemotherapy.

For many curable cancers, the initial therapy is the most important. Any dose reduction, delay or drug substitution can adversely affect response rate. Managers and patients must understand that reducing the drug dosage or number of cycles to save money is unacceptable. Adjuvant chemotherapy is now of proven value in breast and colon cancer. Again, rigid adherence to protocols is essential to maximize results.

Recently several high cost drugs have been marketed for common cancers. Although capable of a significant response rate in patients with metastatic disease, such responses may be of short duration and may only prolong survival by weeks. To what extent some of these new agents should replace older and cheaper generic agents has not yet been determined in well designed trials with relevant endpoints, which include cost benefit analysis [2]. Inevitably this will have a subjective element and will vary with the overall allocation of cancer treatment resources in a country.

Categories of effectiveness

Protocols for drug use, and the determination of which agents should be used in the treatment of which cancers, has frequently been determined empirically. Clinical trials are developed for this purpose, and recognized standards, extending from informed patient consent through to adequate statistical analysis, have been established for such trials. Often, cytotoxic drugs are employed (usually in combination) at the maximum possible dose. Dosage is limited by toxicity: the consequence of the agent reaching, and hence affecting, normal tissue. Certain toxicity, such as hair loss, may be of limited significance but death of proliferating cells in the gut, bone marrow or other sites may provoke nausea, myelosuppression or other adverse effects.

There are more than 200 types of cancer and these respond variably to chemotherapy. Tumours can be split into five categories with regard to the relative usefulness of chemotherapy (Table 6.7). This provides a basis for examining the overall health gain of defined interventions. This will of course change as new drugs with greater efficacy are introduced.

Category 1: Tumours for which there is evidence that the use of a single or a combination of drugs used alone or with other therapeutic modalities will result in cure as defined by a normal life span in some and prolongation of survival in most patients.

Category 2: Tumours where the average survival is prolonged when chemotherapy is used as an adjuvant to local surgery or radiotherapy in the early stages of disease.

Category 3: Tumours where there is evidence that a single drug or a combination will produce clinically useful responses in more than 20% of patients. Prolongation of survival occurs in most responding patients but may be of short duration.

Category 4: Tumours where local control may be improved by using chemotherapy before, during or after surgery and radiotherapy.

Category 5: Tumours for which there are currently no effective drugs. Objective responses occur in less than 20% of patients and there is no evidence of survival benefit in randomized controlled trials when compared to best supportive care.

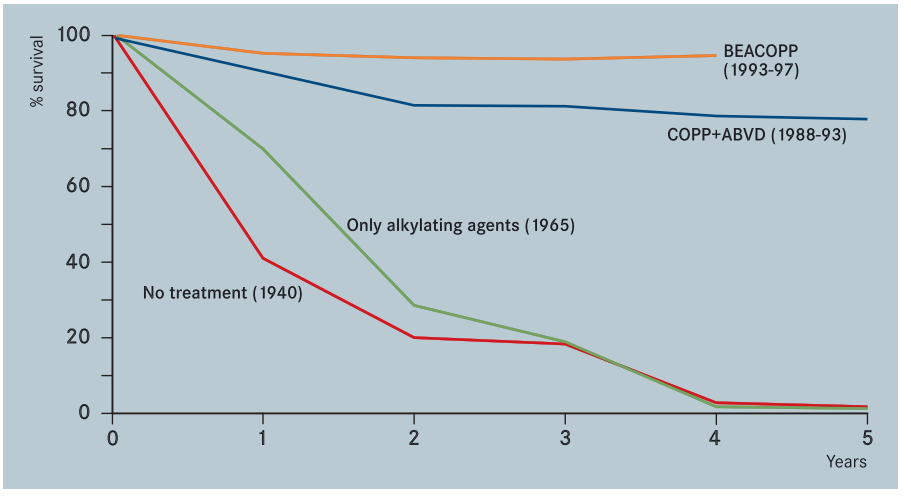

Fig. 6.13 Combination chemotherapy is more effective than a single agent for treatment of Hodgkin disease. (ABVD = adriamycin [doxorubicin], bleomycin, vinblastine and dacarbazine; BEACOPP = bleomycin, etoposide, adriamycin [doxorubicin], cyclophosphamide, oncovin [vincristine], procarbazine and prednisone; COPP = cyclophosphamide, oncovin [vincristine], procarbazine and prednisone).

RESISTANCE TO CANCER CHEMOTHERAPY

While many anticancer drugs, either alone or in combination, dramatically affect the course of malignant disease, success is far from universal. Certain tumour types are relatively refractory to anticancer drugs. In other instances, a marked response to treatment occurs but, over time, the disease process recurs and drugs, both those originally used and agents not previously employed, are ineffective. This phenomenon is referred to as "drug resistance", sub-categorized as either inherent or acquired, as appropriate.

To understand, and ultimately circumvent, drug resistance, massive resources have been directed toward elucidating mechanisms. The primary focus has been malignant tumour cell cultures which are resistant to particular drugs, or cell populations which acquire resistance as a result of being cultured in the presence of progressively increasing drug concentrations. Such cultures partially reflect the clinical behaviour of tumours, particularly to the extent that cultures "selected" using one drug also exhibit resistance to some, but not all, other drugs.

Mechanisms of drug resistance in cultured cells have been elucidated. Typically, resistance is attributable to mutation or altered expression of genes whose products mediate the transport of a drug(s) into or out of the cell, the metabolism and hence the intracellular concentration of the drug, and the structural or enzymatic protein to which the drug binds to cause cytotoxicity, sometimes called the target. Thus the multidrug resistance gene *MDR1* encodes P-glycoprotein which mediates the transport of a family of "natural product drugs" (including vinca alkaloids and epipodophyllotoxins, but excluding, for example, cisplatin) out of the cell thereby reducing their intracellular concentration and hence cytotoxicity (Tan B et al., *Curr Opin Oncol*, 12: 450-458, 2000). Agents tending to inhibit P-glycoprotein, and hence restore drug sensitivity, have been identified (Szabó D et al., *Anticancer Res*, 20: 4261-4274, 2000; Persidis A, *Nat Biotechnology*, 17: 94-5, 1999). Depending upon drug concentrations employed in the selection process, overexpression of P-glycoprotein may be achieved through increased concentration of messenger RNA with or without amplification of the *MDR1* gene. Altered expression of genes affecting apoptosis may also account for resistance (e.g. Helmbach H et al., *Int J Cancer*, 93: 617-22, 2001). Gene amplification and related effects are restricted to malignant cells, and are considered to reflect the genomic instability that is characteristic of cancer biology.

Exploitation of drug resistance mechanisms to improve clinical outcome for patients with relevant cancers has been limited. Surveys have been undertaken to establish overexpression of "resistance" genes in particular tumour types, and such studies may be applied to individual tumours as a basis for designing therapy.

Class of compound	Resistance mechanism(s)
Antimetabolites	
Methotrexate	Defect in active transportation Polyglutamation defect Increased DHFR
5-Fluorouracil (5-FU)	Alterations in activating enzymes Increased thymidylate synthase Increased dUMP
Alkylating agents	
Mustard derivatives	Decreased cellular uptake Increased cellular gluathione Enhanced DNA repair
Nitrosoureas	Enhanced DNA repair via guanine-O^6-alkyl transferase Decreased cellular uptake
Platinum derivatives	Increased cellular gluathione Enhanced DNA repair
Anthracyclines and like agents	P-glycoprotein Altered topoisomerase-II activity Increased cellular gluathione
Natural alkaloids	
Taxanes	Alterations in tubulin P-glycoprotein

Table 6.10 Some causes of cytotoxic drug resistance.

Drug resistance mechanisms operating in clinical cancer are demonstrable. However, the findings overall are complex: few specific generalizations can be made and effective therapy is often restricted to individual cases. Likewise, the results of clinical trials of *MDR1* inhibitors, or novel drugs specifically developed to circumvent particular resistance processes, have not become the dominant features of cancer chemotherapy. However, accumulated knowledge tends to confirm the efficacy of drug combinations rather than single agents as offering the best basis for cancer chemotherapy. Indeed, the vulnerability of single agents to resistance mechanisms has been demonstrated in relation to the drug STI-571 ("Gleevec") which was developed to specifically inhibit the gene product which has a critical role in the etiology of chronic myeloid leukaemia (McCormick F, *Nature*, 412, 281-282, 2001).

Most of the world's most common cancers fall into category 3 (Table 6.7).

Prioritizing cancer care

Chemotherapy is only one of many approaches to cancer control (*Cancer control*, p303). In all environments, skilled prioritization is necessary to maximize the overall benefit of medical intervention. This must include the prevention, education, early diagnosis, and the other treatment modalities outlined elsewhere. Recently, the WHO has published its recommendations for prioritizing anticancer drugs with the creation of an essential drugs list [3]. The drugs were banded by their utility in treating category 1, 2 and 3 tumours and related to the global incidence of the responding tumours. Thirteen drugs were identified which provide beneficial outcomes against certain cancers, with a further four drugs necessary to treat leukaemia. Thus 17 drugs can be considered as the first priority (Table 6.8). All are generic and relatively cheap and should be made widely available before the more recent, heavily promoted high cost drugs are purchased.

