TREATMENT OF CANCER

EDITED BY
Pat Price
Karol Sikora
Sixth Edition

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Foreword

I haven’t opened a textbook in years, so don’t have a comparator! But this book has caught up with the times and will be available online.

I founded a free online journal called ecancer.org because none of the staff under 40 years of age in my hospital, the European Institute of Oncology, had ever, ever opened a paper journal. So welcome to the future, and I trust many more oncologists and other professionals involved in the care of cancer patients will buy this excellent book, consult it through cyberspace – and learn from it.

The layout is in a very conventional textbook style, and the multidisciplinary nature of cancer caring is reflected in the authorship – about three per chapter representing each of the main trade unions of cancer, surgery, radiation and medical oncology. Almost all are from the United Kingdom, a few are from the United States, but most are young up-and-coming oncologists.

And there’s a serious bibliography – averaging 200 articles per chapter. And acronyms – hundreds of them – reflecting the camouflage of language which we have adopted to make it more difficult for non-oncology professionals, and importantly cancer patients, to understand what we are talking about!

The next edition will be radically different I predict, hopefully without a paper version, as ‘Personalised Medicine’ begins to impact on the way oncology is practised. The didactic nuts and bolts which characterise this edition will still be there, but each patient’s genome scan will cost £10, and their proteome, not much more. So modelling and managing the sequence, choice and delivery of treatment modalities will have changed dramatically. Imaging too, extensively portrayed here, will be cheaper, more sophisticated, and more accessible to patients outside the large comprehensive cancer centres.

The future patient, of course, will own and control their own health records and will be a partner in decision making all the way along the care path. A companion online book for patients will accompany the next edition.

Well done, editors Pat Price and Karol Sikora, for bringing this excellent book to light and in a reasonably short time – rather an important factor, given the speed of change we and our patients are now enjoying.

Professor Gordon McVie
Director of Cancer Intelligence
European Institute of Oncology
Milan, Italy
Welcome to the new style *Treatment of Cancer*. Since the previous edition, there has been a revolution in the use of online resources and there are now a huge number of ways to obtain and assess information, via hard copy, online links, or on phones and tablets which are all accessible 24/7. Information is openly available to all and most of it is free which has been hugely beneficial to colleagues in poorer parts of the world in recent times. The combination of WiFi and a laptop are becoming powerful tools in the dissemination of medical knowledge.

For the first time, through the Internet, patients and health professionals are able to share the same resources, effectively removing the ‘private’ signs on the world’s medical libraries where only doctors could enter. Patients are becoming increasingly involved in the choice of their own treatment while cancer lobby groups and charities have driven new patient-directed information networks. The fully engaged cancer patient understands his/her disease, the pros and cons of different therapies, and the concept of risk assessment in differing clinical situations. Patients are able to balance this risk in exactly the same way as they do in their financial planning. Numbers of these expert patients, who know more about their own condition than their health professionals, are inevitably arising and should be welcomed; however, not all have the education, intelligence or ability to understand the complexity, and here, the physician must be the guide. The chapters here provide a framework on which to base discussions with patients.

Cancer is becoming more prevalent across the world, its incidence rising as the world’s population ages. The increase in life expectancy is something we should celebrate but brings challenges to health care systems. There is now a continuous flow of new very expensive therapies bringing double-digit inflation to cancer care costs. Understanding the cost–benefit equation for any intervention has become an essential component of clinical decision-making in all health care systems.

Oncology has seen many developments even in the short period since the publishing of fifth edition in 2008 and we have striven to include these by completely updating the chapters. We also are responding to a need for a useful, practical guide to the management of cancer and so this version has concentrated solely on the management of individual tumour types. The basic building blocks of surgery, radiotherapy and chemotherapy are best obtained from specialist text or current literature, and we have included available treatment guidelines that people may find useful. This is an international textbook written from a U.K. perspective, and we trust our international colleagues will appreciate seeing how the United Kingdom’s evidence-based guidance on the treatment of cancer is implemented in a predominantly single-payer health system.

The role of the textbook in this exciting new world is uncertain. Publishers have consolidated and are experimenting with new formats of information flow because the expensive huge tomes of the past are beginning to disappear in all disciplines. Streamlined and concise summaries of different subjects with good electronic referencing must be the future, adding interpretive value to Internet searching. Our title, *Treatment of Cancer*, has certainly changed to reflect these developments and is now almost unrecognizable from the first edition of 1980. It is shorter, presenting critical reviews of cancer management strategies for different tumour types. In revising this edition, we have tried to retain the characteristic didactic approach to patient care but perhaps with much greater consideration of the options available. This sixth edition is available as both hard copy and on eBook, and we hope you will use both media platforms for different purposes.

Who can predict what will happen to textbooks in the next decade, but we are certain they will evolve with greater speed than ever before. We thank all those who have contributed to this edition for sharing their expertise and hope you will find it a helpful contribution to aid excellence in cancer patient care.

Pat Price and Karol Sikora, London
An overview of cancer care

KAROL SIKORA

This book is written by many authors around one common theme – the optimal treatment of cancer. The problem at first seems relatively simple. There are about $10^{13}$ cells in the human body. From the fertilized egg to death in old age, a human being is the product of $10^{16}$ cell divisions. Like all complex systems, growth control can go wrong, resulting in the loss of normal territorial restraint, producing a family of cells that can multiply indefinitely. But it is not just the local growth of tumour cells that makes them so lethal. It is their spread, directly through invasion and by metastases, to other sites of the body. Tumours that remain localized can usually be cured by surgery or radiotherapy, even when enormous. Patients with large, eroding basal cell skin cancers, for example, can be treated successfully, as these tumours seldom invade deep into the skin or spread to lymph nodes. Yet, a breast lump less than 1 cm in diameter, which causes the patient no problems and is picked up in a screening clinic, can be lethal if metastases have already arisen from the primary site. It is this spread that provides the plethora of clinical problems. Just as no two individuals are alike, no two tumours behave in exactly the same way, although we can make some broad generalizations from clinical experience. The physical and psychological interactions of a patient with a growing cancer require careful analysis and action by those involved in the patient’s care.

Cancer is not universally fatal despite much public misconception. Tremendous advances have been made in the treatment of leukaemia, lymphoma, testicular cancer, choriocarcinoma and several other rare tumours, and cure of even widespread disease is now common. Even with lung cancer, the most common single tumour type throughout the world, about 8% of patients survive for many years and die of other causes. However, although there are some pointers, we do not understand why this 8% should be spared. If they can be cured, why not the rest? What makes these patients different?

Vast sums of money are currently spent worldwide on research, and yet for most common tumours, there has been little change in overall cure rates over the last 30 years. The recent dramatic inflation in the costs of providing optimal care by using drugs costing several thousand pounds a month to provide survival gains measured in weeks is clearly not sustainable in any health economy.

As an intellectual problem to the scientist, malignant disease has always appeared eminently soluble. After all, it would seem a relatively straightforward task to identify the differences between normal and malignant cells and devise a selective destruction process. Yet, we still do not know precisely the first biochemical step that takes a cell down the road to neoplasia. The recent advances in molecular biology seem poised to rectify this and to give us new avenues for clinical exploitation, but we have to treat our patients now – providing for them the best of today’s technology with the skill of the caring physician.

CANCER’S TIMELINE

The first recorded reference to cancer was in the Edwin Smith Papyrus of 3000 BC, in which eight women with breast cancer are described. The writings of Hippocrates in 400 BC contain several descriptions of cancer in different sites. But our understanding of the disease really began in the nineteenth century with the advent of cellular pathology.

Successful treatment by radical surgery became possible in the later part of that century, thanks to advances in anaesthetics and antiseptics. Radical surgery involved the removal of the tumour-containing organ and draining its lymph nodes in one block. Within a short time frame, similar procedures were devised for different parts of the body. Halsted at Johns Hopkins was the main protagonist of the radical mastectomy, Wertheim in Vienna of the hysterectomy, Trotter in London of the pharyngectomy, Whipple in New York of the pancreatico-duodenectomy and Miles in London of the abdomino-perineal resection of the rectum. These diverse surgical procedures all followed the same principle of removing the cancer in contiguity with the lymph node drainage pathways.

Following such destructive surgical approaches, the twentieth century ended with the conservation of organs by minimizing the destruction caused by surgery and replacing it with radiotherapy and, for some sites, effective adjuvant therapy with drugs and radiotherapy (Table 1).
Radiotherapy has come a long way since the first patient with a nasal tumour was treated in 1899, only a year after the discovery of radium by Marie Curie. Although radiobiology developed as a research discipline, it has really contributed little to clinical practice. The rationale behind modern fractionated radiotherapy comes as much from empirical trial and error as from experimental results. Radiotherapy is remarkably successful for certain areas of the body. Increasing sophistication in equipment coupled with dramatic strides in imaging have led to great precision in the planning and execution of treatment, thus sparing critical normal tissues and increasing the dose to the tumour.

The sinking of the U.S. Liberty ship SS John Harvey in Bari Harbour in Italy by the Germans in 1942 led to the development of effective chemotherapy. The warship was carrying canisters of mustard gas for use in chemical warfare. Survivors developed leukopenia and this led the naval physicians back in the United States to experiment with halogenated alkylamines in patients with high white cell counts – lymphomas, leukaemias and Hodgkin’s disease. From the first publication in 1946, the field has blossomed, with more than 200 drugs now available in our global pharmacopoeia. But as with radiotherapy, our clinical practice is based mainly on empiricism. Most currently used drugs were found serendipitously from plants or fungi – paclitaxel, vincristine, doxorubicin – and not by rational drug design. Although very successfully used in combination for lymphoma, leukaemia, choriocarcinoma, testicular cancer and several childhood cancers, results in metastatic common solid tumours have been disappointing, with little more than palliative benefit. The advent of molecularly targeted drugs promises to change this at least for certain patients.

**EPIDEMIOLOGY**

The global incidence of cancer is soaring due to the rapid increase in the number of elderly people in most countries. By the year 2020, there will be 20 million new cancer patients each year, and 70% of them will live in countries that collectively will have less than 5% of the world’s resources for cancer control. We have seen an explosion in our understanding of the disease at a molecular level and are now poised to see some very significant advances in prevention, screening and treatment.

Dramatic technological change is likely in surgery, radiotherapy and chemotherapy, leading to increased cure rates, but at a price. The Human Genome Project and the development of sophisticated bioinformatic networks will almost certainly bring sophisticated genetic risk assessment methods requiring careful integration into existing screening programmes. Preventive strategies could considerably reduce the global disease burden at low cost, and palliative care to relieve pain and suffering should be a basic right of all cancer patients. The next 25 years will be a time of unprecedented change in the way in which we will control cancer. However, the optimal organization of prevention and detection programmes as well as of treatment services is a universal problem in all economic environments.

The world is in a health transition. Infection, a major cause of suffering and death, is giving way to new epidemics of non-communicable disorders such as cardiovascular disease, diabetes and cancer. Different countries are in different stages of this transition depending on their age structure and economy. Some countries are faced with a double burden, with increasing infection problems compounded by surging cancer rates. This is fuelled in part by the globalization of unhealthy lifestyles.

**PREVENTION**

**Tobacco**

Optimal use of current knowledge could reduce the overall cancer incidence by at least 3 million. Tobacco control is the most urgent need. We need to look for long-term solutions here. The politics of tobacco is a complex conspiratorial web of industrialists, farmers, manufacturers, politicians and the pensions business, all looking after their own interests. Reduce cigarette consumption in many countries and the economy simply collapses. Governments are naturally cautious. In democracies, they are subject to intense lobbying. In less democratic societies, corruption, using the mass media and the pensions business, all looking after their own interests. Reduce cigarette consumption in many countries and the economy simply collapses. Governments are naturally cautious. In democracies, they are subject to intense lobbying. In less democratic societies, corruption, using the mass media and the pensions business, all looking after their own interests.

**Diet**

Dietary modification could result in a further 30% reduction across the board. The problem is refining the educational message and getting it right in different communities. Changing our current high-fat, low-fibre diet with a low fruit and vegetable intake is a common theme for cancer control. We have seen an explosion in our understanding of the disease at a molecular level and are now poised to see some very significant advances in prevention, screening and treatment.

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**Diet**

Dietary modification could result in a further 30% reduction across the board. The problem is refining the educational message and getting it right in different communities. Changing our current high-fat, low-fibre diet with a low fruit and vegetable intake is a common theme for cancer control. We have seen an explosion in our understanding of the disease at a molecular level and are now poised to see some very significant advances in prevention, screening and treatment.

Dramatic technological change is likely in surgery, radiotherapy and chemotherapy, leading to increased cure rates, but at a price. The Human Genome Project and the development of sophisticated bioinformatic networks will almost certainly bring sophisticated genetic risk assessment methods requiring careful integration into existing screening programmes. Preventive strategies could considerably reduce the global disease burden at low cost, and palliative care to relieve pain and suffering should be a basic right of all cancer patients. The next 25 years will be a time of unprecedented change in the way in which we will control cancer. However, the optimal organization of prevention and detection programmes as well as of treatment services is a universal problem in all economic environments.

The world is in a health transition. Infection, a major cause of suffering and death, is giving way to new epidemics of non-communicable disorders such as cardiovascular disease, diabetes and cancer. Different countries are in different stages of this transition depending on their age structure and economy. Some countries are faced with a double burden, with increasing infection problems compounded by surging cancer rates. This is fuelled in part by the globalization of unhealthy lifestyles.

**PREVENTION**

**Tobacco**

Optimal use of current knowledge could reduce the overall cancer incidence by at least 3 million. Tobacco control is the most urgent need. We need to look for long-term solutions here. The politics of tobacco is a complex conspiratorial web of industrialists, farmers, manufacturers, politicians and the pensions business, all looking after their own interests. Reduce cigarette consumption in many countries and the economy simply collapses. Governments are naturally cautious. In democracies, they are subject to intense lobbying. In less democratic societies, corruption, using the mass media and the pensions business, all looking after their own interests. Reduce cigarette consumption in many countries and the economy simply collapses. Governments are naturally cautious. In democracies, they are subject to intense lobbying. In less democratic societies, corruption, using the mass media and the pensions business, all looking after their own interests.
Table 2 Common dietary guidelines for cancer prevention

- Avoid animal fat
- Increase fibre intake
- Reduce red meat consumption
- Increase fruit and vegetable intake
- Avoid obesity and stay fit
- Avoid excess alcohol

prevention. But many features of the modern Western diet are now being adapted globally as branded fast-food makers seek out new markets. Again, political will is necessary to reduce the costs to the public of healthy foods. We need to obtain more data so that we can make firmer recommendations. The European Prospective Investigation into Cancer and Nutrition study currently in progress is a good example of how painstaking data and serum collection from 400,000 Europeans, over the years, provide a vast resource for investigating prospectively the complex inter-relationships between diet and cancer. Cancer incidence varies enormously across Europe, providing an excellent natural laboratory for such studies. Interventional epidemiology using rigorously controlled studies could produce the evidence that could lead to major changes. The current problem is the difficulty in making dietary advice specific and, in some countries, affordable. Although several groups have produced guidelines, there are so far few data about their uptake or significance in large populations. Table 2 provides a summary of the main consensus from several sources.

Infection

Infection causes around 15% of cancer worldwide and is potentially preventable. This proportion is greater in the developing world, where an estimated 22% of cancer has an infectious cause. Hepatitis B immunization in children has significantly reduced the incidence of infection in China, Korea and West Africa. Shortly, we will see if it has reduced the incidence of hepatoma, which begins in endemic regions by the third decade of life. The unconfirmed trends are already encouraging. Cancer of the cervix, the most common women's cancer in parts of India and South America, is clearly associated with certain subtypes of human papilloma virus. Vaccines are now becoming available and entering trial. Helicobacter pylori is associated with stomach cancer. Here, without any intervention, there has been a remarkable downward trend in incidence worldwide. Dissecting out the complex factors involved, including food storage, contamination, preparation and content, is a considerable challenge. Other cancer-causing infections are schistosomiasis, the liver fluke, the human T-cell leukaemia virus and the ubiquitous hepatitis B virus. Although geographically localized, their prevention by lifestyle changes and vaccination programmes is a realistic short-term goal. Clearly, the effectiveness of any infection control or immunization programme at reducing the cancer burden will depend on many factors and require careful research and field evaluation.

Targeting

The key to success in cancer prevention is careful targeting. Targeted prevention programmes are very cost effective and can be shared by different countries with similar cancer patterns, and therefore countries with limited resources need not keep reinventing the wheel. Prevention packages can be tailored and adapted widely. To do this, we need good data of incidence in relation to geography. Descriptive epidemiology provides a fertile hunting ground for patterns of carcinogenesis. Relating genetic changes in cancer to their cause and geography – the emerging discipline of molecular epidemiology – will complete the circle and point the way to specific interventions. The future of prevention will almost certainly be about using such techniques carefully to target preventive strategies to those who would benefit most. In the post-genomic era, it is likely that cancer prevention programmes, at least in developed countries, will be completely individualized: a combination of environmental and lifestyle data will be used to construct very specific personalized messages.