A second group of drugs is listed as priority 2. These have well documented benefits in certain clinical situations but are not truly essential, as either drugs from priority 1 can be used as substitutes or their effects are only palliative. Cheaper and simpler forms of palliation with radiotherapy or analgesics may be more appropriate in low resource environments. Few of these drugs are available as generics.

The practical problems in assessing the role of a particular drug are exemplified by the case of the taxanes – paclitaxel and docetaxel. A randomized controlled trial in the USA demonstrated a 13-month survival advantage for women given paclitaxel and cisplatinum as first-line treatment for ovarian cancer when compared to cyclophosphamide and cisplatinum, the previously most widely used treatment [4]. The additional cost of paclitaxel per quality-adjusted life year may be as much as US$ 20,000 per patient. Whether to recommend the routine use of paclitaxel in this situation must relate to the total health care economy of a country [5]. Of course the wealthy will simply buy the drug or go abroad for it, but state health care systems will increasingly have to take rationing decisions - something politicians try to avoid. The suggestion is often made that the pharmaceutical industry should make more effort to create a pricing structure that reflects local economies. Unfortunately parallel importing – the purchasing of a drug in a low-priced country and exporting it to one in which the price is high and selling it for profit – is a flourishing trade. This makes imaginative pricing schemes unpopular with major manufacturers who would see price erosion in their most profitable markets.

The drugs in the priority 3 group are recent, expensive and some are of low efficacy. About 50% of patients with metastatic breast cancer respond to docetaxel but the duration of benefit is usually only about six months. A similar order of benefit is seen with gemcitabine for non-small cell lung cancer, irinotecan for colorectal cancer and luteinizing hormone-releasing hormone (LHRH) agonists for prostate cancer. Manufacturers disseminate positive information through press releases and by using public relations agencies which support patient advocacy groups, as well as the more conventional advertising in medical journals. This fuels demand and disturbs the financing of public sector drug supply. Education of political decision-makers as well as the public is essential to correct this imbalance. A good example is the common desire to invest in stem cell rescue systems in the developing world. Although there is compelling evidence for a strong relationship between dose intensity of chemotherapy and tumour response rate, there is no good randomized data to show that dose escalation with bone marrow support pro-

The WHO essential cancer drug list

Bleomycin	Procarbazine
Chlorambucil	Tamoxifen
Cyclophosphamide	Vincristine
Doxorubicin	Vinblastine
Etoposide	Cytarabine
5-Fluorouracil	Dactinomycin
Methotrexate	Daunorubicin
Prednisolone	6-Mercaptopurine
Cisplatinum	Plus two anti-emetics

Table 6.8

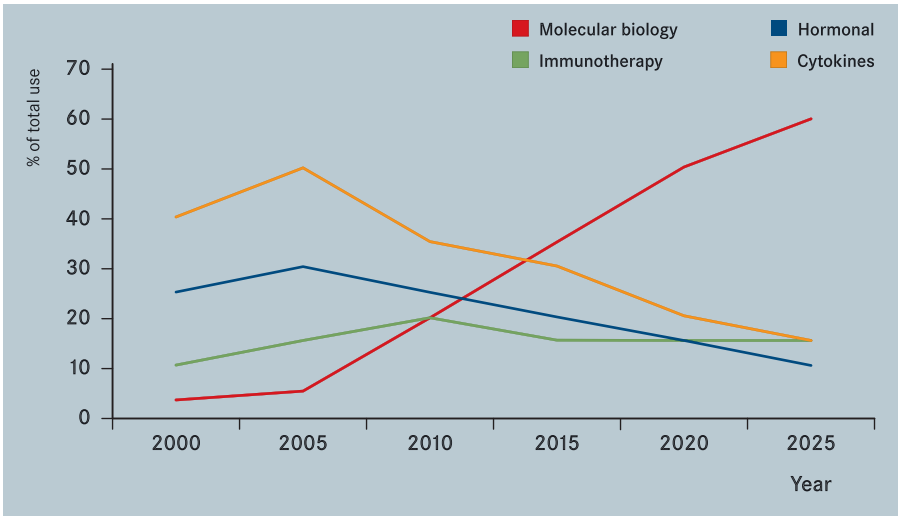

Fig. 6.14 Prediction for likely changes in approaches to chemotherapy, 2000 – 2025.

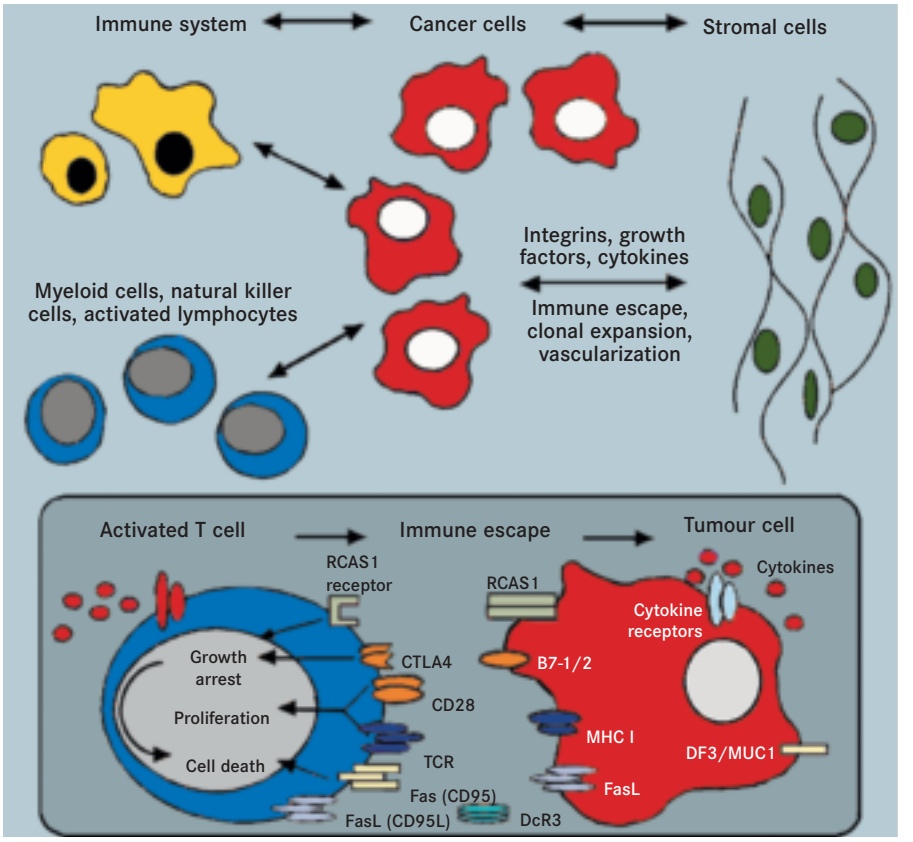

Fig. 6.15 Tumour cells are under selective pressure to escape the body's growth-restricting mechanisms. Upper panel: complex three-way interactions occur between tumour cells, their microenvironment and the immune system. Neighbouring stromal cells transfer nutrients and growth-stimulatory signals to cancer cells and stimulate vascularization. Cells of the innate and adaptive immune systems may attack cancer cells. Lower panel: different mechanisms may lead to evasion or counter-attack of cancer cells towards the immune system, including impaired antigen presentation, limited activation of cytotoxic T-cells, expression of Fas ligand which kills tumour-infiltrating cytoxic T-cells, natural killer cells, granulocytes or macrophages and production of mucins which block T-cell proliferation.

duces more cures in common cancers. The cost is enormous, often exceeding US$ 50,000 per patient.

Drugs for supportive care

Most effective cancer chemotherapy has significant side-effects. Effective antiemetics are available and should be routinely administered in advance with most chemotherapy combinations. Steroids (prednisolone or dexamethasone), a dopamine receptor antagonist (domperidone, metoclopramide) and a 5-hydroxytryptamine (5-HT3) receptor antagonist (ondansetron, granisetron) are essential. Local pricing should be used to determine choice within each category.

Neutropenia (subnormal levels of circulating neutrophils) and the risk of infection is one of the most common dose-limiting side-effects of cancer chemotherapy, leading to reduced dosages, delayed cycles and reduced effectiveness. Recom- binant colony stimulating factors are available which mobilize marrow stem cells. There is little evidence that their routine use enhances the overall effectiveness of standard chemotherapy and yet two are billion dollar blockbusters.

A wide range of relatively cheap drugs is available for the relief of the many symptoms experienced by cancer patients. Especially important are the opioid analgesics, which are often strictly controlled and unavailable in many countries. The education of politicians, legislators and health care professionals is necessary to reduce the immense amount of needless suffering caused globally by inadequate analgesic use (*Palliative care*, p297).

Future developments

Several pieces of technology are coming together to drive forward chemotherapy in the next decade [6]. Molecular biology has provided some remarkable new targets for drug design. The Human Genome Project will yield huge volumes of information to categorize cancer risk and to define likely responses to treatment (Box: *Impact of the Human Genome Project,* p324). Understanding and measuring gene expression patterns will lead to novel agents to interfere with signal transduction, gene transcription, apoptosis and angiogenesis. Gene therapy (*Box: Gene therapy for cancer*, 289) holds promise to correct the basic defects that lead to cancer. It is likely that use of new therapeutic approaches centring on molecular biology will increase rapidly in the near future (Fig. 6.14) but advances will be expensive to implement. There is no doubt that the treatment of cancer is set to improve dramatically over the next decade. The greatest challenge facing all of us is how to fund the implementation of an equitable system of cancer care in an increasingly material world.

IMMUNOTHERAPY

Treatment of cancer with vaccines to stimulate the host's own immune system to reject the cancer has been a goal of tumour immunologists for much of the 20th century. Apart from vaccines and the administration of other agents such as bacterial products, which constitute "active" immunotherapy, exogenous immunity may be provided by the giving of antibodies or lymphoreticular cells in "passive" immunotherapy. Progress has been substantial but there is still a long way to go before immunotherapy is accepted as an important modality in the

treatment of cancer. The problems largely stem from the fact that most cancer antigens (proteins displayed on the tumour cell surface which elicit a response from the host immune system) are also expressed in normal tissue, albeit at different levels or developmental stages (e.g. reappearance of fetal antigens such as alpha-fetoprotein and carcinoembryonic antigen). This lack of "foreignness" has meant that immunization against tumours has proved difficult. It is also clear that the method by which the antigen is presented to the immune system is critical in that T-cells can be "tolerized" to the tumour antigen, rather than activated. Immune responses can be qualitatively different and vary in their ability to reject tumours. The determinants of these different responses by the immune system are becoming better understood and are becoming incorporated into the design and administration of vaccines. On the other hand, the plasticity of the genome of tumour cells allows for the rapid generation of antigen-loss variants, which in some cases exceeds the adaptive processes of the immune system. Products of the tumour cell may have direct suppressive effects on immune responses. Certain tumour cells also appear resistant to programmed cell death induced by the immune cells.

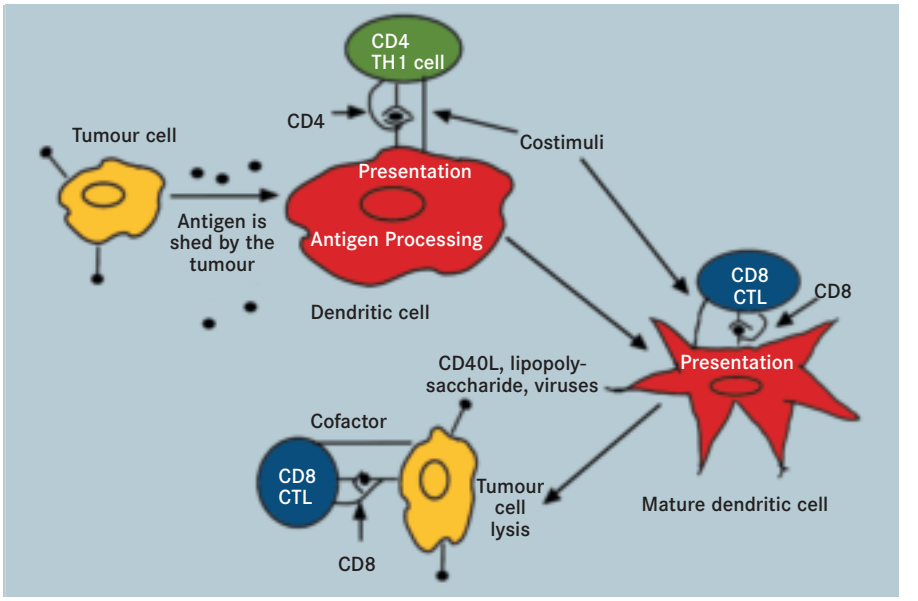

Fig. 6.16 Generation of cytotoxic T lymphocyte activity is dependent on interaction with mature dendritic cells (a distinct set of antigen-producing cells). CTL = cytotoxic T cell, THL = T-helper cell.

Problems to be overcome in immunotherapy

There are inherent problems which limit the effectiveness of immune therapy (Fig. 6.15). Cancer cells can receive nutrients and growth-stimulatory signals from neighbouring stromal cells and stimulate neovascularization. Cells of both the innate (or non-specific, e.g. myeloid cells such as macrophages and neutrophils) and adaptive (or acquired, requiring the production of antibodies, e.g. lymphoid cells such as T-, B- and natural killer cells) immune systems may attack cancer cells. Myeloid cells can attack tumour cells in an antigen- and major histocompatibility complex (MHC)-independent way, for example, natural killer (NK) cells are triggered by cells lacking MHC class I molecules. In contrast, cytotoxic T lymphocytes must be activated by antigen-derived peptides presented by MHC molecules. The lack of "foreignness" of a tumour is reflected in the number of precursor T-cells that are available in the host to reject the tumour. The higher the number of T-cells that recognize the tumour, the more likely it is that tumour rejection will occur. An extreme example of this is the rejection of allotransplants (grafts between two genetically different individuals) due to the host's possession of a high frequency (approximately 1 in 300) of precursors against alloantigens. Although it is unlikely that immunization against a single tumour cell antigen will achieve this frequency of T-cells, it is quite possible that immunization against several antigens will summate to these levels.

It has long been suspected that T-cells in cancer patients were tolerant to tumour antigens. Impaired antigen presentation results in limited cytotoxic T lymphocyte activation. This may follow from the expression of decoy receptor DcR3 on cancer cells and the neutralization of Fas ligand (CD95L) produced by cytotoxic T lymphocytes and natural killer cells (Fig. 6.15, lower panel). Expression of Fas ligand may kill tumour-infiltrating cytotoxic T lymphocytes, natural killer cells, granulocytes or macrophages. Mucins, such as DF3/MUC1, or the new ligand RCAS1 (a growth inhibitory molecule expressed in many ovarian and uterine carcinomas), may block T-cell proliferation, adding to the arsenal of weapons that tumours may use to evade control by the immune system.

Measurement of tolerance has been facilitated by the introduction of tetramer technology. Tetramers are formed by linking biotinylated human leukocyte antigen (HLA) class I molecules to avidin and then adding peptides to the complex that are recognized by T-cells. Studies in transgenic mouse models and in melanoma patients have shown that tolerance of T-cells appears to correlate with low avidity of the T-cell receptor for the corresponding antigen [7].

In addition to the requirement for a high frequency of high avidity T-cells targeted against the antigen, it is also important that the responding T-cells produce cytokines, such as IFN-γ and IL-2, that recruit type 1 helper T-cell (TH1)-mediated responses, rather than IL-4- and IL-10-recruited type 2 helper T-cell (TH2) responses, which induce antibody pro-

GENE THERAPY FOR CANCER

Technology developed for manipulation of genetic material in an experimental context gave rise to the notion of altering gene structure or expression in the context of clinical treatment. Adenosine deaminase deficiency was the first inherited disease for which clinical gene therapy was performed (Blaese RM et al., *Science*, 270: 475-80, 1995). Infusion of T- cells in which the adenosine deaminase gene had been retrovirally transferred led to sustained detection of transduced and functional T-cells at least in two cases. Advancing knowledge about the genetic lesions present in cancer cells has allowed the emergence of gene therapy as a new method of intervention against cancer, which is targeted at the level of gene expression. Gene therapy has the potential to achieve a much higher level of specificity of action than conventional drug therapeutics owing to pinpoint targeting of control and regulatory mechanisms of gene expression (Gomez-Navarro J et al., *Eur J Cancer*, 35: 2039-2057, 1999).

A number of strategies for cancer gene therapy have been developed to the point of phase I or II trials:

Mutation compensation – includes replacement of a deficient function, e.g. of a tumour suppressor gene (e.g. retinoblastoma) by administering the wild-type gene, or ablating the function of a dominant oncogene (e.g. E1A). However, tumours are typically heterogeneous in their patterns of oncogene/tumour suppressor gene expression and possess more than one abnormality. Development of such therapy may require the "permanent" expression of the modified gene.

Molecular chemotherapy – includes delivery of a gene which is toxic to a cancer cell (e.g. thymidine kinase), or increases its sensitivity to conventional therapies (e.g. the *P450* gene sensitizes breast cancer to cyclophosphamide), or protects bone marrow from myelosuppression induced by chemotherapy. Problems to be overcome include a low transfection rate when the vector is injected loco-regionally, dose-limiting toxicity and the appearance of drug-resistant subpopulations.