SCREENING

Cancer screening is one of the great controversies of modern medicine. At the interface between public health and specialist care, economics creates tension between professional groups, politicians and the public: a screening test may be cheap, but applying it to a population (with rigorous quality control and effective processing of patients with abnormal results) creates a huge workload and, therefore, cost. Screening can also have psychological effects on individuals with false-positive results who require investigation but are eventually found not to have cancer. Unless screening can be shown to reduce the mortality from a specific cancer, the money used is better spent on improving care, and this has led to a disparity in screening recommendations among countries. Large-scale tumour banking and subsequent bioinformatic analysis are likely to provide new approaches to cancer risk assessment and will bring challenges to this complex area. Cancer screening is defined as the systematic application of a test to individuals who have not sought medical attention. It may be opportunistic (offered to patients consulting their doctors for other reasons) or population based (covering a predefined age range, with elaborate call and recall systems). The risk of dying from cancer increases with its degree of spread or stage; thus, the aim of screening is to detect cancer in its early, asymptomatic phase. The problem is that many screening tests are relatively crude, and cancers may have metastasized before they are detected.

Sensitivity varies between tests. A 100% sensitive test detects all cancers in the screened population. The most rigorous means of calculating sensitivity is to determine the proportion of expected cancers not presenting as interval cases between screens. Good cancer registration is essential when making this calculation. Specificity is the proportion of negative results produced by a test in individuals without
A 100% specific test gives no false-positive results. Investigation of patients without cancer is a major factor in the cost of screening.

Advantages and disadvantages of screening

The advantages and disadvantages of screening must be considered carefully; they vary between cancers and tests. The three main problems in assessing the benefit of any screening test for cancer are lead-time bias, length bias and selection bias, all of which impair the effectiveness of screening as a method of reducing cancer mortality. Lead-time bias advances the diagnosis but does not prolong survival, as occurs when the disease has already metastasized although the primary tumour is still small – patients die at the same time as they would if the disease had not been detected early. Length bias results in the diagnosis of less aggressive tumours.

Rapidly growing cancers with a poorer prognosis present in the screening interval, reducing the value of the screening process. Selection bias occurs even in the best organized health care systems. Worried but healthy individuals (who would present with cancer symptoms early) comply with screening, whereas less well-educated and socially disadvantaged individuals do not. In the United Kingdom, National Health Service (NHS) breast cancer screening programme compliance rates vary between communities depending on their relative deprivation.

Developing a screening programme

Rational decision-making about cancer screening requires a detailed analysis of factors that may vary between populations. The cancer should be common and its natural history should be properly understood. This allows a realistic prediction of the probable value of the proposed test. The test should be effective (high sensitivity and specificity) and acceptable to the population. Cervical smears, for example, are difficult to perform in many Islamic countries, where women prefer not to undergo vaginal examination, and the take-up rate for colonoscopy is low in asymptomatic individuals because it is uncomfortable and sometimes unpleasant. The health care system must be able to cope with patients who produce positive results and require investigation. This may be a particular problem at the start of a population-based study. Ultimately, screening must improve the survival rate in a randomized controlled setting. The ultimate measure of success in a screening programme

Assessing the benefits of screening programmes

The ultimate measure of success in a screening programme is a demonstrable reduction in mortality in the screened population. This needs large numbers of individuals, however, and at least 10 years’ assessment for most of the common cancers. Although randomized studies may show conclusive benefit, it must be remembered that the expertise and professional enthusiasm available to a study population may be considerably greater than those achievable under subsequent field conditions. Quality of mammography interpretation and investigation of breast abnormalities are good examples of this, and may explain the relatively disappointing results of breast screening in practice.
Case-control studies using age-matched individuals from the same population and non-randomized comparison between areas providing and not providing screening may provide useful indicators, but are not as conclusive as randomized trials.

Surrogate measures of effectiveness can be used to assess a programme with relatively small numbers of patients soon after its implementation, but are insufficient to prove that screening saves lives. When a population is first screened, a higher-than-expected incidence of cancer should be seen because screening is detecting cancer that would not present with symptoms for several years. Subsequent rounds of screening are less productive. Tumour downstaging is a second measure of impact. An increase in early-stage cancer detection and, consequently, reduction in advanced disease are expected over 3–5 years. The third, short-term evaluation is a comparison of the survival of screen-detected patients with that of patients presenting symptomatically. Success in terms of these three indices may not necessarily be translated into a useful screening programme. In the 1970s, a study of routine chest radiography and sputum cytology to detect lung cancer showed a 5-year survival of 40% in screen-detected patients compared with an overall figure of 5%, but a reduction in mortality from lung cancer in large populations has not been seen.

**DIAGNOSIS**

Cancer presents with myriad symptoms depending on the site, size and growth pattern of the tumour. Although some symptoms alarm patients more than others, there is tremendous variability in the speed at which cancer can be diagnosed. A lump can be biopsied, but many deep-seated tumours present late, long after they have already spread: most patients have actually been harbouring the cancer for several years before it becomes apparent.

Trying to speed up the diagnostic process and to get on with definitive treatment makes good sense. But delays plague all health care systems. In Britain, the current obsession is for all patients with cancer-related symptoms to be seen within 2 weeks. This was politically inspired to show something could be achieved quickly. The problem is defining what constitutes a cancer-related symptom – there are just so many. Studies show that having two queues for entry into the hospital system – one urgent and one not – leads to either excess system capacity or serious delays in the slow queue. Forming a unified entry system and shortening it make more sense. A far bigger problem is getting a complex series of investigations performed with a reasonable start time for definitive therapy. Attempts to do this have been hampered by poor information technology systems, which are fragmented, non-communicative and primitive. In an age when a cell phone can be used to book instantly a complex travel itinerary including hotels and opera tickets, it is a huge indictment that general practitioners (GPs) in many parts of the world cannot fix a hospital appointment for a potential cancer patient without posting a letter.

The two drivers of the improvement of cancer diagnosis are imaging and biomarkers. The last two decades have seen a massive rise in the use of computed tomography (CT) and magnetic resonance imaging (MRI) scans to outline beautifully and in great detail the anatomy of a cancer and its surrounding normal structures. Positron emission tomography (PET), in which a molecule is labelled with a radioactive marker, allows us to examine the living biochemistry of the body. The future of imaging is coupling high-definition structural information with real-time functional change. In this way, the precise effects of drug or other treatment can be monitored in three dimensions. It is also likely that the telecom revolution will produce new devices for examining the interior compartments of the body without causing distress to the patient.

Biomarkers are biochemical changes produced by the presence of a cancer. They may be synthesized directly by the cancer, such as PSA, or represent a complex change in an organ system, such as abnormal liver function tests caused by liver metastases. As we understand more about the molecular abnormalities that lead to cancer through the science of genomics and proteomics, novel biomarkers will be identified. These will give us the ability not only to diagnose cancer at an earlier stage but also to predict the probable natural history of the cancer – whether it will spread rapidly or invade neighbouring structures. This information will be essential for planning optimal care. The basic tests are likely to be converted to kits sold in pharmacies. It is possible that a cancer screening kit for the four major cancers will be on sale within the next decade. There is great variation in the practice of cancer screening in different countries, and it is likely that the availability of commercial kits will increase consumerism. There will be a rise in cancer screening and prevention clinics in the private sector, almost certainly attached to the ‘cancer hotels’ of the future.

Looking further forward, it is likely that continuous monitoring for potentially dangerous mutations will be possible. Up-market car engines have systems to measure performance against baseline, sending a signal to the driver if a problem arises. Implanted devices to identify genomic change and signal abnormalities to a home computer may allow the detection of cancer well before any metastasis. It will be essential to carry out careful outcome research on such new diagnostic and screening techniques to validate their benefits.

**SURGERY**

Cancer surgery has been a dramatic success. Effective cancer surgery began in the late nineteenth century when it was realized that tumours could be removed along with their regional lymph nodes. This enhanced the chances of complete cure, as it had the greatest possibility of avoiding any spread of the cancer. Surgery still remains the single most effective modality for cancer treatment. Increasingly, it has become far more conservative, able to retain organs and structures and, in turn, to maintain good function in many parts of the body. Breast cancer is an excellent example.
The radical mastectomy performed up until 30 years ago left women with severe deformity of the chest wall. This was replaced first by the less mutilating simple mastectomy and now by simple excision followed by radiotherapy, the breast remaining fully intact. New technology permits minimally invasive (keyhole) surgery for many cancer types. The science of robotics allows completely automated surgical approaches with enhanced effects and minimal damage to surrounding structures. Ultimately, it is likely that surgery will disappear as an important treatment and become confined simply to biopsy performed under local anaesthetic with image guidance to check that the correct sites are biopsied (Table 3). The surgeon of the future will be a combination of a robotic engineer with well-honed information technology (IT) skills and an interventional radiologist.

**RADIOThERAPY**

Radiotherapy was first used for cancer treatment over 100 years ago. Originally, crude radium was used as the radiation source, but we now have a variety of sophisticated techniques available. Modern linear accelerators – the workhorses for radiotherapy – allow precise dose delivery to the shape of the tumour. Conformal therapy aims to deliver a high dose just to the tumour volume in three dimensions, killing the cancer cells and avoiding sensitive normal surrounding tissue. Novel computer-based imaging techniques have revolutionized our ability to understand the precise anatomy of cancer in a patient and therefore to deliver far more effective radiotherapy. The future of radiotherapy is about further computerization with multimedia imaging and optimized conformal planning. We have also learnt to understand the biological differences between different tumours in patients and can begin to plan individualized treatment courses to optimize selective destruction. With remarkable technological changes in imaging and computerization, continued development is essential (Table 4).

Radiotherapy, in many parts of the world, is the Cinderella of cancer care.

Radiotherapy works by destroying cancer cells and – as far as possible – leaving normal tissue undamaged. This selectivity is the key to the efficacy of radiotherapy. This is enhanced by fractionating treatments making radiation more damaging to cancer cells as they have limited DNA repair capacity and by the geographical limitation of the deposited energy. The challenge therefore comes in targeting the diseased tissue with the required radiation and leaving as much healthy tissue as possible untouched.

Radiation is delivered to the patient via a linear accelerator (LINAC), which generates beams of ionising radiation by accelerating electrons in an electrical gradient initially and then using microwave radiation down a linear wave-guide (1 to 2 m long). The electrons, which by then are moving close to the speed of light, hit a tungsten target that converts their energy into heat and high energy, deeply penetrating x-rays. As they emerge from the LINAC, they can be collimated using specially cut metal-alloy blocks or more recently by a computer-controlled, dynamic collimator consisting of small interweaving tungsten leaves – a multileaf collimator (MLC).

The treating clinicians have to carefully plan the delivery of radiotherapy, breaking treatments down into fractions – which are given to the patient over a number of weeks. The oncologist – working with a dosimetrist who may be a physicist or radiographer – calculates how to deliver a geographically precise deposition of radiation energy to the tumour. Good radiotherapy planning involves the careful assessment of risk to surrounding normal tissues and the subsequent modification of the plan to design the optimal balance of benefit versus collateral damage. The concepts of a planning target volume (PTV), gross tumour volume (GTV), clinical target volume (CTV) in conjunction with organs at risk (OAR) are used to optimize the risk-benefit ratio of any planned treatment.

The potential sources of error in radiation delivery are listed in Table 5. Image-guided radiotherapy (IGRT) with immediate corrective action before treatment reduces the risk of the last four having a major impact on the precision of treatment. Delivering radiotherapy without continual imaging can be compared to firing a gun blindfolded. Technological advances such as four-dimensional (4D) radiotherapy and new image comparison software are likely to further refine the accuracy of the delivery process.

### Table 3 Future of surgery

- Organ conservation
- Minimally invasive surgery
- Robotic surgery
- Distance surgery
- Tailored adjuvant approaches
- Biopsy only for many cancers
- All fast tracked – next-day service

### Table 4 Future of radiotherapy

- Multi-media imaging
- Robotic set-up
- Intensity modulated radiotherapy (IMRT)
- Image guided radiotherapy (IGRT)
- Biological optimization
- Designer fractionation

### Table 5 Errors in delivering radiotherapy

- Uncertainties in target delineation
- Poor treatment planning
- Calibration of hardware and software
- Errors in delivery of treatment – human and machine
- Movement of patient or target – intra- and inter-fraction, poor immobilisation, patient discomfort, patient anxiety
- Physiological shifts – lung, heart, intestine
- Tumour shrinkage during fractionalised treatment
- Movement of the tumour between treatments
Image-guided radiotherapy

Traditionally, tattoos or painted ink marks on the skin have been used to position a patient on the LINAC couch for every treatment. X-ray films taken on a treatment simulator at right angles (orthogonal films) were used before treatment to verify the plan. Subsequently, the megavoltage treatment beam has been used to produce planar images, on film or digital detectors, to image the bony anatomy and so verify the position of the treatment fields. This assumes the position and shape of the tumour and critical surrounding normal tissues are fixed with respect to the bony anatomy, which is often not the case, and relies on planar megavoltage images, which are often not very clear.

Both of these problems have been solved by the advent of IGRT in which kilovoltage (kV) imaging equipment, as used in diagnostic radiology, has been attached to the LINAC to produce high-quality 2D planar images (superior to traditional MV images) and 3D cone-beam CT data at the time of treatment. The IGRT process begins on the treatment planning computer where the clinician delineates, on the patient 3D CT dataset, the target volumes and organs at risk (OAR), which the dosimetrist uses in generating an optimal 3D radiation dose distribution and treatment plan. IGRT images are obtained before or during the treatment delivery process on the LINAC. In 2D IGRT, planar images are taken and compared with digitally reconstructed radiographs, while in 3D IGRT, a full cone-beam CT dataset is taken at treatment and compared to the CT dataset used on the treatment planning system. The patient’s position is then adjusted based on the congruence of these image datasets such that the images align to within some predetermined localization criteria. In this way, the treatment is delivered precisely and accurately according to the treatment plan approved by the oncologist.

For many years, the only means of verifying the proper orientation of treatment beams during radiotherapy was the use of megavoltage port films obtained periodically during the course of treatment. Such images can indicate that the location of a beam iso-centre and field edges agree reasonably well relative to bony landmarks. However, the tumour being treated is often a mobile soft-tissue mass within the body and patient repositioning based on bony landmarks alone is subject to error. One solution to address this error would be to expand the radiation field sizes adequately to cover the entire range of potential tumour positions within the body. This approach by default incorporates a large volume of normal tissue that might receive unnecessary radiation in the process. Therefore, it would be preferable to limit the radiation field size, if possible.

Radiotherapy equipment and techniques have evolved in recent years so that methods of imaging a tumour or target volume within a patient have been coupled with treatment delivery technology that allows near simultaneous localization of the tumour and repositioning of the patient. Cone-beam CT, in particular, enables soft tissues to be imaged so that tumour position and shape as well as organs at risk can be visualized before and during treatment. The goal is to direct the radiation beam towards the true location of the tumour volume within the patient, allowing for more tightly focused treatment fields, and avoiding organs at risk as far as possible. In this manner, the images are used to guide the radiotherapy, hence the term image-guided radiation therapy.

Guidelines for the use of IGRT have recently been published by the American Society for Therapeutic Radiology and Oncology (ASTRO) and are in widespread use in the United States. Critical to their implementation are the governance arrangements and the division of responsibilities between the health care professionals involved in adjustment of the beam after each image.

Toxicity of radiotherapy

The side effects of radiotherapy are classified into those occurring within weeks to months of treatment and those occurring later—often many years after successful treatment. The late side effects are particularly difficult to manage and can result in considerable reduction in the quality of life for a patient. They may also require costly interventions to attempt to palliate the symptoms caused by fistulae, fibrosis and obstruction. Optimal radiotherapy planning is a balance between ensuring an adequate tumour dose and the avoidance of as much normal tissue as possible. Different normal tissues have different susceptibility to radiation damage. IGRT systems include software with the capacity to accomplish an automated fusion of the acquired images with the expected image appearance. The software then calculates the vector displacement in 3D space of the actual target location from the expected location. In some cases, rotational distortion is calculated in addition to linear misalignment. The x-, y- and z-axis displacements and sometimes rotational error are then corrected by moving the couch on which the patient is immobilized.

Although not all cancers require such targeting radiation, IMRT/IGRT is now standard practice internationally. In countries with sophisticated radiotherapy services, such as the United States, a wide range of tumour types—including lung, prostate, breast, head and neck and gynaecological cancers—are now routinely treated with IMRT/IGRT. As outcomes improve, patients are increasingly likely to live for many years after treatment and so reducing the potential for long-term collateral damage is essential.

CHEMOTHERAPY

The current position of chemotherapy for advanced cancer is shown in Table 1. Essentially, there are three groups of cancers, in the first of which we can achieve a high complete response rate and a high cure rate. This first group includes diseases such as Hodgkin’s disease, childhood leukaemia and testicular cancer. Unfortunately, this group of cancers that can be successfully treated represents less than 5% of the global cancer burden. At the other end of the spectrum, we have a group with a low complete response
and low cure rate, such as lung, colon and stomach cancers. So far, chemotherapy has made few inroads into their treatment, although some useful palliation and prolongation of survival, sometimes for months, can be achieved. In the middle, we have a group of diseases with a high complete response but a low cure rate. These cause problems to those involved in rationing cancer care. The use of taxanes in breast and ovarian cancers is a classic example. High-cost drugs can achieve extension of life by several months for many patients, and when deciding on priorities, we have to assess how much we are willing to pay for a month of reasonable quality of life.

We are at the beginning of a revolution in cancer care. The pharmaceutical industry has taken on the new challenge, and is now going through a massive transition from an era of classical chemotherapy drugs (not too dissimilar to nitrogen mustard) that were discovered by screening programmes for their potential to destroy cells, to a molecular targeted approach. Currently, there are 770 molecules in clinical development by 49 pharmaceutical companies. It is likely that fewer than 30 will actually make it to the marketplace, and fewer than 5 will make a really significant impact on cancer care. Increasing consolidation in the industry has resulted in a shrinking of the total number of key players in cancer drug development. However, there has been a dramatic increase in research into molecular therapies. The Human Genome Project has created a dictionary of the genome, but we can now interrogate it through sophisticated bioinformatic systems. Not only do we have the library but we also have the search tools. We can now predict the 3D structural biology of many proteins and create images of drugs in silico using computers to design small molecules that can then be synthesized in the laboratory to check their activity. A platform approach to drug discovery is creating a massive increase in new candidate molecules for cancer therapy.

One of the problems currently is the large number of cellular targets that have been identified and to which new drugs can be developed. These targets include growth factors, cell-surface receptors, signal transduction cog molecules, transcription factors, apoptosis-stimulating proteins and cell-cycle-control proteins. Which one to target and invest research funds into is a difficult decision. The total cost of bringing an anti-cancer drug to market exceeds £600 million. Well-defined targets are the starting point on the road to our future treatments. It is likely that classical cytotoxic drugs will continue to be used for the next 25 years, although they will have a declining share of the total marketplace. By 2020, it is likely that successful molecular targeted approaches will overtake cytotoxics and transform cancer medicine. These new drugs will be individualized, chosen on the basis of molecular measurements of the patient’s tumour and normal cells, and taken orally for long periods.

The classical way in which we develop cancer drugs is split into three phases. In phase I, maximally tolerable doses are determined by gradually escalating the dose in patients with cancer. From this, we can determine a workable dose that patients can tolerate and yet is likely to have a therapeutic effect based on animal studies. We then carry out phase II studies, in which a series of patients with cancers that can be easily measured by x-rays or photographs is given the drug to see what effect it has on their cancer. This allows us to determine the response rate. Phase III is the last and longest phase, in which patients are randomized to receive either the new drug or the best available treatment and their long-term survival is determined.

This traditional approach may not be appropriate for many of our new agents. Toxicity may be minimal and effectiveness may be greatest well below the maximally tolerated dose. Furthermore, tumours may not actually shrink but just become static, so no responses are seen. As the new agents have been discovered by measuring their effect on specific molecular targets in the laboratory, it should be feasible to develop the same assay for use in patients. This gives us a short-term pharmacodynamic endpoint and tells us that we are achieving our molecular goals in a patient. Genomic technology has come to our aid. Gene chips allow us to examine the expression of thousands of genes simultaneously before and after administration of the drug. If a second biopsy can be obtained for the tumour, we can compare gene expression patterns in both tumour and normal cells in the same patient after exposure to a new drug. This enables us to get the drug to work in the most effective way. A particularly intriguing approach for the future is to use gene constructs, which signal tiny light pulses when their molecular switches are affected by a drug.

We would also like to obtain information about how a drug distributes itself within the body, and ideally to get a picture of the changes it causes in a tumour. Functional imaging allows us to do just this. The aim is to understand the living biochemistry of a drug in the body: we label the drug with a radioactive tracer and then image using PET. Such techniques promise to revolutionize our ability to understand drug activity and to select and improve the way in which we choose anti-cancer drugs for further development.

The next decade is likely to be a new golden age for cancer drug discovery, with many novel targeted molecules coming into the clinic. These agents will eventually transform cancer care forever.

FUTURE – GETTING INNOVATION INTO PRACTICE

Over the last 20 years, a huge amount of fine detail of the basic biological processes that become disturbed in cancer has been amassed. We now know the key elements of growth-factor binding, signal transduction, gene transcription control, cell-cycle checkpoints, apoptosis and angiogenesis. These have become fertile areas to hunt for rationally based anti-cancer drugs. This approach has already led to a record number of novel compounds currently being in trials. Indeed, targeted drugs such as rituximab, trastuzumab, imatinib, sunitinib, sorafenib, bevacizumab and cetuximab are now all in routine clinical use. Over the next decade,
there will clearly be a marked shift in the types of agents used in the systemic treatment of cancer.

Because we know the precise targets of these new agents, there will be a revolution in how we prescribe cancer therapy. Instead of defining drugs for use empirically and relatively ineffectively for different types of cancer, we will identify a series of molecular lesions in tumour biopsies. Future patients will receive drugs that target these lesions directly. The Human Genome Project provides a vast repository of comparative information about normal and malignant cells. The new therapies will be more selective, less toxic and given for prolonged periods, in some cases for the rest of the patient’s life. This will lead to a radical overhaul of how we provide cancer care.

Investment in more sophisticated diagnostics is now required (Table 6). Holistic systems such as genomics, proteomics, metabolomics and methylichromics provide fascinating clues as to where needles can be found in the haystack of disturbed growth. By developing simple, reproducible and cheap assays for specific biomarkers, a battery of companion diagnostics will emerge. It is likely that for the next decade these will be firmly rooted in tissue pathology, making today’s histopathologists essential in moving this exciting field forward. Ultimately, the fusion of tissue analysis with imaging technologies may make virtual biopsies of any part of the body – normal and diseased – a possibility.

Individual cancer risk assessment will lead to tailored prevention messages and a specific screening programme to pick up early cancer and will have far-reaching public health consequences. Cancer preventive drugs will be developed that will reduce the risk of further genetic deterioration. The use of gene arrays to monitor serum for fragments of DNA containing defined mutations could ultimately develop into an implanted gene chip. When a significant mutation is detected, the chip would signal the holder’s home computer and set in motion a series of investigations based on the most likely type and site of the primary tumour.

There will be an increase in the total prevalence of cancer as a result of improved survival, as well as change in cancer types in those of older age groups, such as prostate cancer which has a longer survival. This will create new challenges in terms of assessing risks of recurrence, designing care pathways, use of IT and improving access to services. There will be new opportunities for further targeting and development of existing therapies as experience grows with risk factors over the longer term. Careful monitoring of patient experiences could help in improving results. Cancer could soon be a long-term management issue for many patients who would enjoy a high quality of life even with a degree of chronic illness.

The funding of cancer care will become a significant problem. Already we are seeing inequity in access to the taxanes for breast and ovarian cancers and gemcitabine for lung and pancreatic cancers. These drugs are only palliative, adding just a few months to life. The emerging compounds are likely to be far more successful and their long-term administration considerably more expensive. Increased consumerism in medicine will lead to increasingly informed and assertive patients seeking out novel therapies and bypassing traditional referral pathways through global information networks. It is likely that integrated molecular solutions for cancer will develop, leading to far greater inequity than at present. Cost-effectiveness analyses will be used to scrutinize novel diagnostic technology as well as therapies.

Within 20 years, cancer will be considered a chronic disease, joining conditions such as diabetes, heart disease and asthma — conditions that impact on the way people live but will not inexorably lead to death. The model of prostate cancer — many men dying with it rather than from it — will be more usual. Progress will be made in preventing cancers. Even greater progress will be made in understanding the myriad causes of cancer. Our concepts will be different to those of today, and the new ways in which cancer will be detected, diagnosed and treated will be crucial to understanding in the future.

When a cancer does develop, refinements of current technologies and techniques – in imaging, radiotherapy and surgery – together with the availability of targeted drugs will make it controllable. Cure will still be sought, but will not be the only satisfactory outcome. Patients will be closely monitored after treatment, but the fear that cancer will definitely kill, which is still prevalent in the early years of the twenty-first century, will be replaced by an acceptance that many forms of cancer are a consequence of old age.

Looking into the future is fraught with difficulties. Who could have imagined in the 1980s the impact of mobile phones, the Internet and low-cost airlines on global communication. Medicine will be overtaken by similarly unexpected step changes in innovation.

For this reason, economic analysis of the impact of developments in cancer care is difficult. The greatest benefit will be achieved simply by assuring that the best care possible is on offer to most patients, irrespective of their socioeconomic circumstances and of any scientific developments. But this is unrealistic. Technologies are developing fast, particularly in imaging and the exploitation of the human genome. Well-informed patients, with adequate funds, will ensure that they have rapid access to the newest and the best – wherever it is in the world. More patients will benefit from better diagnosis and newer treatments, with greater emphasis on quality of life. Innovation will bring more inequality to health. The outcome of the same quality of care differs today between socioeconomic groups and will continue to do so.

Table 6  The challenges of cancer care

| • Increasing the focus on prevention. |
| • Improving screening and diagnosis and the impact of this on treatment. |
| • New targeted treatments – how effective and affordable will they be? |
| • How expectations of patients and their carers will translate into care delivery. |
| • Reconfiguration of health services to deliver optimal care. |
| • The impact of reconfiguration on professional territories. |
| • Will society accept the financial burden of these opportunities? |
Clinicians in Europe will continue to be dependent on technologies primarily designed for the major health market in the world – the United States, which currently consumes nearly 65% of the cost of cancer medication but contains less than 5% of the world’s population. European legislation covering clinical trials could bring research in the United Kingdom to a grinding halt, while ethicists – zealously interpreting privacy legislation – could impose restrictions on the use of tissue. Targeted niche drugs will be less appealing to industry, as the costs of bringing each new generation of drugs to market will not be matched by the returns from current blockbusters. The delivery of innovation will be underpinned by patient expectation. The well informed will be equal partners in deciding the health care they will receive, much of which will take place close to their homes using mechanisms devised by innovative service providers.

This has huge implications for the training of health professionals and the demarcations between specialties. Emerging technologies will drive the change. Intra-professional boundaries will blur – doctors from traditionally quite distinct specialties may find themselves doing the same job – and clinical responsibilities will be taken up by health professionals who will not be medically qualified. All professionals are likely to find challenges to their territory hard to accept. Table 6 shows the challenges that need to be addressed to deliver most health benefit.

**Prevention and screening**

At the beginning of the twenty-first century, 10 million people in the world develop cancer each year. The cause of these cancers is known in roughly 75% of cases: 3 million are tobacco related; 3 million are a result of diet; and 1.5 million are caused by infection. In the United Kingdom, 120,000 people die from cancer each year, even though many of these cancers are preventable, a third being related to smoking. But cancer prevention absorbs only 2% of the total funding of cancer care and research. Anti-smoking initiatives are considered to be successful, although it has been 50 years since the association between smoking and cancer was first identified. In the 1960s, 80% of the population smoked; by 2014 the average was under 30%. This masks real health inequality: the percentage of smokers in the higher socioeconomic classes is in low single figures, whereas the percentage among socioeconomically deprived classes is still about 50% in parts of the country. Despite the known risks, if friends and family smoked and there was no social pressure to stop, there was no incentive to do so. Banning smoking in public places will lead to a further drop of about 4%. Increases in tax were a powerful disincentive to smoke, but the price of a packet of cigarettes is so high that smokers turn to the black market: As many as one in five cigarettes smoked is smuggled into the country. Lung cancer, for example, is a rare disease in higher socioeconomic groups – it is therefore a disease of poverty.

Lessons from anti-smoking initiatives will be instructive for prevention in the future. Although the link between poor diet, obesity and lack of exercise, and cancer has not been confirmed, there is sufficient circumstantial evidence to suggest that strong associations will be found. There will be bans on advertising for crisps, sweets and soft drinks on television, the introduction of a health tax on these products and a ban on the sponsorship of any public event by manufacturers of these products. By 2015, obesity among the middle classes will be socially unacceptable, but it will remain common among the economically disadvantaged. Creating meaningful, imaginative incentives for people to adopt healthy lifestyles will be a major challenge.

The future prevention picture will be coloured by post-genomic research. In 2014, it is accepted that about 200 genes are associated with the development of a whole range of cancers. The detection of polymorphisms in low-penetrance cancer-related genes – or a combination of changed genes – will identify people at increased risk. Within 20 years, most people will be genetically mapped and the information – gained from a simple blood test – will be easily stored on a smart-card. Legislation will be required to prevent this information being used to determine an individual’s future health status for mortgage, insurance and employment purposes. However, the process of mapping will reveal that every person who has been screened will carry a predisposition to certain diseases – and people will learn to live with risk.

Today, the average age of diagnosis of cancer is 68. Improvements in screening, detection and diagnosis will reduce this. A predisposition for some cancers that manifests itself in a patient’s seventies or eighties will be found in young adult life and detected and corrected successfully in the patient’s thirties. Increasing age will remain the strongest risk predictor. Little of what has been described is not happening already in some form, but the computing power of the future will bring accurate calculation of risk, and predictions will take place on an unimaginable scale. Screening programmes will be developed on a national basis if they are simple, robust and cheap. Patients will expect the screening to take place at a venue that is convenient for them – for example in shopping malls – and not be painful or overly time consuming. Health professionals will demand that any programme is accurate and does not give misleading results, and governments will demand that its costs will lead to the more effective use of other resources. Novel providers of risk assessment services are likely to emerge (Table 7).

**Table 7 Balancing cancer risk**

- Great health inequity exists in smoking-related diseases.
- Novel prevention strategies are likely to lead to similar inequity.
- Creating meaningful incentives to reduce risk will be essential.
- Individually tailored messages will have greater power to change lifestyles.
- Biomarkers of risk will enhance the validation of cancer preventive drugs.
- Novel providers of risk assessment and correction will emerge.
Detecting cancer

Cancers are fundamentally somatic genetic diseases that result from several causes: physical, viral, radiation and chemical damage. There are other processes implicated, for example chronic inflammatory change, immunosurveillance and failure of apoptosis. In the future, cancer will no longer be understood as a single entity; it will be considered to be a cellular process that changes over time. Many diseases labelled as cancer today will be renamed, as their development will not reflect the new paradigm. Patients will accept that cancer is not a single disease and will increasingly understand it as a cellular process. Many more old people will have increased risk or a pre-cancer. This has huge implications for cancer services. Today, most diagnoses of cancer depend on human interpretation of changes in cell structures seen down a microscope. Microscopes will be superseded by a new generation of scanners to detect molecular changes. These scanners will build up a picture of change over time, imaging cellular activity rather than just a single snapshot. We will have the ability to probe molecular events that are markers for early malignant change. This dynamic imaging will lead to more sensitive screening and treatments: imaging agents that accumulate in cells exhibiting tell-tale signs of pre-cancer activity will be used to introduce treatment agents directly.

Imaging and diagnosis will be minimally invasive and enable the selection of the best and most effective targeted treatment (Table 8). Even better imaging will be able to pick up pre-disease phases and deal with them at a stage long before they are currently detectable. These techniques will also be crucial in successful follow-up. A patient who has a predisposition to a certain cancer process will be monitored regularly and treatment offered when necessary. However, not all cancers will be diagnosed in these earliest of stages – some patients will inevitably fall through the screening net. Nevertheless, there will be opportunities to offer less invasive treatment than at present. Surgery and radiotherapy will continue, but in greatly modified form as a result of developments in imaging. Most significantly, surgery will become part of integrated care. The removal of tumours or even whole organs will remain necessary on occasion. However, the surgeon will be supported by 3D imaging, by radiolabelling techniques to guide incisions and by robotic instruments. Although many of the new treatments made possible by improved imaging will be biologically driven, there will still be a role for radiotherapy – the most potent DNA-damaging agent – to treat cancer with great geographical accuracy. The targeting of radiotherapy will be greatly enhanced, enabling treatment to be more precise.

In addition to the reconfiguration and merging of the skills of clinicians, the delivery of care will also change. Minimally invasive treatments will reduce the need for long stays in hospital. As more patients are diagnosed with cancer, the provision of care close to where patients live will be both desirable and possible and, as this book will show later, expected. The prospect of highly sophisticated scanning equipment and mobile surgical units being transported to where they are required is not unrealistic. Technicians, surgical assistants and nurses would provide the hands-on care, while technical support would be provided by the new breed of clinician – a disease-specific imaging specialist working from a remote site. Cost control will be an essential component of the diagnostic phase. Health care payers will create sophisticated systems to evaluate the economic benefits of innovative imaging and tissue analysis technology.