Genetic immunopotentiation – attempts to enhance the anti-tumour activity of cells of the immune system (e.g. tumour-infiltrating lymphocytes) or to increase the immunogenicity of the tumour cell itself (e.g. transfer of granulocyte-macrophage colony stimulating factor (GM-CSF), the B7 family of co-stimulatory molecules, or major histocompatibility complex (MHC)). Obstacles to success include low transfer rate, tolerance of tumour antigens, and inhibition of immune response.

The promise of gene therapy has been realized in limited contexts. Primary immunodeficiencies have long been considered as a possible experimental field for gene therapy. As noted, adenosine deaminase deficiency was the first inherited disease for which clinical gene therapy was performed. The low number of cells transduced with the required gene, however, was not sufficient to provide sustained clinical benefit.

Nevertheless, Severe Combined Immunodeficiencies (SCID) represent unique conditions in which currently available vectors can still be considered for a therapeutic approach. This assumption is based on the expected selective advantage conferred to transduced cells in this setting. X-linked SCID is characterized by an absence of mature T and natural killer (NK) lymphocytes due to gamma c chain cytokine receptor deficiency. The ability of gamma c chain-transduced CD34+ cells from SCID-X1 patients to mature into T-cells (Hacein-Bey S et al., *Blood*, 92: 4090-7, 1998), as well as NK cells (Cavazzana-Calvo M et al., *Blood*, 88: 3901-9, 1996), sets the basis for a clinical trial of *ex-vivo* gene transfer into CD34+ cells from SCID-X1 patients.

The clinical trial was approved in January 1999 and initiated in March of the same year. Five patients were enrolled. *Ex-vivo* gene transfer led to an infection rate of CD34+ cells of 40% and 14 - 26.5 x 10^6/kg CD34+ cells were infused back to the patients without prior chemoablation. In all patients but one, T lymphocyte counts were detected from day 30 and rose progressively to reach values ≥ 3500/µl for the first two patients (Cavazzana-Calvo M et al., *Science*, 288: 669-72, 2000) and about 4800/µl for the fourth patient. These results are promising, although preliminary, and may open the door to treatment of other immunodeficiencies, and possibly cancer, by *ex-vivo* gene transfer.

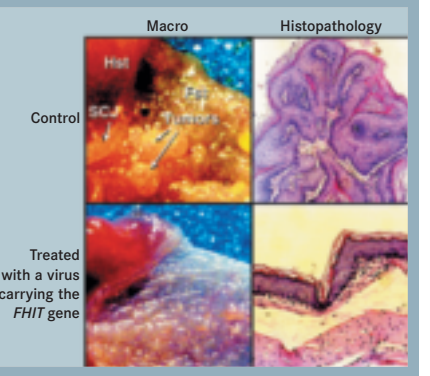

Fig. 6.17 Tumours are evident in the forestomach (Fst) and at the squamocolumnar junction (SCJ) with the hindstomach (Hst) in mice who possess only one normal copy of the *FHIT* tumour suppressor gene. Oral administration of a virus carrying a wildtype *FHIT* gene results in a substantial reduction in numbers and size of these tumours, and near normal stomach epithelia. K.R. Dumon et al. (2001) *Proc Natl Acad Sci USA* 98:3346-51.

Website:

Clinical trials in human gene transfer, Office of Biotechnology Activities, NIH:

http://www4.od.nih.gov/oba/clinicaltrial.htm

duction. It is clear that tumour cells are not passive targets for destruction by the immune system but become selected partly on the basis of products which inhibit host responses (Table 6.9).

Mechanism	Factors involved
Inhibition of antigen presentation	Vascular endothelial growth factor (VEGF), interleukin-10 (IL-10)
Inhibition of cytokine production	IL-10, transforming growth factor-β (TGF-β) α- melanocyte-stimulating hormone
Tolerance of T cells	Tumour antigen, hydrogen peroxide, lack of co-stimulation
Inhibition of migration of leukocytes from blood vessels	Prostaglandin E2, VEGF
Tumour-mediated destruction of T cells	Fas Ligand, Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)
Resistance of tumour cells to killing	IL-10, immunoselection of human leukocyte antigen (HLA) and antigen loss variants

Table 6.9 Mechanisms involved in inhibition of host immune responses to tumours.

Principles of immunotherapy

The considerations above and the experience gained from past studies on immunotherapy suggest it is possible to formulate principles that might apply irrespective of the cancer under study.

Immunization at sites removed from the tumour reduces the influence of the tumour on the antigen-presenting cell. Administration of a vaccine can be optimized in terms of dose, frequency and duration. Adjuvants (substances mixed with an antigen to enhance the immune response to this antigen) may increase numbers of antigen-presenting cells and processing thereby.

Induction of high affinity T-cell responses is becoming an important objective and underlies much of the interest in the use of dendritic cell vaccines. This is because studies in several animal models have shown it is possible to break tolerance by immunization with the antigen displayed on dendritic cells that have been activated by suitable agents, such as CD40 ligand, TNF-α and others [8-10]. Figure 6.16 illustrates recent concepts of how helper T-cells may act to cause maturation of dendritic cells to a stage where they can induce cytotoxic T-cell activity. Dendritic cells are induced to mature by interaction with helper T-cells which express the CD40 ligand. Dendritic cells can also be matured by lipopolysaccharide, TNF-α and viruses. Activated cytotoxic T lymphocytes can kill tumour cells expressing the relevant antigens. Tumour cells may inhibit dendritic cell maturation by release of factors such as interleukin IL-10 and vascular endothelial growth factor.

Immunization with low doses of antigen, such as with plasmid DNA, also appears to favour the induction of high affinity T-cells. The optimal antigens to be used in vaccines will differ between different types of cancer but in general the aim is to include antigens that are expressed at relatively high concentrations on the tumour cell and against which there are relatively high numbers of precursor cells [11-13]. Increasing the relative numbers of T-cells targeted against a particular antigen has not proven an easy task and approaches to this include depletion of overall T-cell numbers prior to immunization. The most effective antigens in animal models have been individual-specific antigens. The same may apply in humans but use of autologous tumours cells or tumour extracts (derived from the host's own tumour) has practical difficulties in most patients. The general aim, however, is to use antigens in the vaccine which will increase the number of T-cells above the required threshold for rejection of the tumour.

Cancer vaccine trials

Melanoma remains the most studied human cancer, in terms of potential for treatment by immunotherapy. A number of phase III (comparison of the relative value of the new drug with the current standard treatment) and phase I/II trials (initial evaluation of a drug's safety and pharmacokinetics, generally in patients with advanced disease/focus on the activity of the new product as a single agent in a noncomparative, open study) have been conducted. Multiple centres have reported phase III trials based on use of whole cells or lysates of whole cells [14]. Most recently, the emphasis in vaccine development has shifted to the use of well-defined antigens in vaccines, such as peptide epitopes recognized by T-cells or whole proteins [7]. Immunotherapy with dendritic cells is also being tested in a number of centres. The objective of inducing apoptosis by the TNF family of ligands has received very little attention as a therapeutic strategy in immunotherapy but may hold the key to whether the immunotherapy is successful or not. Interferon-α2 (IFN-α2) is able to induce TRAIL (TNF-related apoptosis-inducing ligand) (*Apoptosis*, p113) on a variety of different lymphocytes such CD4 T-cells, natural killer cells and monocytes [15].

Broad perspectives

Insights into the complexity of tumour cells and the host immune system are gradually evolving. The lack of foreignness of most tumour antigens, tolerance of the immune system to the antigens and release of immunosuppressive factors by

tumour cells provides a formidable problem to development of effective vaccine therapy. Most of the existing phase III trials are based on use of whole cell or lysates of whole cells and were initiated before some of the more recent concepts in tumour immunology were known. The results of three randomized trials in patients with melanoma have shown no substantial benefit from vaccine therapy but several major studies have yet to be completed. The advent of many "start-up" biotechnology companies and new information about cancer antigens has generated many new approaches in cancer vaccine therapy, particularly in the use of dendritic cell vaccines. The next few years promise therefore to be an exciting period in the evolution of immunotherapy.

HORMONAL THERAPY

Adjuvant endocrine therapy is a standard component in the management of tumours of the breast and prostate gland. In breast cancer, anti-estrogenic treatment is recommended for all post-menopausal women with newly-diagnosed metastatic disease if the tumour biopsy shows evidence of estrogen receptor (ER) or progesterone receptor (PR) expression. Similarly, this treatment is given if the receptor status is unknown, whereas ER/PR-negative carcinomas are not treated since they cannot be expected to respond. For many years, tamoxifen has been the drug of choice as many clinical trials have shown that it significantly increases progression-free survival; it may also prevent or delay the development of breast cancer in high-risk women [16]. As second-line treatment, the selective aromatase inhibitor anastrozole has been shown to be similarly effective. About one-quarter of breast carcinomas overexpress the HER2/neu protein (the *ERBB2* gene product) and these may respond to therapy with a monoclonal antibody (Herceptin) that binds to the receptor.