New treatment approaches

Future cancer care will be driven by the least invasive therapy consistent with long-term survival. Eradication, although still desirable, will no longer be the primary aim of treatment. Cancers will be identified earlier and the disease process regulated in a way similar to that for chronic diseases such as diabetes. Surgery and radiotherapy will still have a role, but the extent of their role will depend on the type of cancer a patient has and the stage at which the disease is identified, as well as on how well the drugs being developed today perform in the future.

Cancer treatment will be shaped by a new generation of drugs (Table 9). What this new generation will look like will critically depend on the relative success of agents currently in development. Over the next 3–5 years, we will understand more fully what benefits compounds such as kinase inhibitors are likely to provide. It is estimated that there are about 700 drugs currently being tested in clinical trials. Of these, around 500 inhibit specific molecular targets. But this number is set to rise dramatically: 2000 compounds will be available to enter clinical trials by 2015 and 5000 by 2020. Many of these drug candidates will be directed at the same molecular targets, and industry is racing to screen those most likely to make it through to the development process. Tremendous commercial pressures are coming from the loss of patent protection of the majority of high-cost drugs.

Table 8 Innovation in diagnostics

- Radiology and pathology will merge into cancer imaging.
- Dynamic imaging will create a changing image of biochemical abnormalities.
- Cancer changes will be detected prior to disease spread from primary site.
- Greater precision in surgery and radiotherapy will be used for pre-cancer.
- Molecular signatures will determine treatment choice.
- Cost control will be essential for health care payers to avoid inefficient diagnostics.

Table 9 Drivers of molecular therapeutics

- Human Genome Project and bioinformatics
- Expression vectors for target production
- In-silico drug design
- Robotic high-throughput screening
- Combinatorial chemistry
- Platform approach to drug discovery
- Huge increase in number of molecular targets
chemotherapy drugs by 2015. Unless new premium-priced innovative drugs are available, cancer drug provision will come from global generic manufacturers currently gearing up for this change.

So what will these drug candidates look like? Small molecules are the main focus of current research, most of which are designed to target specific gene products that control the biological processes associated with cancer such as signal transduction, angiogenesis, cell-cycle control, apoptosis, inflammation, invasion and differentiation. Treatment strategies involving monoclonal antibodies, cancer vaccines and gene therapy are also being explored. Although we do not know exactly what these targeted agents will look like, there is growing confidence that they will work. More uncertain is their potential overall efficacy at prolonging survival. Many could just be expensive palliatives. In the future, advances will be driven by a better biological understanding of the disease process.

Already we are seeing the emergence of drugs targeted at a molecular level – trastuzumab, directed at the HER2 protein, imatinib, which targets the Bcr-Abl tyrosine kinase, gefitinib and erlotinib, directed at epidermal growth factor receptor (EGFR) tyrosine kinase and crizotinib at the ALK mutation. These therapies will be used across a range of cancers. What will be important in the future is whether a person’s cancer has particular biological or genetic characteristics. Traditional categories will continue to be broken down and genetic profiling will enable treatment to be targeted at the right patients. Patients will understand that treatment options are dependent on their genetic profile, and the risks and benefits of treatment will be much more predictable than today.

Therapies will emerge through our knowledge of the human genome and the use of sophisticated bio-informatics. Targeted imaging agents will be used to deliver therapy at screening or diagnosis. Monitoring cancer patients will also change as technology allows the disease process to be tracked much more closely. Treatment strategies will reflect this, and drug resistance will become much more predictable. Biomarkers will allow those treating people with cancer to assess whether a drug is working on its target. If it is not, an alternative treatment strategy will be sought. Tumour regression will become less important as clinicians look for molecular patterns of disease and its treatment response.

There will be more of a focus on therapies designed to prevent cancer. A tangible risk indicator and risk-reducing therapy along the lines of cholesterol and statins would allow people to monitor their risk and seek intervention. Delivering treatment early in the disease process will also be possible because subtle changes in cellular activity will be detectable. This will lead to less aggressive treatment. The role of industry in the development of new therapies will continue to change. Smaller, more specialized companies linked to universities will increasingly deliver drug candidates and innovative diagnostics to the large commercially driven multinational pharmaceutical companies who will market them globally.

People will be used to living with risk and will have much more knowledge about their propensity for disease. Programmes will enable them to determine their own predisposition to cancer. This in turn will encourage health-changing behaviour and will lead people to seek out information about the treatment options available to them. Patients will also be more involved in decision-making as medicine becomes more personalized. Indeed, doctors may find themselves directed by well-informed patients. This, and an environment in which patients are able to demonstrate choice, will help drive innovation towards those who will benefit. However, inequity based on education, wealth and access will continue (Table 10).

**Table 10** The uncertainty of novel drugs for cancer

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will the new generation of small-molecule kinase inhibitors really make a difference or just be expensive palliation?</td>
</tr>
<tr>
<td>How will big pharma cope with most high-value cytotoxics recently becoming generic?</td>
</tr>
<tr>
<td>Can expensive late-stage attrition really be avoided in cancer drug development?</td>
</tr>
<tr>
<td>How will sophisticated molecular diagnostic services be provided?</td>
</tr>
<tr>
<td>Will effective surrogates for cancer preventive agents emerge?</td>
</tr>
<tr>
<td>Will patient choice involve cost considerations in guiding therapy?</td>
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</tbody>
</table>

**Barriers to innovation**

Innovation in cancer treatment is inevitable. However, there are certain prerequisites for the introduction of new therapies. First, innovation has to be translated into usable therapies. These therapies must be deliverable, to the right biological target, and to the right patient in a way that is acceptable to the patient, health care professional and society. Innovation must also be marketed successfully so that professionals, patients and those picking up the cost understand the potential benefits. Those making the investment in research will inevitably create a market for innovation even if the benefits achieved are minimal. The explosion of new therapies in cancer care is going to continue, and pricing of these drugs will remain high. The cost of cancer drugs in 2014 is estimated to be $84 billion globally, of which $70 billion is spent in the United States. If effective drugs emerge from the research and development pipeline, the cancer drug market could reach $300 billion globally by 2025, with this cost spreading more widely around the world.

But parallel to this explosion in therapies and increase in costs, a number of confounding factors will make markets smaller. The technology will be available to reveal which patients will not respond to therapy, so making blockbuster drugs history. Doctors will know the precise stage of the disease process at which treatment is necessary, and as cancer transforms into a chronic disease, people will have more co-morbidities, which will bring associated drug–drug interactions and an increase in care requirements.

**Patient’s experience**

Two separate developments will determine the patient’s experience of cancer care in future. Increasing expectations of patients as consumers will lead health services to become much more responsive to the individual, in the way that other service industries have already become. Targeted approaches
to diagnosis and treatment will also individualize care. People will have higher personal expectations, be less deferential to professionals and more willing to seek alternative care providers if dissatisfied. As a result, patients will be more involved in their care; they will take more responsibility for decisions rather than accepting a paternalistic ‘doctor knows best’ approach. This will be fuelled partly by the Internet and competitive provider systems. By 2025, the overwhelming majority of people in their seventies and eighties will be familiar with using the Internet to access information through the massive computing power that they will carry personally.

With patients having access to so much health information, they will need someone to interpret the huge volumes available and to help them assess the risks and benefits as well as to determine what is relevant to them. These patient brokers will be compassionate but independent advocates who will act as patients’ champions, guiding them through the system. They will be helped by intelligent algorithms to ensure patients understand screening and the implications of early diagnosis, and they will spell out what genetic susceptibility means and guide patients through the treatment options. Patients and health professionals will have confidence in computer-aided decision-making because they will have evidence that the programs work.

How the service will be designed around patients’ needs and expectations will be determined by the improved treatments available and their individualization (Table 11). When cancer centres developed in the mid-twentieth century, the diseases were relatively rare, and survival was low. Although distressing for patients when they were referred to a centre, their existence concentrated expertise. Cancers will be commonly accepted chronic conditions and therefore even when inpatient care is required, patients will be able to choose from many places in the world where they will receive care at a ‘cancer hotel’. But for many patients even that option will not be necessary: most new drugs will be given orally, so patients will be treated in their communities. However, this approach to cancer and other concomitant chronic conditions will place a huge burden on social services and families. Systems will be put in place to manage the ongoing control of these diseases and conditions – psychologically as well as physically. Pain relief and the control of other symptoms associated with cancer treatment will be much improved.

Today, 70% of the cancer budget in the United States is spent on care associated with the last 6 months of people’s lives. Although many recognize that such treatment has more to do with the management of fear than with the management of cancer, medical professionals have relatively few treatment options available and there has been limited awareness of which patients would benefit. There is also an institutional reluctance to destroy patients’ hopes, which led to confusion between the limits of conventional medicines, and a reluctance to face the inevitable – by patients and their families and doctors. There is a widespread perception that if patients are continuing to be offered anti-cancer treatment, there is a possibility that their health might be restored.

With better treatments, consumers of services will be able to focus on quality of life, and much of the fear now associated with cancer will be mitigated. Demand for treatments with few side effects or lower toxicity will be high, even if there are only quite modest survival gains. The transition between active and palliative care is often sudden, but in the future, because patients will be in much greater control of their situation, the change in gear will not be as apparent.

### Professional reconfiguration

One of the greatest challenges to providing the best cancer care in future will be having the right people in the right jobs. It will be essential not to continue to train people for jobs that will no longer exist. Policy makers have begun to grasp some of the workforce difficulties that lie ahead, and there are moves to ensure that health care professionals have responsibilities commensurate with their level of education and professional skills. Nurses and pharmacists are being encouraged to take over some responsibilities that have been held firmly by doctors, such as prescribing, while their traditional roles have been handed on to technicians and other support staff.

The appropriate skill mix will become even more critical (Table 12). Barriers between health care professions will have to be broken down in order for the new approaches to the care of patients with cancer and many other diseases to be delivered. The work of pathologists and radiologists will become one, as their traditional skills are augmented by the new generation of diagnostic and treatment devices. Oncologists will find that many forms of chemotherapy will be delivered with the aid of the new technology, and surgeons will be using robots to enable them to operate. Fewer of the most highly trained specialists will be required, since much of their responsibility will be delegated to specialist technicians and nurses working to protocols. In addition, the most highly trained individuals will be able to work at a number of sites on the same day, since the technology will be mobile and skills will be used remotely. The balance between skills will be driven by a number of factors: the size of the medical workforce and the capacity of the system to provide care, as well as the availability of trained support staff.

### Table 11 Experiencing cancer in future

- Patient brokers will guide people with cancer through the system.
- Choice will be real and will involve cost decisions.
- Patients will make a contribution to their care costs.
- Complementary therapies will be widely available and well regulated.
- Themed death chosen by patients will be possible.

### Table 12 The right person for the right job – key challenges

- Manpower planning for new technology.
- Doctors and other health care specialists.
- Prescribing cancer drugs by nurses, pharmacists and others.
- Training carers for elderly people with co-morbidities.
- Making patients equal partners in decision-making.
CONCLUSION

Cancer will become incidental to day-to-day living. Cancers will not necessarily be eradicated, but that will not cause patients the anxiety that they do today. People will have far greater control over their medical destinies. Patients in all socioeconomic groups will be better informed. In addition, surgery and chemotherapy will not be rationed on grounds of age, since all interventions will be less damaging – psychologically as well as physically.

How true this picture will be will depend on whether the technological innovations emerge. Will people, for example, really live in ‘smart houses’ where their televisions play a critical role in monitoring their health and well-being? It is also dependent on health care professionals working alongside each other, valuing the input of carers who, even more than today, will provide voluntary support because of the number of people in older age groups compared with those of working age. The reality for cancer care may be rather different: the ideal may exist for a minority of patients, but the majority may not have access to the full range of services. Some older people having been relatively poor all their lives may suffer from cancer and a huge range of co-morbidities that will limit their quality of life. Looking after them all – rich and poor – will place great strains on younger people: will there be enough of them to provide the care? As with all health issues, the question of access will be determined by cost and political will. In 2005, a cancer patient consumed about £25,000 worth of direct medical care costs, with 70% being spent in the last 6 months of life. Conservatively, with patients living with cancer, rather than dying from it, and with access to new technologies, this could reach £100,000 per patient per year by 2025. Table 13 shows the annual cost of currently marketed targeted therapies. In theory, cancer care could absorb an ever-increasing proportion of the health care budget. Would this be a reflection of what patients want? Probably ‘yes’. Surveys reveal that three-quarters of the U.K. population believe cancer care should be the NHS priority, with no other disease area coming even a close second.

But to achieve that expenditure – and assuming that part of the health service will be funded from taxation – the tax rate might have to rise to 60%. Inevitably, there will be conflicting demands on resources: the choice may be drugs or care costs. How are the costs computed? Although the technology will be expensive, it will be used more judiciously since it will be better targeted. Another argument suggests that when patients are empowered they use less and fewer expensive medicines, in effect lowering the overall costs. An extension of that argument is that although costs will increase for treating each individual patient, the overall costs will decrease because more care will be delivered at home. But because people will live longer, the lifetime costs of cancer care will rise along with co-morbidity costs. Politicians will be faced with a real dilemma: if the prevalence of cancer increases, the cost of delivering innovative care could be massive. Will cancer care need to be rationed in a draconian way?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Cancer</th>
<th>Cost £ per year</th>
<th>Survival months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zactima</td>
<td>Vandetanib</td>
<td>Lung</td>
<td>80,000</td>
<td>4</td>
</tr>
<tr>
<td>Yervoy</td>
<td>Ipilimumab</td>
<td>Melanoma</td>
<td>120,000</td>
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<tr>
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<td>Sipuleucel T</td>
<td>Prostate</td>
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<td>Aributerone</td>
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<td>Ofatumumab</td>
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<tr>
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<td>Prostate</td>
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<td>Crizotinib</td>
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<tr>
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<td>CML</td>
<td>80,000</td>
<td>6</td>
</tr>
</tbody>
</table>

One dilemma for the future will be the political power of old people. More will be living longer and their chronic problems will not necessarily incapacitate them physically or mentally. This educated gerontocracy will have high expectations that are being sharpened through the first two decades of the twenty-first century and they will not tolerate the standards of care now offered to many old people. They will wield considerable influence. Will a tax-based health system be able to fund their expectations? Politicians will have to consider the alignment between patients’ requirements and the wishes of taxpayers and voters. Fewer than 50% of voters now pay tax, and the percentage of tax-paying voters is set to fall as the population ages. Will the younger taxpayers of the future tolerate the expensive wishes of non-taxpayers? The interests of voters may be very different from the interests of taxpayers. It seems likely, therefore, that the days of an exclusively tax-funded health service are numbered. Co-payments and deductibles will be an inevitable part of the new financial vocabulary for cancer.

Whatever system is put in place, there is the prospect of a major socio-economic division in cancer care. A small percentage of the elderly population will have made suitable provision for their retirement, in terms of both health and welfare, but the vast majority will not be properly prepared.
Policy-makers need to start planning now, as they are doing for the looming pensions crisis. The most productive way forward is to start involving cancer patient and health advocacy groups in the debate, to ensure that difficult decisions are reached by consensus. Societal change will create new challenges in the provision of care. A decline in hierarchical religious structures, a reduction in family integrity through increasing divorce, greater international mobility and the increased selfishness of a consumer-driven culture will leave many lonely and with no psychological crutch to lean on at the onset of serious illness. There will be a global shortage of carers – the unskilled, low-paid but essential component of any health delivery system. The richer parts of the world are now harnessing this from the poorer, but eventually the supply of this precious human capital will evaporate.

New financial structures will emerge with novel consortia from the pharmaceutical, financial and health care sectors enabling people to buy into the level of care they wish to pay for. Cancer, cardiovascular disease and dementia will be controlled and will join today’s list of chronic diseases such as diabetes, asthma and hypertension. Hospitals will become attractive health hotels run by competing private sector providers. Global franchises will provide speciality therapies through these structures similar to the internationally branded shops in today’s malls. Governments will have long ceased to deliver care. Britain’s NHS, one of the last centralized systems to disappear, will convert to U.K. Health – a regulator and safety net insurer – by the end of this decade.

The ability of technology to improve cancer care is assured. But this will come at a price: the direct costs of providing it and the costs of looking after the increasingly elderly population it will produce. We will eventually simply run out of things to die from. New ethical and moral dilemmas will arise as we seek the holy grail of compressed morbidity. Living long and dying fast will become the mantra of twenty-first-century medicine. Our cancer future will emerge from the interaction of four factors: the success of new technology, society’s willingness to pay, future health care delivery systems and the financial mechanisms that underpin them.

**USEFUL WEBSITES**

**Regional websites**

**UNITED KINGDOM**

**www.pennybrohncancercare.org**

All about U.K. complementary cancer care. The charity offers free information, courses at a dedicated centre in Bristol and a helpline on using complementary therapies and self-help techniques.

**www.mariecurie.org.uk**


**www.nhs.uk/cancer**

The NHS lowdown on cancer. This site gives an overview of the disease, medicines and trials and a more in-depth A to Z of all the different types of cancer.

**www.nhstadidirectory.org**

NHS guide to complementary therapies and register of practitioners. Consult this annual guide for advice about how to access practitioners, overviews of each therapy and an NHS-approved register.

**www.icnm.org.uk**

U.K. register of complementary therapists. The website of the non-profit Institute for Complementary and Natural Medicine also has a register of accredited therapists and information about regulation of the industry.

**www.actioncancer.org**

Early detection and support services in Northern Ireland. Action Cancer runs free courses on positive living and one-to-one emotional and practical support sessions.

**www.canceractive.com**

A patient-founded cancer charity which provides A to Z information including on both conventional and complementary treatment and inspirational "survivor stories". A little alternative but otherwise very useful. A fun site generally.

**www.cancerandcanceruk.org**

Resource for working women with cancer. Set up by a non-profit professional group.

**Cosmetic Executive Women, Cancer and Careers provides information and advice on handling work with a cancer diagnosis. There is a downloadable guide that lists support services, cancer-specific beauty treatments and legal and financial options. Innovative.**

**www.chaicancercare.org**

Support for the United Kingdom’s Jewish community. Chai provides free counselling, complementary therapies, advice and help with rights to services, centre-based rehabilitative and palliative care, group activities and home-based help. A truly excellent organisation.

**www.dimblybcancercare.org**

U.K. hospital-based centres for patients. Charity named after broadcaster Richard Dimbleby that operates two centres in London hospitals that offer psychological and complementary therapy services, information and benefits advice.

**www.helenrollason.org.uk**

Free support for patients and carers in south-east England. The charity runs three centres that can give you free complementary therapies, counselling and support groups. The charity’s nurses at two hospital bases also ease access to clinical trials.

**http://maggiescentres.org**

A U.K. network of free patient-focused centres. Maggie’s 13 U.K. centres, one in Hong Kong and one in Barcelona bring emotional support, relaxation, information and practical advice. A little uncertain on its relationship to alternative medicine.

**www.rarercancers.org.uk**

U.K. support for patients with rarer cancers. The Rarer Cancers Foundation provides a free helpline, free interactive online profiles for users, patient stories and information. Very useful indeed if you have one of the uncommon cancers for which there is often little information.

**www.tenovus.org.uk**

Wales-based support. Tenovus runs a free phone helpline and a mobile cancer support unit that gives patients easy access treatment, including chemotherapy, in partnership with the NHS.

**www.ulstercancer.org**

Belfast-based help in Northern Ireland. Ulster Cancer Foundation maintains a free drop-in centre in Belfast and a free helpline that give access to counselling, advice and support groups.

**www.fountaincentre.org**

Support for patients at the Royal Surrey County Hospital. The Fountain Centre in the St Luke’s unit of the hospital offers advice, counselling and a range of complementary therapies.

**www.holisticcancercarecentre.org.uk**

Free supportive therapies for patients treated at the James Cook University Hospital.

**www.actioncancer.org**

The Holistic Cancer Care Centre provides various therapies at its purpose built centre in the grounds of the hospital. Run on charitable donations, the therapies are given by trained practitioners free of charge. The “bra clinic” for women with breast cancer and “headstrong” for people with hair loss are also based at the centre.
www.cancerindex.org
A one-man-band guide to cancer on the Internet. Set up by U.K. tech geek Simon Cotterill, the Guide to Internet Resources for Cancer aims to unscramble everything the web throws at you and point you towards the best sites under 12 helpful headings. A very interesting approach.

CANADA
www.cancer.ca
Free info, support and networking. The Canadian Cancer Society runs free information lines that will do their best to come up with an answer to your queries about cancer. You can hook up with a trained volunteer, matched to your cancer experience and also access an online network of blogs, forums and messaging in English and French.
http://canada.thewellnesscommunity.org
Support for all cancer patients in Canada. Cancer Support Community offers access to an online community and support groups, information and links to local affiliates.

UNITED STATES
www.lookgoodfeelbetter.org
Learn beauty techniques for free keep your confidence topped up. Patients undergoing cancer treatment can opt for group or one-to-one free beauty treatments that will show you make-up, hair and nail techniques to offset the harsher side effects.
www.cancer.net
Oncologist approved cancer data, stats and facts. A to Z information from the American Society of Clinical Oncology. Look up your cancer and find out about all your options. Find an oncologist in your area on the database.
www.nlm.nih.gov
Free legal services for U.S. cancer patients and survivors. If you're struggling with the financial and legal consequences of your cancer, you can use the National Cancer Legal Services Network to find free legal services to help you solve anything from insurance disputes to housing and employment issues to plans for future care and custody.
www.cancersupportcommunity.org
Support for all cancer patients. Cancer Support Community offers access to an online community and support groups, information and links to local affiliates.
www.oncolink.org
Solid support for U.S. patients. You can dial toll free for counselling and speak to oncology social workers, find help with money worries including limited funds from CancerCare itself and update on the latest scientific findings by telephone and web conference. CancerCare can also connect you to support groups and plug you in to the New York, New Jersey or Connecticut community and there are monthly sessions of ask-the-expert.
www.inspire.com
Health and social networking. www.inspire.com is a networking forum for members interested in health issues. You can read posts, join groups and blog about all that interests you.

http://ontopofcancer.org
Guide to the internet from cancer survivors. On Top of Cancer.org can point you in the right direction if you money, insurance or legal worries, or if you need emotional support and help.

AUSTRALIA
The Australian central government's cancer website gives an overview of cancer in Australia and links to the main support organisations.
In-depth information and helpline about every type of cancer in Australia. CancerCouncil Australia's local cost helpline gives emotional and practical support and there is detailed info on anything from stats to treatment to finding a specialist.
www.thewarwickfoundation.org.au/
Help and time out for young adults. The Warwick Foundation puts young adults with cancer in touch with each other, organises “get spoilt” events and arranges free mid-week stays at countryside retreats. There is also an information kit tailored to the age group.
Information, advice and poetry for children affected by the cancer of a parent or guardian.

General guidelines and information
http://www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines
Practice Guidelines Europe
www.nccn.org
Website log-in is necessary.
Cancer outcomes in the United States.
www.cancer.gov
The National Cancer Institute’s website.
http://www.cancer.net/
http://www.ncin.org.uk/home
https://cancerstaging.org/Pages/default.aspx
http://www.uptodate.com/home
Up-to-date – Regularly updated reviews on all cancers written by recognised experts in the field. Requires subscription but many institutions have access for their employees.
www.cancerresearchuk.org
CancerResearchUK. Very good, easy to read information on staging systems for each cancer and details of outcomes. Also contains Cancerhelp site. The most informative site on the technical aspects of cancer care.
www.macmillan.org.uk
The most informative U.K. site about services on offer to cancer patients. A superb set of clinical care guidelines for all major cancers. Created by 21 leading cancer centres in the United States, it represents the gold standard of cancer care globally. Aspirational even for Britain! www.cancer.org
A useful site from the American Cancer Society brimming with information on how to get better cancer care.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAF</td>
<td>IFN-alpha-activated factor</td>
</tr>
<tr>
<td>17-AAG</td>
<td>17-allylaminogel-danamycin</td>
</tr>
<tr>
<td>AAVs</td>
<td>adeno-associated viruses</td>
</tr>
<tr>
<td>ABC</td>
<td>Adjuvant Breast Cancer trial</td>
</tr>
<tr>
<td>ABVD</td>
<td>doxorubicin, bleomycin, vinblastine, dacarbazine</td>
</tr>
<tr>
<td>AC</td>
<td>Audit Commission doxorubicin, cyclophosphamide</td>
</tr>
<tr>
<td>ACE</td>
<td>Adult Comorbidity Evaluation</td>
</tr>
<tr>
<td>ACNU</td>
<td>1-(4-amino-2-methylpyrimidine-5-yl) methyl- 3-(2-chloroethyl)-3-nitrosurea</td>
</tr>
<tr>
<td>ACT</td>
<td>adoptive cell transfer</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>ACTION</td>
<td>Adjuvant Cytotoxic Chemotherapy In Older Women (trial)</td>
</tr>
<tr>
<td>ADC</td>
<td>apparent diffusion coefficient</td>
</tr>
<tr>
<td>ADDC</td>
<td>antibody dependent directed cytotoxicity</td>
</tr>
<tr>
<td>ADEPT</td>
<td>antibody-directed enzyme prodrug therapy</td>
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<tr>
<td>AEs</td>
<td>adverse events</td>
</tr>
<tr>
<td>AF</td>
<td>accelerated fractionation</td>
</tr>
<tr>
<td>AFP</td>
<td>alpha-fetoprotein</td>
</tr>
<tr>
<td>AIM</td>
<td>doxorubicin, ifosfamide, mesna</td>
</tr>
<tr>
<td>AIN</td>
<td>anal intra-epithelial neoplasia</td>
</tr>
<tr>
<td>AIs</td>
<td>aromatase inhibitors</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>ALA</td>
<td>5-aminolevulinic acid</td>
</tr>
<tr>
<td>ALL</td>
<td>acute lymphoblastic leukaemia</td>
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<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloid leukaemia</td>
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<tr>
<td>AP</td>
<td>antero-posterior fields</td>
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<tr>
<td>APC</td>
<td>adenoamatory polyposis coli</td>
</tr>
<tr>
<td>APCs</td>
<td>antigen presenting cells</td>
</tr>
<tr>
<td>APL</td>
<td>promyelocytic leukaemia</td>
</tr>
<tr>
<td>APT</td>
<td>Antiplatelet Trialists Collaborative Group</td>
</tr>
<tr>
<td>ara-CTP</td>
<td>cytarabine triphosphate</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>ASCT</td>
<td>autologous stem-cell transplantation</td>
</tr>
<tr>
<td>ASH</td>
<td>American Society of Hematology</td>
</tr>
<tr>
<td>ASTEC</td>
<td>A Study in the Treatment of Endometrial Cancer trial</td>
</tr>
<tr>
<td>AT</td>
<td>ataxia telangiectasia</td>
</tr>
<tr>
<td>ATG</td>
<td>anti-thymocyte globulin</td>
</tr>
<tr>
<td>AT/RTs</td>
<td>atypical teratoid/rhabdoid tumours</td>
</tr>
<tr>
<td>ATAC</td>
<td>Arimidex or Tamoxifen Alone or in Combination trial</td>
</tr>
<tr>
<td>ATBC</td>
<td>Alpha-Tocopherol, Beta-Carotene study</td>
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<tr>
<td>ATLAS</td>
<td>Adjuvant Tamoxifen Longer Against Shorter trial</td>
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<tr>
<td>ATLL</td>
<td>adult T-cell leukaemia/lymphoma</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine phosphate</td>
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<tr>
<td>ATRA</td>
<td>all-trans retinoic acid</td>
</tr>
<tr>
<td>aTTom</td>
<td>adjuvant Tamoxifen Treatment offer more trial</td>
</tr>
<tr>
<td>AUC</td>
<td>area under time/concentration curve</td>
</tr>
<tr>
<td>BAL</td>
<td>bronchoalveolar lavage</td>
</tr>
<tr>
<td>BCG</td>
<td>bacillus Calmette—Guerin</td>
</tr>
<tr>
<td>BCIRG</td>
<td>Breast Cancer International Research Group</td>
</tr>
<tr>
<td>BCNU</td>
<td>1,3-bis-(2-chloroethyl)-1-nitrosourea (carmustine)</td>
</tr>
<tr>
<td>BDs</td>
<td>beam direction shells</td>
</tr>
<tr>
<td>BEACOPP</td>
<td>bleomycin, doxorubicin, cyclophosphamide, prednisone, gemcitabine</td>
</tr>
<tr>
<td>BEM</td>
<td>BCNU, etoposide, cytarabine, melphalan</td>
</tr>
<tr>
<td>BU</td>
<td>busulphan</td>
</tr>
<tr>
<td>BIPSS</td>
<td>bilateral inferior petrosal sinus sampling</td>
</tr>
<tr>
<td>BNCT</td>
<td>boron neutron capture therapy</td>
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<tr>
<td>BrdUrd</td>
<td>bromodeoxyuridine</td>
</tr>
<tr>
<td>BRT</td>
<td>brachytherapy</td>
</tr>
<tr>
<td>BSO</td>
<td>bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>BP</td>
<td>base pair</td>
</tr>
<tr>
<td>BOLD</td>
<td>blood oxygen level-dependent</td>
</tr>
<tr>
<td>BP</td>
<td>base pair</td>
</tr>
<tr>
<td>C225</td>
<td>cetuximab</td>
</tr>
<tr>
<td>CA</td>
<td>carbohydrate antigen; carbonic anhydrase</td>
</tr>
<tr>
<td>CAD</td>
<td>computer-aided diagnosis</td>
</tr>
<tr>
<td>CAV</td>
<td>cyclophosphamide, doxorubicin and vincristine</td>
</tr>
<tr>
<td>C-HDT</td>
<td>conventional high-dose therapy</td>
</tr>
<tr>
<td>CALG</td>
<td>Cancer and Leukaemia Group</td>
</tr>
<tr>
<td>CAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CaSR</td>
<td>calcium-sensing receptor</td>
</tr>
<tr>
<td>CARET</td>
<td>Beta-Cardenone and Retinol Efficacy Trial</td>
</tr>
<tr>
<td>CASH</td>
<td>Cancer and Steroid Hormone study</td>
</tr>
<tr>
<td>CCNU</td>
<td>lomustine</td>
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<tr>
<td>CD</td>
<td>cytosine deaminase</td>
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<tr>
<td>CDC</td>
<td>complement-dependent cytotoxicity</td>
</tr>
<tr>
<td>CD38</td>
<td>syndecan</td>
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<tr>
<td>CDKs</td>
<td>cyclin-dependent kinases</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>CEA</td>
<td>carcinoembryonic antigen</td>
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<tr>
<td>CED</td>
<td>convection-enhanced delivery</td>
</tr>
<tr>
<td>CEUS</td>
<td>contrast enhanced ultrasound</td>
</tr>
<tr>
<td>CEV</td>
<td>etoposide, cyclophosphamide and vincristine</td>
</tr>
<tr>
<td>CF</td>
<td>conventional fractionation</td>
</tr>
<tr>
<td>CGH</td>
<td>comparative genomic hybridization</td>
</tr>
<tr>
<td>CHART</td>
<td>continuous hyperfractionated accelerated radiotherapy</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CHI/NAO</td>
<td>Commission for Health Improvement/ National Audit Office</td>
</tr>
<tr>
<td>CIN</td>
<td>conjunctival (or corneal) intra-epithelial neoplasia</td>
</tr>
<tr>
<td>CIRs</td>
<td>chimeric immune receptors</td>
</tr>
<tr>
<td>CIS</td>
<td>carcinoma-in-situ</td>
</tr>
<tr>
<td>CLDR</td>
<td>continuous low-dose-rate</td>
</tr>
<tr>
<td>CLIP</td>
<td>Cancer of the Liver Italian Programme</td>
</tr>
<tr>
<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>CM</td>
<td>complete hydatidiform mole disease</td>
</tr>
<tr>
<td>CMF</td>
<td>cyclophosphamide, methotrexate, 5-fluorouracil</td>
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<tr>
<td>CML</td>
<td>chronic myeloid leukemia</td>
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<tr>
<td>CMV</td>
<td>cisplatin, methotrexate, vinblastine; cytomegalovirus</td>
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<td>CNS</td>
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<td>COG</td>
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<td>COX-2</td>
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<td>cardio-pulmonary resuscitation</td>
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<td>CPT-11</td>
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<td>CR3-DCC</td>
<td>complement-receptor-3-dependent cellular cytotoxicity</td>
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<td>CR</td>
<td>complete response</td>
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<td>CRC</td>
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<td>CRE</td>
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<td>CRM</td>
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<td>D&amp;C</td>
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<td>DALM</td>
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<td>DC, NOS</td>
<td>Ductal Carcinoma, Not Otherwise Specified</td>
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<td>or NST</td>
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<td>EASL</td>
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<td>EBCCTCG</td>
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<td>EUS</td>
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<tr>
<td>EV</td>
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<td>FAC</td>
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<td>FAMMM</td>
<td>familial atypical mole/malignant melanoma</td>
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<td>FASG</td>
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<td>FBC</td>
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<td>FdUMP</td>
<td>5-fluoro-deoxyuridine monophosphate</td>
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<td>forced expiratory volume</td>
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<td>FFTF</td>
<td>freedom from treatment failure</td>
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<td>FGF</td>
<td>fibroblast growth factor</td>
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<td>FHDR</td>
<td>fractionated high-dose-rate</td>
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<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
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<tr>
<td>FIHP</td>
<td>familial isolated hyperparathyroidism</td>
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<td>FISH</td>
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<td>FLR</td>
<td>future liver remnant</td>
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<td>FLT-3</td>
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<td>FPGS</td>
<td>folypoly-gamma-glutamate synthetase</td>
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<td>FT</td>
<td>farnesyl transferase</td>
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<td>5-FU</td>
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<td>FUTP</td>
<td>fluorouridine triphosphatase</td>
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<td>GBM</td>
<td>glioblastoma multiforme</td>
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<tr>
<td>GC</td>
<td>gemcitabine/cisplatin doublet</td>
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<td>GCSF</td>
<td>granulocyte colony-stimulating factor</td>
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<td>GCT</td>
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<td>Gd-BOPTA</td>
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<td>Gd-EOB-DTPA</td>
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<td>GDEPT</td>
<td>gene-directed enzyme prodrug therapy</td>
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<td>GDNF</td>
<td>glial-cell-derived neurotropic factor</td>
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<tr>
<td>GEP</td>
<td>gastro-enteropancreatic, gene expression profiling</td>
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<tr>
<td>GERD</td>
<td>gastro-oesophageal reflux disease</td>
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<tr>
<td>GFAP</td>
<td>fibrillary acidic protein</td>
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<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
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<td>GH</td>
<td>growth hormone</td>
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<td>GHSG</td>
<td>German Hodgkin Study Group</td>
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<td>GISTs</td>
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<td>Gastrointestinal Tumour Study Group</td>
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<td>GM CSF</td>
<td>granulocyte–macrophage colony-stimulating factor</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>GnRH</td>
<td>gonadotrophin-releasing hormone</td>
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<td>Gynaecologic Oncology Group</td>
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<td>GRE</td>
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<td>GTD</td>
<td>gestational trophoblastic disease</td>
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<tr>
<td>GTT</td>
<td>gestational trophoblastic tumours</td>
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<td>GTV</td>
<td>gross tumour volume</td>
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<td>GVHD</td>
<td>graft-versus-host disease</td>
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<td>GVL</td>
<td>graft-versus-leukaemic effect</td>
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<td>GVT</td>
<td>graft-versus-tumour effect</td>
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<td>HAMA</td>
<td>human anti-mouse antibody</td>
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<td>HATS</td>
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<td>HAV</td>
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<td>HB-EGF</td>
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<td>HCC</td>
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<td>HDCT</td>
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<td>high dose rate</td>
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<td>human leukocyte antigen</td>
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<td>ICE</td>
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<td>IES</td>
<td>Intergroup Exemestane Study trial</td>
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<td>IF-RT</td>
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<td>IFA</td>
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<td>IFIs</td>
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<td>kinase inhibitor therapy</td>
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<td>lobular carcinoma-in-situ</td>
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<td>STR</td>
<td>short tandem repeat</td>
</tr>
<tr>
<td>STS</td>
<td>soft tissue sarcoma</td>
</tr>
<tr>
<td>START</td>
<td>STANDARDization of breast Radiotherapy Trial</td>
</tr>
<tr>
<td>SUPREMO</td>
<td>Selective Use of Postoperative Radiotherapy aftEr Mastectomy</td>
</tr>
<tr>
<td>SUV</td>
<td>standard uptake value</td>
</tr>
<tr>
<td>SVCO</td>
<td>superior vena caval obstruction</td>
</tr>
<tr>
<td>SWOG</td>
<td>South West Oncology Group study</td>
</tr>
<tr>
<td>T1/T2W</td>
<td>weighted MRI image effects</td>
</tr>
<tr>
<td>TAA</td>
<td>tumour-associated antigen</td>
</tr>
<tr>
<td>TACE</td>
<td>transarterial chemoembolization</td>
</tr>
<tr>
<td>TAH</td>
<td>total abdominal hysterectomy</td>
</tr>
<tr>
<td>Taxol</td>
<td>taxanes paclitaxel</td>
</tr>
<tr>
<td>TBI</td>
<td>total body irradiation</td>
</tr>
<tr>
<td>TCCs</td>
<td>transitional cell carcinomas</td>
</tr>
<tr>
<td>TCDD</td>
<td>tetrachlorodibenzo-dioxin</td>
</tr>
<tr>
<td>TCH</td>
<td>taxotere, carboplatin, herceptin</td>
</tr>
<tr>
<td>TCNU</td>
<td>tauromustine</td>
</tr>
<tr>
<td>TCP</td>
<td>tumour cure probability</td>
</tr>
<tr>
<td>TCR</td>
<td>T cell receptor</td>
</tr>
<tr>
<td>TD</td>
<td>total physical dose</td>
</tr>
<tr>
<td>TDF</td>
<td>time–dose factor</td>
</tr>
<tr>
<td>TE</td>
<td>time to echo</td>
</tr>
<tr>
<td>TEXT</td>
<td>Tamoxifen and Exemestane Trial</td>
</tr>
<tr>
<td>6-TG</td>
<td>6-thioguanine</td>
</tr>
<tr>
<td>TGF</td>
<td>transforming growth factor</td>
</tr>
<tr>
<td>TH1</td>
<td>T helper 1 cytokines</td>
</tr>
<tr>
<td>TILs</td>
<td>tumour-infiltrating lymphocytes</td>
</tr>
<tr>
<td>TME</td>
<td>total mesorectal excision</td>
</tr>
<tr>
<td>TMP</td>
<td>tumour marker production</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>tumour necrosis factor-alpha</td>
</tr>
<tr>
<td>TNM</td>
<td>tumour, node, metastasis</td>
</tr>
<tr>
<td>TP</td>
<td>thymidine phosphorylase</td>
</tr>
<tr>
<td>TR</td>
<td>time to repeat</td>
</tr>
<tr>
<td>TRAIL</td>
<td>TNF-related apoptosis-inducing ligand</td>
</tr>
<tr>
<td>TRAM</td>
<td>transverse rectus abdominis myocutaneous-free flap</td>
</tr>
<tr>
<td>TREGS</td>
<td>regulatory T cells</td>
</tr>
<tr>
<td>TRUS</td>
<td>transrectal ultrasound</td>
</tr>
<tr>
<td>TRM</td>
<td>transplant related mortality</td>
</tr>
<tr>
<td>TS</td>
<td>thymidylate synthase</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid-stimulating hormone</td>
</tr>
<tr>
<td>TSP</td>
<td>thrombospondin</td>
</tr>
<tr>
<td>TTF-1</td>
<td>thyroid transcription factor-1</td>
</tr>
<tr>
<td>TTP</td>
<td>thrombocytopenic purpura, time to progression</td>
</tr>
<tr>
<td>TUR</td>
<td>transurethral resection</td>
</tr>
<tr>
<td>TURBT</td>
<td>transurethral resection of bladder tumour</td>
</tr>
<tr>
<td>TURPS</td>
<td>transurethral resection of the prostate</td>
</tr>
<tr>
<td>TUUS</td>
<td>transurethral ultrasound</td>
</tr>
<tr>
<td>TVUS</td>
<td>transvaginal ultrasound</td>
</tr>
<tr>
<td>UAPI</td>
<td>uterine artery pulsatility index</td>
</tr>
<tr>
<td>UC</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>UCAs</td>
<td>ultrasound contrast agents</td>
</tr>
<tr>
<td>UCNT</td>
<td>undifferentiated carcinomas of the nasopharynx</td>
</tr>
<tr>
<td>UCSF</td>
<td>University California San Francisco</td>
</tr>
<tr>
<td>UFT</td>
<td>uracil/tegafur</td>
</tr>
<tr>
<td>UICC</td>
<td>Union Internationale Contre Cancer</td>
</tr>
<tr>
<td>UKCTOCS</td>
<td>UK Collaborative Trial of Ovarian Cancer Screening</td>
</tr>
<tr>
<td>USPIO</td>
<td>ultra-small particles of iron oxide</td>
</tr>
<tr>
<td>V-DMSA</td>
<td>pentavalent dimercapto succinic acid</td>
</tr>
<tr>
<td>VAIN</td>
<td>vaginal intra-epithelial neoplasia</td>
</tr>
<tr>
<td>VATS</td>
<td>video-assisted thoracic surgery</td>
</tr>
<tr>
<td>VDAs</td>
<td>vascular disrupting agents</td>
</tr>
<tr>
<td>VDR</td>
<td>vitamin D receptor</td>
</tr>
<tr>
<td>VEE</td>
<td>Venezuelan equine encephalitis</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>VHL</td>
<td>von Hippel–Lindau syndrome</td>
</tr>
<tr>
<td>VI</td>
<td>vascular invasion</td>
</tr>
<tr>
<td>VICE</td>
<td>vincristine, ifosfamide, carboplatin and etoposide</td>
</tr>
<tr>
<td>VIN</td>
<td>vulvar intra-epithelial neoplasia</td>
</tr>
<tr>
<td>VIP</td>
<td>vasoactive intestinal peptide</td>
</tr>
<tr>
<td>VLPs</td>
<td>virus-like particles</td>
</tr>
<tr>
<td>VNPI</td>
<td>Van Nuys prognostic scoring index system</td>
</tr>
<tr>
<td>VNTRs</td>
<td>variable number of tandem repeats</td>
</tr>
<tr>
<td>VOD</td>
<td>veno-occlusive disease</td>
</tr>
<tr>
<td>VUDs</td>
<td>volunteer unrelated donors</td>
</tr>
<tr>
<td>VP-16</td>
<td>etoposide</td>
</tr>
<tr>
<td>WAGR</td>
<td>Wilms–Aniridia–Gentitourinary–Retardation syndrome</td>
</tr>
<tr>
<td>WBD</td>
<td>whole-body dose</td>
</tr>
<tr>
<td>WBRT</td>
<td>whole-brain radiotherapy</td>
</tr>
<tr>
<td>WL</td>
<td>window level</td>
</tr>
<tr>
<td>WW</td>
<td>window width</td>
</tr>
<tr>
<td>Z-Dex</td>
<td>dexamethasone</td>
</tr>
</tbody>
</table>
Evidence scoring