Prostate cancer was the first human neoplasm to be successfully treated with hormonal therapy, which has been used in the treatment of advanced disease for more than six decades. Androgen suppression may be achieved by luteinizing hormone-releasing hormone (LHRH) agonists or surgical orchidectomy. The majority of patients with metastatic prostate cancer show an initial response, often with significant relief of symptoms, but treatment is rarely curative and in most cases tumours become resistant to anti-androgen therapy.

Hormonal therapy, commonly with progestational agents, is also indicated and useful in the treatment of metastatic cancer of the endometrium, being associated with significant improvements in survival.

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http://www.nlm.nih.gov/medlineplus/druginformation.html

US Food and Drug Administration Oncology Tools website:
http://www.fda.gov/cder/cancer/

American Society of Clinical Oncology:
http://www.asco.org

REHABILITATION

SUMMARY

> Rehabilitation involves restoring cancer patients to their highest achievable level of physical and psycho-intellectual capacity despite the impact of disease, thus improving quality of life.

> Medical, physical, cultural, financial and emotional needs of individuals must be considered.

> A comprehensive interdisciplinary team provides the optimal means.

Definition

Contemporary medicine places an emphasis on comprehensive patient care. In the cancer patient, this encompasses not only the patient's immediate condition and treatment, but also longer-term effects, physical disabilities, vocational issues and social reintegration.

Rehabilitation is the process of returning a person to their highest level of function following illness, injury or other debilitating events, the physical, psychological, social and vocational effects of which can lead to impairment, disability or handicap [1].

Impairment results from a loss or abnormality of physiological or anatomical structure or function [2]. These can be the clinical features or manifestations of a disease, such as weakness or confusion from a brain tumour [3].

A disability is a restriction or lack of ability to perform a task or activity within the normal range. This is the functional consequence of the impairment. An example may be the inability to walk due to weakness caused by a brain tumour.

A handicap results from the interaction of a person with their environment leading to a disadvantage in performing a role otherwise normal for an individual. An example would be the inability to continue work as a mail carrier due to the inability to walk from weakness caused by a brain tumour.

Cancer rehabilitation is the process by which those with cancer maximize their function and minimize their disability from the impairments of cancer, while attempting to maintain their quality of life (Table 6.11). Quality of life can be defined as a sense of well-being from current life experiences "in the context of the value systems in which they live, and in relation to their goals and concerns." [5].

Overall perspective

Due to earlier diagnosis and improvements in treatment, people are living longer following the diagnosis of cancer. The average five-year survival rate for cancer patients is 50% in developed countries, 30% in developing countries. However, cancer patients are frequently left with deficits in mobility, cognition and self-care. Cancer rehabilitation helps people live better with cancer. There is thus an increasing need for rehabilitation professionals to care for cancer patients and survivors [4].

Cancer rehabilitation can improve quality of life by eliminating or decreasing the

Objectives of cancer rehabilitation
Maximize functional abilities.
Minimize disability from cancer-related impairments.
Maintain quality of life.
Provide treatments for symptom control.

Table 6.11

Fig. 6.18 Occupational therapy focuses on the restoration of bodily functions, mechanical movements and increasing patients' quality of life.
Von Kantor and Associates, Fort Lauderdale, USA.

Year	Physiatrists certified	
	No. certified in that year	Total certified
1975	65	1,163
1978	114	1,469
1980	101	1,709
1985	166	2,378
1990	287	3,454
1995	298	4,940
1998	317	5,886
1999	334	6,220

Table 6.12 The number of physiatrists (physical medicine and rehabilitation specialists) certified by the American Board of Physical Medicine and Rehabilitation has increased six-fold since 1975.

"burden of care" needed for cancer patients. Quality of life is subjectively defined by each individual but usually includes a sense of dignity. Dignity may simply be using a commode rather than a bedpan, being able to dress oneself, or being able to get from bed to chair with little assistance. Cancer rehabilitation strives to enable patients to keep their respect and dignity.

Due to the aggressive nature of many cancers, treatment has rightly been the focus of most clinicians. However, there can also be tremendous disability associated with cancer and its treatments, and thus rehabilitation is appropriate for patients throughout their disease. It is important that the primary care physician, medical oncologist, surgeon, radiation oncologist and palliative care physician are aware of the benefits of rehabilitation, minimizing disability as early as possible in the course of the disease. However, unlike diseases and injuries traditionally seen in rehabilitation medicine, cancer can be progressive in nature, and medical interventions may be ongoing.

Cancer rehabilitation must balance the benefits of continued rehabilitation therapies with the physiological effects of tumour progression and advanced cancer treatments. With advanced cancer, further therapies may not be able to make appreciable differences in function and actually prevent patients from doing things they want to do by expending their limited time and energy resources. Therefore, as with many other treatments for cancer patients, it is very important to recognize when "enough is enough". In patients with advanced cancer, rehabilitation can often provide an objective view of the patient through their functional abilities and activity, thus providing important information for palliative care-type decisions (*Palliative care*, p297).

It is important to know of further planned cancer treatments as these can impact upon the patient's condition and abilities. Aggressive chemotherapy can result in fatigue, decreased nutritional intake and immunosuppression, which can affect function as well as participation in a rehabilitation programme. Surgery to debulk or remove tumour can lead to neurological and musculoskeletal deficits, not to mention other complications associated with major surgery in a high-risk population. If major surgery is planned for the near future, therapy to address current functional deficits may be wasted as other deficits may be acquired after surgery. It may therefore often be advantageous to delay intensive rehabilitation until these treatments are completed.

Responsibility for rehabilitation

Due to complex medical, physical, social, financial and emotional issues, cancer rehabilitation is best facilitated by a comprehensive interdisciplinary team. Effective communication and teamwork is essential in formulating and carrying out plans to achieve successful rehabilitation outcomes. Team members may include a physiatrist (i.e. a physical medicine and rehabilitation specialist), the primary care physician, a medical oncologist, surgeon, radiation oncologist, physical therapist, occupational therapist, speech therapist, case manager, social worker, nutritionist, rehabilitation nurse and chaplain (Table 6.13).

The physiatrist can diagnose and treat deficits in neuromuscular function, prescribe physical, occupational and speech therapies, prescribe therapeutic modalities such as tens (a method of producing electroanalgesia through electrodes applied to the skin) and ultrasound, perform joint and soft tissue injections for symptom control, perform electrodiagnostic studies, and coordinate the comprehensive rehabilitation programme created by the interdisciplinary team to meet the needs of the patient (Table 6.14).

The physical therapist can evaluate patient strength, range of motion and functional mobility, and follow this by appropriate treatments.

The occupational therapist can evaluate deficits in activities of daily living such as feeding, grooming, bathing, dressing and toileting, and again follow this with appropriate treatments.

The speech therapist can evaluate deficits in communication, cognition and swallowing. Proposed treatments may include oral strengthening exercises, use of laryngeal or oesophageal speech techniques, alternative communication devices, aphasia education and swallowing strategies.

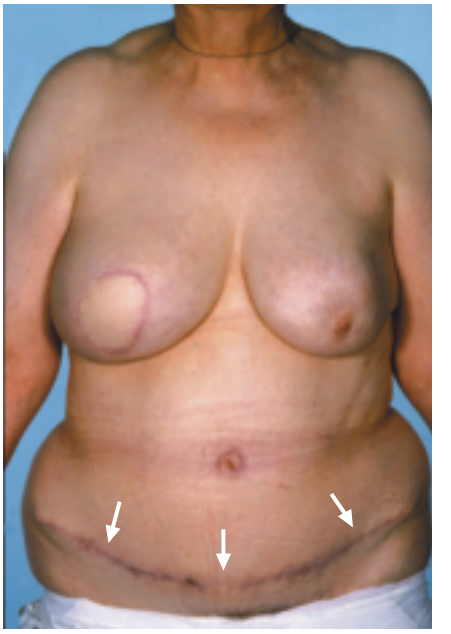

Fig. 6.19 In the TRAM flap procedure, the trans rectus abdominus muscle, which lies in the lower abdomen, is used to reconstruct the breast after mastectomy. Arrows indicate the resulting abdominal scar.

A nutritionist or dietician can evaluate the current nutritional status of the patient and make recommendations on dietary needs based on maintaining current activity level and also, if possible, increasing strength and endurance. Dietary recommendations may include supplements or additional tube feeding if the nutritional needs of the patient are not being met.

Rehabilitation nursing provides the necessary medical and surgical nursing care for complicated rehabilitation inpatients. They must also reinforce mobility and self-care techniques taught by the other therapists and provide family education in skin care, bowel and bladder management, medication administration, feeding tube use, wound care and many other patient care issues.