★★★ Systematic review or meta-analysis
★★ One or more well designed randomized controlled trials
★ Nonrandomized controlled trials, cohort study etc.

Reference annotation

The reference lists are annotated, where appropriate, to guide readers to key primary papers and major review articles as follows:

● Key primary papers as indicated by
◆ Major review articles as indicated by
★ Papers that represent the first normal publication of a management guideline are indicated by

We hope that this feature will render extensive lists of references more useful to the reader and will help to encourage self-directed learning among both trainees and practising physicians.
The central nervous system (CNS) is host to a remarkable variety of primary tumours that demonstrate an equal diversity of clinical behaviour, response to treatment and prognosis. Although most malignant tumours still carry a bleak prognosis, worthwhile extension of life can be achieved in many patients. For those with more responsive tumours, adequate management can provide prolonged survival or cure. An accurate diagnosis is required in almost all cases, and advances in neuro-imaging, neurosurgical technique and neuropathology now facilitate this. Molecular analysis is having an increasing impact on the management of brain tumours, with a number of useful prognostic and predictive markers having emerged over the past decade.

**PATHOLOGY**

### Incidence

The overall incidence (see also Table 1.1) of primary CNS tumours in the United Kingdom is around 15 per 100,000, of which around half are malignant. In 2010, there were 9156 new cases in the United Kingdom, with equal numbers in men and women.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma</td>
<td>1.5</td>
</tr>
<tr>
<td>AA</td>
<td>1.0</td>
</tr>
<tr>
<td>GBM</td>
<td>3</td>
</tr>
<tr>
<td>Meningioma</td>
<td>3</td>
</tr>
<tr>
<td>CNS lymphoma: immune competent</td>
<td>0.3</td>
</tr>
<tr>
<td>CNS lymphoma: overall</td>
<td>0.8–6.8</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>0.5</td>
</tr>
<tr>
<td>Germ cell tumours</td>
<td>0.2</td>
</tr>
<tr>
<td>Pinealoma/pineoblastoma</td>
<td>0.1</td>
</tr>
<tr>
<td>Metastases</td>
<td>8</td>
</tr>
</tbody>
</table>

### Aetiology

Ionizing radiation is the only environmental factor that is clearly associated with an increased risk of developing a brain tumour. Radiation-induced tumours include astrocytomas of all grades, benign and malignant
meningiomas, sarcomas and nerve sheath tumours. A number of genetic syndromes is associated with an increased risk of brain tumour; these are described in Table 1.2. Immunosuppression (e.g., transplant recipients and AIDS) predisposes to primary CNS lymphoma (PCNSL), which is also associated with the Epstein–Barr virus genome in 95% of cases. There is no evidence that any other aetiological factor plays a role in brain tumour carcinogenesis. In particular, industrial chemicals, bacteria, head injury, exposure to non-ionizing radiation (e.g., power lines and mobile phones), diet and tobacco have all been studied but do not appear to be linked. 

**Tumour types**

A robust pathological classification system that can be used by clinicians to predict tumour behaviour and inform management is essential. The World Health Organization (WHO) classification for CNS tumours was updated in 2007 and is almost universally accepted for this purpose. A modestly abridged version is shown in Box 1.1. The classification separates tumour types according to tissue of origin and subsequently cell of origin. Further classification recognizes features of the tumour and assigns a ‘grade’ to each tumour according to its degree of malignancy. Care must be taken when comparing modern studies with older clinical series that may have used different classification schemes.

Conventional light microscopy provides the backbone of pathological analysis but is often insufficient to produce a complete diagnosis, and the discriminatory role of immunohistochemistry is now indispensable. Glial fibrillary acidic protein (GFAP) is valuable in identifying normal astrocytes and tumour cells of astrocytic origin, but non-astrocytic and even some non-glial tumours may be positive. Diagnosis of lymphomas, germ cell tumours, sarcomas and metastasis is often confirmed by immunostaining (see entry under each tumour type later in this chapter).

A major change over the past decade has been the growing role of molecular and genetic diagnostic tools, in identifying and classifying tumours, in providing prognostic information and in some cases predicting response to treatment.

**Table 1.2  Genetic syndromes associated with an increased risk of brain tumour**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Brain tumour</th>
<th>Other associations</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis I</td>
<td>Neurofibromas</td>
<td>Pigmentation</td>
<td>NF1 on 17q11</td>
</tr>
<tr>
<td></td>
<td>Gliomas</td>
<td>Peripheral neurofibromas</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Sarcomas</td>
<td>Osseous and vascular lesions</td>
<td></td>
</tr>
<tr>
<td>NF2</td>
<td>Schwannomas (acoustic neuromas)</td>
<td>Cerebral calcification</td>
<td>NF2 on 22q12</td>
</tr>
<tr>
<td></td>
<td>Meningiomas, Gliomas (especially spinal)</td>
<td>Lens opacities</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Von Hippel–Lindau</td>
<td>Haemangioblastoma</td>
<td>Retinal haemangioblastoma</td>
<td>VHL on 3p25–26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal carcinoma</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phaeochromocytoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visceral cysts</td>
<td></td>
</tr>
<tr>
<td>Cowden’s</td>
<td>Dysplastic gangliocytoma of cerebellum</td>
<td>Peripheral hamartomas</td>
<td>PTEN/MMAC1 on 10q23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroid neoplasia</td>
<td></td>
</tr>
<tr>
<td>Turcot’s</td>
<td>GBMs Medulloblastomas</td>
<td>Colorectal tumours</td>
<td>MLH1 or PMS2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>APC Inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>unclear</td>
</tr>
<tr>
<td>Tuberose sclerosis</td>
<td>Subependymal giant-cell astrocytoma</td>
<td>Angiofibromas</td>
<td>TSC1 on 9q34 TSC2</td>
</tr>
<tr>
<td></td>
<td>Hamartomas</td>
<td>Hypomelanotic patches</td>
<td>on16p13</td>
</tr>
<tr>
<td>Li Fraumeni</td>
<td>Gliomas</td>
<td>Sarcomas</td>
<td>TP53 on 17p13</td>
</tr>
<tr>
<td></td>
<td>PNETs</td>
<td>Breast cancer</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Basal naevus</td>
<td>Medulloblastomas</td>
<td>Basal–cell carcinomas</td>
<td>PTCH on 9q22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone abnormalities Palmer pits</td>
<td>Autosomal dominant</td>
</tr>
</tbody>
</table>

PNET, primitive neuro-ectodermal tumour; PTCH, patched gene.
Box 1.1 World Health Organization grading of tumours of the central nervous system (2007)

<table>
<thead>
<tr>
<th>Tumours of neuroepithelial tissue</th>
<th>WHO grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astrocytic tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>1</td>
</tr>
<tr>
<td>Pilomyxoid astrocytoma</td>
<td>2</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>1</td>
</tr>
<tr>
<td>Pleomorphic xanthoastrocytoma</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse astrocytoma (variants: fibrillary, gemistocytic and protoplasmic)</td>
<td>2</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>3</td>
</tr>
<tr>
<td>Glioblastoma (variants: giant cell and gliosarcoma)</td>
<td>4</td>
</tr>
<tr>
<td>Gliomatosis cerebri</td>
<td></td>
</tr>
<tr>
<td><strong>Oligodendroglial tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Oligodendrogioma</td>
<td>2</td>
</tr>
<tr>
<td>Anaplastic oligodendrogioma</td>
<td>3</td>
</tr>
<tr>
<td><strong>Oligoastrocytomas</strong></td>
<td></td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>2</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>3</td>
</tr>
<tr>
<td><strong>Ependymal tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Subependymoma (variant: myxopapillary ependymoma)</td>
<td>1</td>
</tr>
<tr>
<td>Ependymoma (variants: cellular, papillary, clear cell and tanyctic)</td>
<td>2</td>
</tr>
<tr>
<td>Anaplastic ependymoma</td>
<td>3</td>
</tr>
<tr>
<td><strong>Choroid plexus tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Choroid plexus papilloma</td>
<td>1</td>
</tr>
<tr>
<td>Atypical choroid plexus carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Choroid plexus carcinoma</td>
<td>3</td>
</tr>
<tr>
<td><strong>Other neuroepithelial tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Astroblastoma</td>
<td>1</td>
</tr>
<tr>
<td>Angiocentric glioma</td>
<td>1</td>
</tr>
<tr>
<td>Chordoid glioma of the third ventricle</td>
<td>2</td>
</tr>
<tr>
<td><strong>Neuronal and mixed neuronal–glial tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Gangliocytoma</td>
<td>1</td>
</tr>
<tr>
<td>Gangglioglioma</td>
<td>1</td>
</tr>
<tr>
<td>Anaplastic gangglioglioma</td>
<td>3</td>
</tr>
<tr>
<td>Desmoplastic infantile astrocytoma and gangglioglioma</td>
<td>1</td>
</tr>
<tr>
<td>Dysembryoplastic neuroepithelial tumour</td>
<td>1</td>
</tr>
<tr>
<td>Neurocytoma (central or extraventricular)</td>
<td>1</td>
</tr>
<tr>
<td>Cerebellar liponeurocytoma</td>
<td>2</td>
</tr>
<tr>
<td>Paranglioma of the spinal cord</td>
<td>1</td>
</tr>
<tr>
<td>Papillary glioneuronal tumour</td>
<td>1</td>
</tr>
<tr>
<td>Rosette-forming glioneuronal tumour of the fourth ventricle</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pineal tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Pineocytoma</td>
<td>1</td>
</tr>
<tr>
<td>Pineal parenchymal tumour of intermediate differentiation</td>
<td>2, 3</td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td>4</td>
</tr>
<tr>
<td>Papillary tumour of the pineal region</td>
<td>2, 3</td>
</tr>
</tbody>
</table>

Tumours of neuroepithelial tissue

**Embryonal tumours**
- Medulloblastoma: 4
- CNS primitive neuro-ectodermal tumours: 4
- Atypical teratoid/rhabdoid tumour: 4

**Tumours of the cranial and paraspinal nerves**
- Schwannoma (variants: cellular, plexiform and melanotic): 1
- Neurofibroma (variant: plexiform): 1
- Perineurioma: 1, 2
- Malignant perineurioma: 3
- Malignant peripheral nerve sheath tumour: 2, 3, 4

**Tumours of the meninges**

**Meningiomas**
- Meningioma (several variants): 1
- Atypical meningioma: 2
- Anaplastic (malignant) meningioma: 3

**Mesenchymal tumours**
- Haemangiopericytoma: 2
- Anaplastic haemangiopericytoma: 3
- Haemangioblastoma: 1

**Lymphomas and haematopoietic neoplasms**
- Malignant lymphomas
- Plasmacytoma
- Granulocytic sarcoma

**Germ cell tumours**
- Germinoma
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Teratoma (mature, immature, teratoma with malignant transformation)
- Mixed germ cell tumour

**Tumours of the sellar region**
- Craniopharyngioma (adamantinomatous and papillary): 1
- Granular cell tumour: 1
- Pituicytoma: 1
- Spindle cell oncocytoma of the adenohypophysis: 1
- Metastatic tumours

(Source: Abridged and adapted from Louis DN et al., World Health Organization Classification of Tumours of the Central Nervous System, Lyon, France: IARC, 2007.)
PILOCYTIC ASTROCYTOMAS

Abnormalities in the mitogen-activated protein kinase (MAPK) pathway have been reported in up to 90% of pilocytic astrocytomas. Unlike higher grade gliomas, these abnormalities tend to occur in isolation. The most common abnormality is a gene fusion event between KIAA1549 (a gene with an as yet unknown function) and the BRAF oncogene, which constitutively activates MAPK signalling and hence promotes cellular proliferation and oncogenesis. This rearrangement is highly specific to pilocytic astrocytomas. The next most common event is an activating mutation in the BRAF gene that, in contrast to the fusion event, is also observed in many different solid tumours. Although pilocytic astrocytomas are often cured by surgery, the aforementioned new understanding of the biology of the disease opens the door to a wide range of potential therapies that target MAPK signalling.

LOW-GRADE GLIOMAS

Molecular analysis is becoming increasingly important in the classification of WHO grade 2 (or ‘diffuse’) gliomas, which are divided on histopathological criteria into astrocytomas, oligodendrogliomas and oligoastrocytomas. An important recent discovery was that 70%–80% of grade 2 gliomas bear mutations in the IDH1 gene that encodes the metabolic enzyme isocitrate dehydrogenase 1. It seems likely that IDH1 mutations occur very early in the process of gliomagenesis, although the mechanisms by which they might drive this process are yet to be unravelled. Low-grade astrocytomas exhibit mutations in both IDH1 and p53 in 50% of cases and the presence of mutated p53 correlates with shorter survival. In contrast, low-grade oligodendrogliomas are much more likely to combine an IDH1 mutation with the loss of heterozygosity (LOH) of chromosome regions 1p and 19q. LOH 1p19q is strongly associated with both grade 2 and grade 3 oligodendrogliomas. It can be readily detected by fluorescence in situ hybridization and is a powerful and positive prognostic marker. The predictive value of this chromosomal deletion signature is most apparent in the setting of anaplastic tumours. Interestingly, LOH 1p19q is never observed in the same tumour as either p53 mutation or EGFR amplification. Oligoastrocytomas exhibit IDH1 mutations either in combination with p53 mutation or with 1p19q co-deletion (but never both), and this genetic signature appears to be a strong predictor of clinical outcome.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>High frequency</th>
<th>Low frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic astrocytoma</td>
<td>BRAF–KIAA1549 gene fusion (50%–70%)</td>
<td>BRAF activating point mutation (10%)</td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td>IDH1/IDH2 mutations (70%–80%)</td>
<td>MGMT promoter methylation (&lt;10%)</td>
</tr>
<tr>
<td></td>
<td>MGMT promoter methylation (60%–80%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1p And 19q co-deletion (30%–60%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1p And 19q co-deletion (50%–80%)</td>
<td></td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma/oligoastrocytoma</td>
<td>IDH1/2 mutations (50%–70%)</td>
<td>1p And 19q co-deletion (15%)</td>
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<td></td>
<td>MGMT promoter methylation (70%)</td>
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<td>IDH1 mutations, LOH1p, LOH1q</td>
<td>MGMT promoter methylation (35%)</td>
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<tr>
<td></td>
<td>MGMT promoter methylation (25%–30%)</td>
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<td>Medulloblastoma</td>
<td>CTNNB1 mutation</td>
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<td>PTCH1/SMO/SUFU mutation, GLI2/MYC</td>
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<tr>
<td>SHH subgroup</td>
<td>MYC amplification</td>
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<tr>
<td>Group 3</td>
<td>CDK6/MYCN amplification</td>
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<td>Group 4</td>
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<td></td>
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<tr>
<td>Meningioma</td>
<td>NF2 inactivation (50%)</td>
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Glioblastoma

It is widely accepted that there are two main categories of GBM, with quite distinct molecular features. Primary GBMs appear to arise de novo in older patients with no prior history of glioma and have a particularly poor prognosis. They are characterized by oncogene amplification (particularly EGFR, CDKN2A deletions and PTEN mutations). Secondary GBMs arise in younger patients, often from a pre-existing astrocytoma, and have a slightly better prognosis, but they account for only 10% of cases. Common abnormalities in this category are p53 mutations and PDGFR amplification. IDH1 mutations are rare in GBMs, but when present they are associated with the secondary subtype and confer a better prognosis. Recent work by the Cancer Genome Atlas Research Network has begun to reveal the extent of the genetic and chromosomal abnormalities that contribute to the aggressive and treatment-resistant nature of this tumour and demonstrates remarkable heterogeneity across the tumours studied. Although specific mutations, deletions and amplifications varied widely, common themes emerged. It was shown that 87% of tumours exhibited abnormalities in the retinoblastoma (RB) signalling pathway that modulates cell cycle progression, 78% had defects in the p53 pathway (cell cycle and apoptosis) and 88% showed alterations in the epidermal growth factor receptor (EGFR)/PI3 kinase network (proliferation and cell survival).

The most clinically applicable biomarker for GBM to emerge in recent years relates to the DNA repair enzyme MGMT. This enzyme reverses the O6-methylguanine DNA methylation event, which is the key cytotoxic mechanism of temozolomide. Although assays of MGMT protein levels or activity are unreliable in clinical samples, suppression of MGMT gene expression by hypermethylation of the gene promoter can be detected in tumour specimens by a variety of widely available laboratory techniques. In the landmark study that showed benefit from the addition of concomitant and adjuvant temozolomide to radiotherapy in GBM, retrospective analysis of the MGMT promoter methylation status of a subset of patients indicated that hypermethylation of the MGMT promoter was a positive prognostic marker and also predicted whether patients would benefit from the addition of temozolomide. Subsequent studies have supported this finding, but the technique has not yet been widely adopted as a means of determining which patients should receive temozolomide. This is partly because there are as yet no effective alternative treatments and partly because a gold standard laboratory assay and methylation threshold is yet to be established.

Another emerging biomarker and potential therapeutic target is a specific mutation in the EGFR gene that encodes a constitutively active form of this key growth factor receptor. Known as EGFRvIII, this mutation is detected in about 25% of GBMs and appears to be associated with poor prognosis, although the evidence for this is not entirely robust. Vaccination strategies targeting the abnormal receptor have shown promise, and an international randomized phase III study is currently underway.

Meningiomas

The majority of meningiomas incur genetic loss at chromosome 22q12, within which is the locus of the NF2 gene. Mutations in this gene are observed in nearly all meningiomas associated with the hereditary syndrome neurofibromatosis type 2 (NF2) and also in about half of sporadic meningiomas. Atypical meningiomas exhibit a variety of additional chromosomal aberrations and mutations, but the key mechanisms underlying tumour progression remain under investigation.

Local environment

There is increasing awareness that brain tumours exist within a distinct microenvironment that influences tumorigenesis, tumour biology and treatment response. GBMs in particular exhibit a range of abnormal features, including hypoxia, fluctuating pH, aberrant extracellular matrix and infiltrating cells of host origin. Perhaps the most striking feature is the heterogeneity that exists within and between tumours of this type. Large regions of most GBMs are markedly hypoxic, which has implications for the delivery of systemic agents and also for response to radiotherapy, because hypoxic cells are intrinsically resistant to radiation. However, these abnormalities also provide opportunities for therapy and there has been great interest in targeting hypoxia-driven angiogenesis in GBMs. To date, the results have been disappointing overall, but striking individual responses retain the possibility of benefit in selected patients.
Tumour spread

By definition, benign tumours in the brain are non-invasive and non-metastatic. Their clinical effects arise from compression of adjacent structures and the associated functional detriment. Primary malignant tumours, on the other hand, are often highly infiltrative. Cellular motility occurs early in tumour development and often involves dissemination along white-matter tracts. Invasion does not respect boundaries between the lobes of the brain and spread across the corpus callosum is common, particularly in GBM. The term ‘butterfly tumour’ is frequently used to describe a lesion that involves both frontal lobes. Spread via cerebrospinal fluid (CSF) is common in a few tumour types – medulloblastoma, pineoblastoma, germ cell tumours and lymphoma – but it is clinically less apparent in gliomas. Systemic spread of primary CNS tumours is uncommon, with exceptions including medulloblastoma, mesenchymal lesions (e.g., haemangiopericytoma and meningiial sarcoma), lymphomas and germ cell tumours. For the latter two, it may be difficult to determine whether the brain lesion was part of a systemic process from the outset.

IMAGING

The mainstay of brain tumour diagnosis is structural imaging, using either computed tomography (CT) or magnetic resonance imaging (MRI). The use of contrast enhancement in both techniques is indispensable. CT is quick, has scalar integrity, is relatively easy to interpret and is inexpensive. However, tumours less than 0.5 cm and those adjacent to bone may be missed. The basis of CT is differential absorption of x-rays. As this is related to electron density, the derived Hounsfield numbers can be used as input to CT planning systems for radiotherapy. MRI relies on radiofrequency emission from perturbed atoms in a strong magnetic field. It is more expensive, is prone to distortions and may be more difficult to interpret. However, it is much more sensitive than CT, does not suffer from bone artefact and is particularly useful for characterization of diffuse pathological processes and determining the extent and nature of tumour infiltration. Hence, it is the diagnostic modality of choice for brain tumours in most circumstances.

Diffusion tensor imaging is a more recent development in brain MRI. By showing the direction of flow of water, it allows the demonstration of white-matter tracts. Water flow may be disrupted by the presence of tumour cells, leading to more isotropy of movement of the water molecules. Isotropy maps can, in principle, be used to delineate the extent of tumour infiltration and may be used to aid the planning of radiotherapy or to determine response to treatment. The very small changes in blood flow that occur when the brain initiates a particular function (speech, hand movement, etc.) can also be imaged using MRI. By making ‘functional maps’ of the brain in this way, a surgeon can plan an operation to avoid damaging important functional areas.

On imaging, brain tumours appear as infiltrative or space-occupying lesions. The position and distribution of a tumour together with the density variation, particularly after contrast injection, provides important diagnostic information. Tumours enhance with contrast (on CT and MRI) if they are hyper-vascular or if the vessels leak excessive contrast material. Areas of enhancement often indicate actively growing tumours. High-grade gliomas enhance in their actively proliferating regions (Figure 1.1) but not in their necrotic centres or in the associated oedema. Lymphomas, meningiomas and many metastases are usually uniformly enhancing. Slowly growing tumours such as low-grade gliomas (LGG) often fail to enhance at all (Figure 1.2). Some tumours may show calcification. This is particularly common in oligodendroglialomas and craniopharyngiomas, and it may be seen in almost any slow-growing tumour.

Imaging appearances are indicative but not diagnostic. For example, a solitary, mixed-density, enhancing and space-occupying lesion may suggest an intrinsic primary malignant tumour. However, these appearances are also common in metastases and can be seen, less commonly, in meningiomas, lymphoma or non-malignant lesions such as abscess or radiation necrosis. The magnetic resonance properties of a tumour-infiltrated brain can also be used to produce magnetic resonance spectra, which may be typical of a particular tumour type and help identification. However, histological examination is the only sure way to diagnose and categorize a tumour.

Prior surgical intervention can also produce diagnostic problems. Post-operative imaging for residual tumour assessment should be done within 72 hours of the operation.

Figure 1.1 Glioblastoma showing enhancement in the rim of actively proliferating regions but not in the necrotic centres nor in the associated oedema, which is extending into the white-matter tracts.
After this time, appearances can be misleading, particularly due to the presence of altered blood.

Functional imaging provides complementary information. Positron emission tomography (PET) scanning relies on the use of positron-emitting isotopes integrated into metabolically active molecules (e.g., 18F-fluorodeoxyglucose [FDG]). The oppositely directed, co-linear γ-rays can be detected by scintillation counters and turned into a three-dimensional (3D) image that represents the metabolic activity associated with the imaging agent. The use of FDG-PET in brain tumour management is limited because of high levels of uptake in the normal brain. Alternative tracers based on amino acid turnover are under evaluation, and the use of hypoxic tracers such as 18F-misonidazole may find a role if hypoxia-targeting agents become part of treatment protocols.

TREATMENT OF CENTRAL NERVOUS SYSTEM TUMOURS

Surgery

PRIMARY DISEASE

The main aims of surgery in CNS tumours are to establish a tissue diagnosis, palliate symptoms and improve survival. For many tumours, these goals are best achieved by maximal tumour removal. However, because tumours frequently infiltrate normal brain, an increased resection may be accompanied by an increased risk of morbidity or mortality. These risks must be kept within acceptable limits for the procedure. This conflict generates the concept of 'maximal safe resection' (MSR). There is no strict definition of MSR, but rather it reflects the balance between extent of tumour removal and procedural risk as judged by the clinicians involved. For any clinical situation, the surgical approach is best determined by discussion at a pre-operative multi-disciplinary team meeting where the benefits and risks of more or less extensive surgery can be based on a detailed examination of the radiological investigations, the availability of particular surgical techniques and equipment and what additional and/or alternative oncological options there are.