The social worker assists with issues of patient and family adjustment to the can-

cer and its associated disability. Frequently, community resources, family and friends need to be mobilized for a safe discharge of the patient from hospital. The social worker is familiar with agencies and charities that can provide financial assistance as well as equipment and services, if needed.

The case manager can assist patients with home health and equipment referrals, obtain insurance approvals for inpatient rehabilitation hospitalization, and address questions regarding insurance coverage.

The chaplain can provide supportive spiritual services to patients and their families who are having a difficult time coping with the uncertainty of their disease.

It is feasible for knowledgeable primary care physicians, oncologists, or surgeons to coordinate appropriate rehabilitation care. However the time and resources necessary to put together the appropriate rehabilitation team are often not available.

Interdisciplinary rehabilitation team
Physiatrist (rehabilitation physician)
Primary care physician, medical oncologist, surgeon, radiation oncologist
Rehabilitation nurse
Physical therapist
Occupational therapist
Speech therapist
Nutritionist
Case manager
Social worker
Chaplain

Table 6.13

The context of cancer rehabilitation

As previously stated, cancer rehabilitation should occur throughout the course of the disease to lessen and prevent disability. A rehabilitation programme can be prescribed prior to surgery or treatment to improve conditioning or toleration of the treatment. Specific therapies may be prescribed to maintain strength or range of motion in an area that may be adversely affected by proposed treatments. A rehabilitation programme is often initiated during active ongoing treatment to limit the adverse physical affects of the treatment and also provide the patient with an active role that he/she can play in the recovery process. Rehabilitation frequently occurs after surgery or chemotherapy when the effects of disease and treatment have led to deconditioning or specific functional deficits. Rehabilitation for advanced cancer patients with significant tumour burden may focus on therapies designed to improve basic mobility and self-care.

Rehabilitation interventions
Physical therapy for strengthening, range of motion exercises, gait training.
Occupational therapy for training in activities of daily living such as bathing, grooming, dressing, toileting.
Speech therapy for cognitive assessment and training, swallowing evaluation and treatment.
Orthotic devices for functional assistance and pain control.
Pharmacological treatments for pain, spasticity, bowel and bladder control.
Joint injections, trigger point injections, botulism toxin injections for symptom control.

Table 6.14

Finally, rehabilitation for terminal cancer patients may focus on family training for basic care-giving, bowel and bladder issues, skin care, pain control, and palliative care measures.

Cancer rehabilitation can be performed in various settings depending on the extent of the cancer and the extent of the disability. For ambulatory patients with focal weaknesses, physical and occupational therapists can improve mobility and self-care issues. For patients requiring hospitalization, a comprehensive interdisciplinary team may be used to coordinate mobility, self-care, cognitive, nutritional and patient care issues prior to discharge and return home. For advanced cancer patients, the same interdisciplinary team can help teach family members and carers how to move and care for the patient, enabling the patient to spend quality time in familiar surroundings.

Outpatient therapies can be obtained in the office, clinic or therapy gym. Inpatient rehabilitation can occur in a rehabilitation unit that is part of a general hospital or can occur in a free standing rehabilitation hospital with cancer patient experience. Due to extensive medical issues in advanced cancer patients, it is beneficial to have ready access to surgical and medical consultants as well as medical oncologists for urgent assistance. End-stage cancer rehabilitation can be given in the rehabilitation unit, palliative care unit or hospice. At any stage of disease, quality of life is the goal of cancer rehabilitation, which can also be arranged at home as long as it is safe for the patient and family.

CASE EXAMPLES

A 90-year-old patient with lower leg malignant fibrohistiocytoma is one month post-resection, with resulting difficulties in balance and gait. After appropriate tests and studies are performed to rule out post-operative infection, deep venous thrombosis or cancer recurrence, a review of the patient's history reveals that he is tripping over the toes of his affected leg. Physical examination reveals weakness in the ankle and toe dorsiflexors of the affected leg. An orthotist (specialist in orthopaedic appliances) may be contacted to fabricate an ankle foot orthosis, providing dorsiflexion assistance. Physical therapy can then provide gait training with the orthosis and a device such as a cane or walker. Stretching exercises of the ankle plantar flexors will also be important to prevent a plantar flexion contracture. These measures can reduce the fall risk in this elderly patient. Finally, occupational therapy can evaluate the patient and make sure he can dress his lower extremities, providing an adaptive reacher or other equipment as necessary.

A 42-year-old woman with breast cancer treated with modified radical mastectomy followed by transrectus abdominus muscle flap reconstruction is now suffering right shoulder stiffness and right arm swelling, 8 weeks after surgery. Assuming appropriate tests and studies have been performed to rule out recurrence of disease, post-operative wound infection or venous thrombosis, a likely diagnosis would be lymphoedema, secondary to surgical lymph node dissection. Examination of the right upper extremity would include assessment of strength, sensation, and range of motion. A quantitative measurement of oedema may be accomplished by circumferential measurements of the arm at measured distances from the elbow and wrist. Deficits in range of motion can be addressed with a physical or occupational therapy exercise programme. Lymphoedema can be treated with compression wrapping, a compression garment and/or manual lymph drainage exercises. Medications to treat neuropathic pain may be prescribed. Finally, patient education in lymphoedema management and prevention with recommendations on activity modification can be reinforced.

A 60-year-old male patient with metastatic renal cell cancer to the spine with resulting spinal cord compression and paraplegia (paralysis of the legs and lower part of the body) is hospitalized for palliative radiation treatments to the spine. The patient's deficits resulting from his paraplegia may include impaired mobility and self care, impaired sensation to his lower trunk, and neurogenic bowel and bladder (dysfunction of the bowel and bladder due to a malfunction of the relevant nerves). Although his prognosis is poor, a brief concentrated inpatient rehabilitation programme can greatly improve his quality of life by teaching him how to do more for himself, and teaching loved ones how to care for him when he becomes unable to do so. Physical therapy can instruct the patient on bed mobility, on transfer techniques from the bed to wheelchair, on wheelchair use, and also provide a range of motion exercises for spasticity management. Occupational therapy can instruct the patient in upper extremity techniques to facilitate bathing, grooming, toileting and dressing as a paraplegic. Rehabilitation nursing can teach the patient and family a skin maintenance programme, urinary catheterization for bladder management, as well as techniques and medications to manage neurogenic bowel. Patient and family education would also be beneficial in the areas of deep venous thrombosis prevention, autonomic dysreflexia prevention and management, and energy conservation. An in-patient rehabilitation programme with concomitant radiation therapy may be completed within 1-2 weeks, resulting in a paraplegic patient who is able to perform wheelchair mobility and self care without physical assistance.

A 33-year-old patient with left frontal glioblastoma multiforme has been treated with craniotomy (operation on the skull) for tumour resection with resulting right hemiplegia and aphasia (speech dysfunction). The patient may have deficits in mobility, self-care and communication. He may be depressed. He may also have dysphagia and be at risk from aspiration (breathing foreign material into the lungs). A speech therapist can assess his speech and cognition, providing assisted communication as appropriate. A swallow evaluation with radiographic contrast can provide evidence of aspiration, and diet modifications, swallowing strategies, or a feeding tube may be recommended. Physical therapy can address mobility issues such as transfers from bed to chair and ambulation as appropriate. A cane, walker or wheelchair may be necessary depending on the degree of weakness. Occupational therapy can address self-care abilities associated with the hemiparesis such as feeding, grooming, bathing, and toileting. Both physical therapy and occupational therapy can provide a stretching and strengthening programme for the affected side. Rehabilitation nursing can assist in assessment of bowel and bladder function and assessment of skin integrity. It will be necessary to teach the patient and family how to maintain these areas in the home setting. When the patient has reached a level of functioning with mobility and self-care that is safe for home discharge, it may be beneficial to continue some therapies as an outpatient. These can reinforce concepts and techniques learned in the hospital and also provide an opportunity to problem-solve difficulties encountered in the home setting. With the nature of this tumour, it is likely that further neurologic deterioration in the future will lead to further functional deficits. It is important to plan for this decline, providing the patient and family with necessary education and equipment. It is also possible that this patient will have brain irradiation, repeat surgery or chemotherapy, all of which require further rehabilitation assistance.

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WEBSITE

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PALLIATIVE CARE

SUMMARY

> Central to palliative care are symptom relief and support for the patients and their families, including regard for emotional, cultural and other needs.

> A role for palliative care is best considered early in the course of disease, possibly at diagnosis.

> Optimal palliative care depends on adequate infrastructure (personnel, facilities, drugs) and methodology (modes of delivery, dose adjustment by the patient); its outcome should be evaluated.

> Adequate pain control is an essential component of cancer care. Supportive treatment is not limited to immediate medical needs but should also take account of individual and community traditions.

Death from cancer, which is usually preceded by significant morbidity, may occur:
- at the time of diagnosis (especially when diagnosed at an advanced stage as is the norm in less industrialized countries);
- during treatment with some major symptoms the direct result of anticancer treatment (surgery, radiotherapy, chemotherapy);
- when disease is progressive with less or no effectiveness for anticancer treatment (even if available).

In all stages, the patient needs comprehensive care and a patient with an eventually fatal disease requires good palliative care from the time of diagnosis. Comprehensive care should proceed concurrently with anticancer treatment, whether with curative or palliative intent. This approach to palliative care – as relevant to the entire care of a patient with probably eventually fatal disease – is in sharp contrast to other models of cancer care, specifically including those in which palliative care is squeezed into a small section of the overall management.

Principles of palliative care

Goals for patients with probably incurable disease should relate to optimum quality of life as well as achievable prolongation of life, but not to immortality. Hope is not fostered by unrealistic goals; rather, these foreshadow emotional despair.

Decisions should concern the overall care of the patient, including anticancer therapies, where evidence indicates that personal benefit should ensue (tumour response closely but not wholly parallels patient benefit) and truly informed consent is given by the patient under normal circumstances, or by a duly qualified representative if the patient is incompetent [1-4].

Advances in palliative medicine and palliative nursing in the last two decades have markedly increased the options for therapy that may be provided to patients with complications of advanced disease, such as gastrointestinal obstruction. Apart from these broad considerations, the following specific issues must be addressed in the context of palliative care for a particular patient:
- relief of major symptoms in all stages of disease, especially cancer pain relief;
- comprehensive care for patients actually close to death;
- support for family during the illness and after the death of the patient.

The adequacy of palliative care

Evaluation of palliative care may be related to structural issues (e.g. personnel, facilities, drugs), processes (modes of delivery of care) or outcomes [5]. In practice, evaluation properly involves a combination of all three categories which may be assessed at the local, national and international level [6].

Evaluation should include consideration of:
- availability of essential drugs, notably oral morphine;
- availability of educated professionals who can serve as a resource for existing health services and families, and education/training systems [7];
- evidence of sound decision-making with due regard for the patient's wishes;
- measurement of major symptoms and their relief (especially pain), in the course of anticancer treatment as well as on cessation.

The USA has undertaken significant research in "End of Life Care", which has highlighted deficiencies. An authoritative Committee on Care at the End of Life prepared a comprehensive report for the Institute of Medicine, Washington, DC, entitled *Approaching Death* [8]. This report offers a blueprint for change relevant at a global level. Especially significant is the model of care proposed ("mixed management") with palliative care in its core dimensions present from time of diagnosis of eventually fatal illness, and not tied to prognosis (involving failure of all available anticancer treatment). This constitutes a radically new approach, with far reaching implications for clinical practice, education, research, quality assurance and administrators (and funding agencies), and for specialist palliative care practitioners.

Fig. 6.20 At all stages of disease, the cancer patient needs comprehensive care. Mary Potter Hospice, North Adelaide, South Australia.

Cancer pain relief varies and in some instances is largely deficient, even in countries with adequate resources and specialist palliative care services. The barriers to cancer pain relief have been codified and include physician attitudes, availability of crucial drugs, and community barriers, particularly in relation to the use of morphine. Fear of patients becoming addicted often remains a barrier at the physician level, and also at the community level, despite the fact that such addiction is virtually unknown if opioid drugs are used correctly for cancer pain relief. The renowned Wisconsin Cancer Pain Initiative involved drug regulators as well as health professionals in its initial stages and has shown to the satisfaction of all that increased availability of morphine for cancer pain relief did not increase drug diversion in the community.

In less developed countries, the public health approach to pain relief may be the only basis for palliative care, the benefit being not merely islands of excellence, but general population coverage. This approach has proved valuable in countries such as Spain, where the service set up in Catalonia is a model of excellence relying on mobilization of the community and its resources within mainstream health care [9].

Nations should be encouraged to develop national guidelines indicating the importance of cancer pain relief; such guidelines exist in many countries today. WHO guidelines have stressed the importance of:

- a national policy to make drugs available for cancer pain relief;
- actual availability of drugs at the community level as well as in hospitals;
- an education programme.

These may be regarded as three sides of a triangle and must all be present if cancer pain relief is to be achieved. Drugs such as oral morphine should be available readily, with ease of prescription and no geographic or time restrictions. Use of morphine as part of the treatment of cancer pain relief should be dictated by the nature and severity of the pain and not by the prognosis.

The International Narcotics Control Board has strongly supported the liberalization of the availability of morphine for cancer pain relief and has taken the "ensuring of an adequate supply of controlled drugs for medical purposes" as "a principal objective of the international drug control treaties" [10]. Unfortunately, the dramatic increases in morphine use in the last ten years are frequently not correlated with the incidence of advanced cancer: pain relief is almost certainly seriously inadequate, but data are scarce.

Some procedural changes have been found to improve the likelihood of cancer pain relief:

- the listing of pain as a vital sign to be measured in hospital charts;
- public education to increase the expectations of pain relief;
- some system of cancer pain monitoring at a community and national level;
- projecting cancer care as a social justice issue: WHO has recognized cancer pain relief as a right.

There is now the need for a coherent initiative to consolidate the earlier gains achieved by WHO and to prevent unnecessary suffering for many more people worldwide, particularly where strategies for cancer pain relief at low cost exist.

The organization of palliative care

Good palliative care is not necessarily dependent upon the existence of specialist palliative care services, but implies the mobilization of services and recognition of priorities within whatever the mainstream health care system is. In some developed countries, specialist palliative care services are a prominent feature of health care delivery and serve as catalysts and resources for patients and families with problems more difficult than average.

Reference has already been made to the public health approach with mobilization of the whole health care system to care for those patients with eventually fatal disease at all locations. This implies allocation of adequate resources to patients in this category.

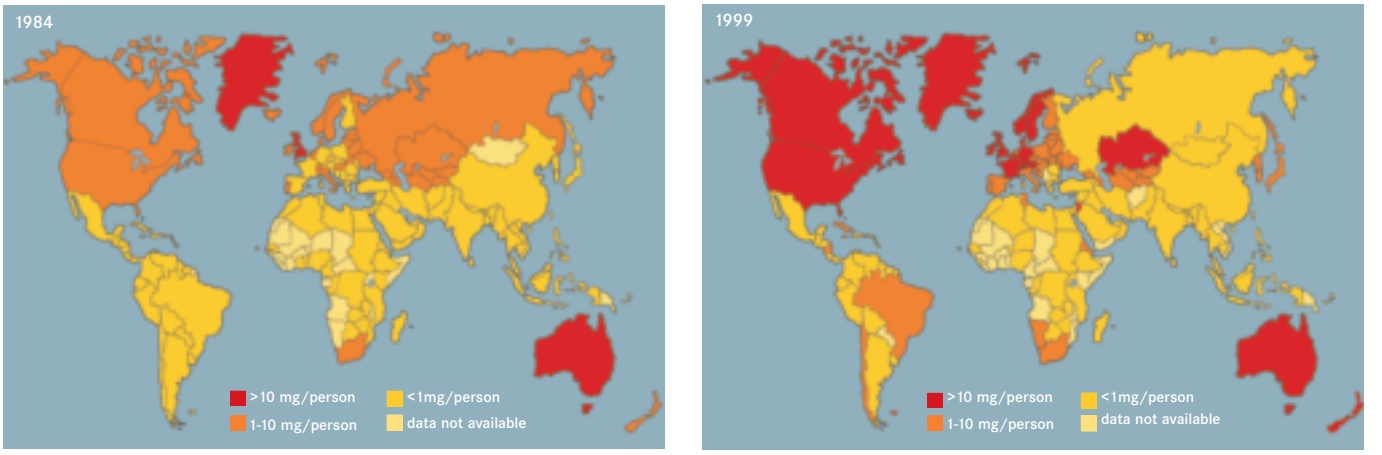

Fig. 6.21 Worldwide morphine consumption nearly tripled between 1984 and 1999, largely as a result of increasing emphasis by WHO on the need to use morphine in the treatment of cancer-related pain.

WHO has recommended that in developed countries one half of the available resources for cancer care should be devoted to palliative care, i.e. that the resources available for palliative care should equal the combined resources available for all anticancer treatment – surgery, radiotherapy and chemotherapy. WHO recommended that in less developed countries at least 80% of resources should be available for palliative care, noting that there is no other measure which can improve the quality of life of the population as much as widely available palliative care.

Palliative care and cancer pain worldwide

Global improvements in palliative care do not depend so much upon the creation of specialized palliative care services separate from mainstream health care, but upon the permeation of the whole health care system by the principles of palliative care. This in turn is dependent upon a major planning exercise with administrative, education and research implications. Specialized demonstration programmes are justified to assist in this undertaking. There is now a vast store of information concerning developments in palliative care internationally, whether involving specialized palliative care services or mainstream health care systems and guidelines have been developed by relevant authorities, including the International Association of Hospice and Palliative Care.

There are problems in all contexts, but improvements have begun to be recognized. Less developed countries vary with regard to palliative care services. In developed countries the problem is that of patchy application of the vast body of

COMPLEMENTARY AND ALTERNATIVE MEDICINE

A majority of cancer patients in most developed countries probably use complementary therapies as adjuncts to mainstream care for symptom management and quality of life. A smaller proportion use "alternative" remedies, unproved methods that typically are invasive, biologically active, and often promoted as literal alternatives to evidence-based oncology treatment. These methods tend to involve considerable travel and expense. Many are associated with significant risks of adverse events or substantial delays in receipt of needed care. Many alternatives, such as high-dose vitamin C supplements, special diets, shark cartilage, Iscador, and laetrile, have been studied and found ineffective.

Conversely, the benefits of some complementary therapies are well documented. Randomized trials support the value of hypnosis and acupuncture for pain and nausea, of relaxation therapies, music therapy and massage for anxiety, pain and depression, of yoga, tai chi and meditation for improved strength and stability. These and other complementary therapies increasingly are provided in mainstream cancer programmes. Some complementary therapies, such as psychological support, humour therapy and spiritual assistance, have been available for decades as "supportive" care in oncology medicine. In this sense, complementary medicine may be seen as an extension and expansion of earlier efforts to focus on patients' broader needs (Cassileth BR, *The Alternative Medicine Handbook: The Complete Reference Guide to Alternative and Complementary Therapies*, WW Norton & Company, 1998).

Botanicals hold largely untapped promise, requiring serious research to document their value against cancer or capacity to enhance well-being (Duke JA, *The Green Pharmacy,* New York, Rodale Press, 1997; Tyler VE, *Herbs of Choice: The Therapeutic Use of Phytomedicinals,* 1993 and Tyler VE, *The Honest Herbal: A Sensible Guide To The Use of Herbs and Related Remedies,* 1994, both by Pharmaceutical Press).

However, many herbal remedies are toxic or contaminated, or interact negatively with pharmaceuticals. St. John's Wort, for example, a useful herb for mild and moderate depression, is now known to decrease blood levels of protease inhibitors, cyclosporine and other immunosuppressive drugs, birth control pills, cholesterol medications, Coumadin, and chemotherapeutic agents. Such problems require that oncologists remain vigilant to potential interactions many, if not most, of which, remain undocumented. It is probably safest for patients to stop herbs and other nonprescription products during receipt of cancer treatments.

Fig. 6.23 Massage as a form of relaxation therapy

Both the helpful and the problematic components of complementary and alternative medicine are likely to persist in cancer medicine. The challenge for the physician and for the patient is to promote and utilize beneficial complementary therapies and discard disproved alternatives. In recent years, increasingly greater integration of complementary and conventional medicine has occurred, creating integrative medicine. This synthesis of the best of complementary therapies and mainstream care lights the way to the more comprehensive, humane, and needed cancer care that hopefully will characterize the future of oncology.

EMERGING ISSUES IN PALLIATIVE CARE

1. Adequacy of resources for care (especially and at least pain relief) from time of diagnosis of probably incurable cancer, in comparison with resources for anticancer treatment (surgery radiotherapy, chemotherapy and the related diagnostic and monitoring processes).
This is an issue throughout the world but precise information is needed. It is worth the attention of health economists with an understanding of WHO principles.

2. Being allowed to die – and allowing oneself to die: an issue in high technology environments.
Attention should be given to the circumstances in which futile treatment should neither be initiated nor maintained.

3. Education of professionals, especially doctors, with respect to the clinical science, attitudes and skills essential for contemporary palliative care.
The courage and excellence of the USA national programme for doctors throughout the country may have global significance.

4. Increasing incidence of cancer (especially the less curable types), notably in less industrialized countries, associated with the ageing of the population and continuing high levels of cigarette smoking and industrial pollution.
In such circumstances the balance between attempts to cure and care becomes more crucial, and delivery of care must be efficient, effective and sustainable at the level of the whole population in need: a massive challenge.

5. Assessment of adequacy of palliative care at total community level.

6. Ethical issues relating to the disparity of care available in different circumstances throughout the world (differences between countries and within countries): can we continue to tolerate such disparities in this millennium?
Daniel Callaghan, the founder of the revered Hastings Institute for Ethics has recently written: "The greatest importance of palliative care medicine is not simply the benefit it can bring at the end of life, but its recasting of the goals of medicine, trying to better balance care and cure, and in all of life not just at its end... Most needed is what I call a 'sustainable medicine'... that accepts death as part of the human condition, that is not obsessed with the struggle against disease, that understands progress as learning better how to live with, and die with, mortality as a fundamental mark of the human condition" (Callaghan D, *J Palliat Care,* 8: 3-4, 2000; Callaghan D, *The troubled dream of life,* New York, 1993).

existing clinical science. Whether or not appropriate patients are referred to specialist palliative care services, as should be the case in difficult situations, depends on referral patterns and this fact may impede the delivery of optimum palliative care.
The obstacles to the achievement of a "good" level of cancer pain relief community-wide in all countries, but especially developing countries, include not only the diffusion of knowledge regarding cancer pain relief, policy change concerning drug availability, and education of health professionals and the public, but also more subtle and sensitive issues. There are countless examples of delays in implementation which are only explicable in terms of cultural factors which must be respected and understood.
Some of these profound issues are spiritual and philosophical, and are felt especially keenly in developing countries. Questions such as the following may be unspoken, or rarely articulated:
- Does the adoption of a recognized strategy for cancer pain relief run the risk of damaging the spiritual fabric of our society, of destroying our way of thinking about the meaning of life, of suffering, of death?
- When we are so short of resources, why should we spend so much time, money and trouble on pain treatment in those who can no longer work, instead of trying to cure more people?
- Why is cancer pain relief still so poor in the West, even in prestigious cancer centres?
These matters need discussion in situations of trust, and in an atmosphere of partnership.
It is essential that those seeking to introduce the WHO approach to pain relief are deeply aware of the personal, cultural and spiritual context into which this new mode of thinking and acting is to be introduced. The beneficial outcomes to the patients and their families are so significant that these outcomes themselves may be the key tool for change: such change must come from within the community. However, wise leadership from senior administrators and clinicians can have dramatic consequences.
The challenge now in achieving better levels of global cancer pain relief is a more appropriate understanding of the psychological matrix within which the means to relieve that pain must operate. Awareness of the total ecological matrix – with its historical, social, economic, psychological and spiritual components – is essential if cancer pain relief is to be achieved. In some respects, psychological and spiritual development in some so-called developing countries is far in advance of the rest of the globe – and there is a need for all to recognize exchange-in-partnership as the most promising means of advance for the third millennium.
Those working in the policy area of health care and with patients should

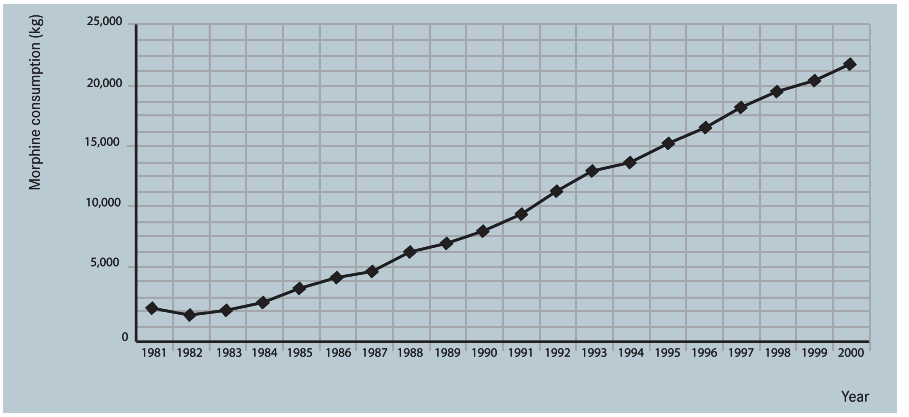

Fig. 6.22 The worldwide medical consumption of morphine is increasing.

understand not only the technical aspects but also the cultural and spiritual significance of new approaches to the patient experiencing pain, the need for recognition (not hiding) of the pain, and the obligation to relieve relievable distress, without denying (and indeed confirming) the precious values forming the fabric of society. Cancer pain relief, and palliative care in general, give expression to the compassion which is one of the most basic values within all human societies.

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National Hospice and Palliative Care Organization, USA:
http://www.nhpco.org/

International Association of Hospice and Palliative Care, USA:
http://www.hospicecare.com

American Pain Foundation:
http://www.painfoundation.org/

Education for Physicians on the End of Life Care (EPEC):
http://www.epec@ama-assn.org

The WHO Collaborating Center for Policy and Communications:
http://www.medsch.wisc.edu/painpolicy

Cancer Pain Release (publication of the WHO global communications programme to improve cancer pain control and palliative and supportive care):
http://www.whocancerpain.wisc.edu/