As an example, most convexity meningiomas are cured by gross total resection with minimal accompanying risk. What is accepted as MSR here is rarely controversial. In contrast, most intrinsic tumours are not surgically curable, although there is extensive evidence correlating extent of surgery with
duration of survival in high-grade gliomas and LGGs. Even if the surgical aim is restricted to achieving a diagnosis, this is more likely to be successful if greater amounts of tissue are removed and examined. A complete diagnosis, often including molecular and immunohistochemical subtyping, is essential for planning post-operative therapy. Such detail may require more tissue than is provided by a single needle biopsy. However, some sites carry such a high risk from surgery (e.g. brain stem) that only a minimal biopsy, or even none at all, may be considered the safe limit.

The concept of MSR is increasingly accepted in spite of the lack of randomized evidence supporting its benefit in improving survival. In medulloblastoma, residual disease >2 cm in cross section is included in the staging system to indicate higher risk disease and multiple attempts at surgery may be recommended to lower the final stage for the patient. For GBM, the association of more complete removal with better outcome has prompted the increased use of resection-enhancing techniques. Even where nearly complete resection is not possible, patients suffering from significant pressure symptoms such as headache and nausea due to tumour volume may benefit from neurosurgical decompression. Likewise, surgery may reduce the frequency and severity of tumour-associated seizure in patients with LGG. At the opposite end of the spectrum, surgery beyond an adequate biopsy has been shown to carry no therapeutic advantage in patients with PCNSL.

Image-guided surgery has long been used to facilitate tumour removal. However, powerful new techniques are now available to assist the surgeon in achieving MSR. Intra-operative MRI is available in many units and has been shown to lead to more complete resections. Direct demonstration of improved patient outcome is awaited. 5-Aminolaevulinic acid (5-ALA) is a prodrug of a fluorescent porphyrin that accumulates preferentially in malignant glioma cells after intravenous injection. Using a modified neurosurgical microscope, these cells can be intraoperatively visualized and selectively removed. The idea that this technique leads to more complete resections and longer progression-free survival than standard image-guided surgery was proved in a randomized trial. Although the trial was not powered directly to examine overall survival, subsequent analysis provided level 2b evidence of an improvement. High-performance 3D ultrasound is a less expensive but still powerful technique that leads to enhanced resection outcomes. Improvements in intra-operative technology and neuro-anaesthesia have led to the increasing popularity of awake craniotomy and cortical mapping as an aid to tumour surgery. The technique has been shown to decrease iatrogenic neurological deficits and permit earlier discharge, as well as improving the extent of resection.

The morbidity associated with neurosurgery for tumours has been greatly reduced by the routine use of corticosteroids. These are prescribed before operating and for a number of days thereafter. In many cases, they can be steadily reduced in the days following surgery as the reaction settles provided the source of pressure has been removed. Drugs that modify platelet function, and other anti-coagulating agents, should be stopped pre-operatively. Anti-convulsants are prescribed routinely in some countries, but in the

*Figure 1.4 (See colour insert.) A mosaic of co-registered CT and MRI images used in the radiotherapy planning process. Note the main mass at the vertex clearly seen on both modalities but also a small satellite lesion in the left temporal region seen only on MR. Although included in the treatment volume this was the site of ultimate relapse.*
United Kingdom they should be given only to patients who are known to suffer from seizures or are at high risk due to the site of the planned operation.

Gliadel is a system comprising a biodegradable polymer wafer impregnated with BCNU (carmustine). The wafers are used to line the cavity after resection whereupon the polymer slowly disintegrates, delivering the carmustine in a more concentrated and protracted fashion than is possible by systemic delivery. As a single agent, Gliadel has been shown in prospective randomized clinical trials to modestly improve the survival of patients undergoing surgery for newly diagnosed (and recurrent) high-grade glioma. However, its use together with temozolomide (see under Individual Tumours, Glioblastoma) is only now being adequately evaluated and is not recommended outside a clinical trial.

Other surgical strategies explore the delivery of therapeutic agents through catheters implanted at the time of surgery or intra-operative radiotherapy. None has yet confirmed survival advantage.

**RECURRENT DISEASE**

Surgery has no well-defined role in recurrent malignant conditions. For low-grade indolent lesions, a second therapeutic operation can be justified if the first surgery produced a good progression-free interval. For high-grade tumours,
surgery to relieve pressure symptoms can be valuable if the result can be consolidated with additional therapy. There is no evidence of a survival gain with repeated surgical intervention in recurrent glioma.

Radiotherapy

The value of radiation in the treatment of CNS tumours largely depends on their intrinsic radiosensitivity. In rare diagnoses like medulloblastoma or germ cell tumours it may be curative, whereas in most conditions it results only in a modest improvement in survival. Post-operative external beam x-ray therapy remains the dominant treatment technique, although some centres continue to explore less usual techniques such as intra-operative radiotherapy, brachytherapy and particle treatments.

As with any cancer, the underlying radiotherapeutic principle is to maximize dose to the target tissue while optimally sparing the surrounding non-involved (normal) tissue. Precise immobilization during treatment is mandatory and is almost universally achieved using a thermolabile immobilization system, usually with the patient in a supine position (Figure 1.3). Importantly, the spatial relationship of the brain to bony landmarks is fixed, particularly around the base of the skull. Orthogonal x-rays or cone beam CT techniques can be used to image the brain and bone during treatment delivery to facilitate inter-fraction re-localization.

Conforming the high-dose radiation region to the selected tumour shape is achieved either with conventional beam-shaping techniques or by using intensity modulation (intensity-modulated radiotherapy [IMRT]) or volumetric modulated arc therapy (VMAT). The latter techniques allow much improved sparing of sensitive structures (e.g., the chiasm) while maintaining the full dose to adjacent tumour. Unfortunately, the tumour edge is normally not well defined. Tumour cells will be found well beyond the edge defined by the T2 abnormality or contrast enhancement limit seen on MRI and normally used to delimit the tumour. How the tumour volume is defined is addressed under the heading for each tumour type later in this chapter.

Sparing the effects of x-radiation by fractionation is usually greater in normal brain than in most brain tumours. It is common therefore in delivering a radical treatment to fractionate as much as possible to improve the therapeutic ratio. Fraction sizes of 1.8–2 Gy are normal.

WHOLE-BRAIN IRRADIATION

Whole-brain irradiation is a simple technique usually reserved for highly palliative situations such as multiple metastatic disease. Parallel-opposed fields are applied to the immobilized, supine patient. The lower border is defined by Reid’s line – a straight line drawn from the tragus to the supra-orbital ridge. The remaining borders enclose the entire brain and its meningeal coverings. The standard collimator jaws of the linear accelerator are used to define the fields. Where more accurate definition is needed (e.g., as part of a prophylaxis protocol), the outline can be defined using a planning CT scan and the field created using shaped lead blocks or a multi-leaf collimator.

CONFORMAL/PARTIAL BRAIN IRRADIATION

Short-course palliative treatments

The planning technique is based on simple simulator screening. Rectangular fields are selected for size and

Figure 1.6 (See colour insert.) A volumetric modulated arc therapy plan of a left temporal high-grade tumour. Note the high degree of conformity possible with specific sparing of the brain stem and optic chiasm.
position by examining a contemporary CT or MRI scan. They are screened on to the immobilized, supine patient to cover the tumour and avoid vital structures as far as possible. Simple blocking can be added to exclude sensitive structures or uninvolved brain. A mid-plane surface outline is defined and the dose prescribed to the midpoint of its central axis. For GBMs, a typical dose might be 30 Gy in six fractions.

**Radical treatment**

Radical treatment for CNS tumours is based on CT planning. The post-operative planning CT scan is performed with the patient immobilized in the treatment position. A post-operative MRI scan fused (co-registered) with the CT enhances the ability to delineate tumours (Figure 1.4). The optimal MRI sequence and contrast requirement will vary according to tumour type. The tumour, at-risk marginal...
tissues and organs at risk (OARs) are outlined on the co-registered images, usually on axial slices. Modern planning systems also allow volumes to be defined in multiple planes, which can be useful in some regions such as the base of the skull.

In conventional conformal treatment, planning may be effected using multiple (typically three) fixed, static beams that are conformed to the tumour outline. The beam central axes are coincident at the isocentre (Figure 1.5). This usually produces an acceptable tumour dose distribution but may deliver significant doses to large volumes of normal brain in the beam entry and exit paths. Maintaining the OARs within tolerance limits may be difficult and may involve compromise of dose to the target. Treatment delivery uses a linac with a multi-leaf collimator to define the fields.

Beam IMRT is a more recent and versatile approach to beam shaping, which uses a greater number of individually conformed beams with the x-ray fluence modulated across each one. By using inverse planning techniques, the doses to the target and OARs can be predetermined—so-called ‘dose painting’. The result is a much more highly conformed treatment with a more satisfactory dose distribution outside the target, including the concavities in the tumour volume (Figure 1.6). A similar result can be obtained with dynamic beams, which are moved and modulated during dose delivery. VMAT takes the process of conformity one step further by rotating the gantry of the linac through one or more arcs that entire vertebral bodies are treated to prevent differential growth. Some units will use compensators or advanced planning techniques to achieve a uniform dose in spite of differences in head width. A collimator rotation on the head fields matches the divergence of the spine field (typically 7°).

**Figure 1.9** A CT scan without contrast showing extensive calcification in a large right frontal oligodendroglioma in a 30-year-old male presenting with seizure.

**Whole-neuraxis radiotherapy (craniospinal irradiation)**

This is a highly complex technique used in specific, rare conditions to treat the entire meningeal content when at risk from tumour dissemination. The difficulties of the technique arise from the need to cover the whole of the brain (best approached with lateral fields) in continuity with the spinal canal, which requires posteriorly placed fields (see Figure 1.7). The standard technique uses a 4–6 MV linear accelerator with the patient immobilized in a prone cast encompassing the head and shoulders. A post-operative CT of brain and spine is used for planning. A co-registered MRI is useful for further defining structures, particularly the lower limit of the sacral sac. The whole of the meningeal surface and content is outlined, with particular care being paid to the cribriform plate, the lower limit of the temporal lobes and the sacral sac. A pair of lateral fields is used to irradiate the head and upper (cervical) spine with individually shaped fields to define the meningeal surfaces. In children, it is important to ensure that entire vertebral bodies are treated to prevent differential growth. Some units will use compensators or advanced planning techniques to achieve a uniform dose in spite of differences in head width. A collimator rotation on the head fields matches the divergence of the spine field (typically 7°).

**Figure 1.10** (See color insert.) Outcome of RTOG trial 9402 of patients with anaplastic oligodendroglioma (AO) or anaplastic oligoastrocytoma (AOA) treated with radiotherapy with or without prior PCV chemotherapy. The figure shows Kaplan-Meier estimates of overall survival by treatment for patients with 1p/19q co-deleted tumours. (From van den Bent MJ et al., J Clin Oncol 31, 344–50, 2013; reprinted with kind permission of the American Society of Clinical Oncology.)

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<td>28</td>
<td>59</td>
</tr>
<tr>
<td>RT</td>
<td>47</td>
<td>67</td>
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No. at risk:

- PCV + RT: 59, 53, 43, 37, 32, 27, 18
- RT: 67, 58, 52, 40, 26, 15, 13

Overall survival (%), $P = .03$ (HR, 0.59 (95% CI, 0.37 to 0.95))
The rest of the spine is treated using a direct posterior field. An additional lower spinal field matched for divergence may be needed in an adult. A compensator is used to produce a uniform dose to the cord (prescribed at the anterior cord surface). The lower border is defined to cover the apex of the sacral sac (normally, at least to the bottom of S2).

The uncertainty of dose to structures at the junction of the spinal fields has classically been addressed by moving the junction at least twice during the treatment program. More recently, IMRT has been used to ‘feather’ the junction over a number of centimetres and eliminate this need. This technique can also eliminate the need for the spinal compensator. Modern on-treatment imaging has allowed patients to be planned and treated in a supine position with advantages in comfort and reliability of setup. The rarity of the need for craniospinal irradiation (CSI) and the complexity of the techniques suggest that such treatments in future may best be managed in a few highly specialized centres.

**Stereotactic radiotherapy (SRT)**

Stereotaxy relates to the method of localization in which the target is defined in relation to an external coordinate system. This has the potential for a greater degree of accuracy but implies the need for rigid immobilization. The fixation may be ‘internal’, using pins screwed into the skull and suitable only for one-off treatments, or ‘external’, based on an accurate, re-locatable anterior and posterior, individualized immobilization mask (or beam direction shell), usually in association with a dental mouth-bite. Externally fixated shells can be used for the delivery of single or multiple fractions of SRT. Accuracies of 1–2 mm are standard.

In the Gamma Knife™ system, treatment is delivered using multiple radiation sources collimated to the same circular cross section. Although the resulting isodose volumes are spherical, more complex shapes can be formed using multiple overlapping spheres. Alternatively, multiple fixed beams or arcs can be used from an adapted linear accelerator or more specialized units (e.g., CyberKnife™). Stereotactic radiosurgery (SRS) refers to the delivery of a single, very high radiation dose. SRS is well established in the treatment of small metastatic deposits and acoustic neuromas. Multiple fraction treatment is referred to as stereotactic radiotherapy (SRT) and may be used to treat tumours in close proximity to OARs (e.g., acoustic neuromas and skull-base tumours). It is also possible to combine the techniques of SRT or SRS with VMAT to deliver extremely accurate, irregularly shaped dose distributions with optimal sparing of surrounding structures. It is important to note that the radiobiologies relating to SRS and SRT are quite different.

**Proton therapy**

Protons travelling in a medium deposit a large amount of energy into the final few millimetres of their path – the Bragg peak. Beyond this, there is effectively no ‘exit dose’. This property can be used to deliver highly localized, three-dimensionally conformed dose distributions, even to volumes with concavities. Protons are used in treating tumours requiring high doses and lying immediately adjacent to vital structures. The most common application in the CNS has been to chordomas of the clivus, but other skull-base tumours are appropriate targets. Proton therapy is particularly favoured in paediatric practice.

The production of high-energy proton beams is expensive. Although plans for centres in the United Kingdom are in place, at the time of this writing, no beam suitable for the treatment of brain tumours exists. A U.K. national panel reviews applications for proton treatment. If the application is thought to be appropriate, the patient is referred to centres in Europe or the United States for treatment.

**RADIOTHERAPY MORBIDITY IN THE CENTRAL NERVOUS SYSTEM**

As in other sites, radiation injury in the CNS depends on a number of factors that may be patient related (age, vasculopathy, and infection) or treatment related (total dose, doseper fraction, and volume irradiated). In general, the CNS is a late-responding tissue; however, both early and intermediate effects also occur.

**Acute effects**

Acute effects of radiation begin within days or even hours and are probably an oedematous response, although this has never been clearly demonstrated. The acute tolerance of the brain is higher in terms of both total dose (up to 80 Gy in standard 2 Gy fractions) and single doses (6–8 Gy for whole-brain treatments) than is acceptable for late effects. The symptoms are generally those of raised intracranial pressure or a worsening of tumour-induced neurological symptoms. They usually respond well to relatively low doses of steroid therapy.

**Early-delayed effects**

An intermediate radiation reaction can begin within weeks of completing radiotherapy to the brain. Typically, it results in a feeling of somnolence, lethargy and sometimes recurrence of presenting symptoms and signs. It lasts between 6 and 10 weeks. It is usually self limiting but sometimes requires steroid therapy. The pathogenesis is unknown but is believed to correlate with interruption to myelin synthesis secondary to damage to oligodendroglial cells. A corresponding condition occurs after spinal irradiation and presents with Lhermitte’s sign. Neither is believed to indicate an increased risk of developing late effects. Patients with an underlying demyelinating condition such as multiple sclerosis have a relative contraindication for radiotherapy to the brain.

Radiotherapy alone, and more commonly combination chemo-radiotherapy, for brain tumours produces in some patients an intermediate morbid state known as pseudo-progression. Radiologically, it is indistinguishable from recurrent or progressive disease. Clinically, it may be asymptomatic or mimic recurrence. The pathogenesis is unknown, but it probably represents an inflammatory
response to tumour cell kill. There is some evidence that pseudo-progression is more common in patients whose tumours have methylated MGMT promoter regions and are therefore more sensitive to temozolomide. The condition is self-limiting but may necessitate high-dose corticosteroid treatment. It can make decisions about treatment and prognosis extremely difficult at a critical time in the patient’s disease.  

Delayed effects

Delayed radiation damage can onset from a few months to many years after radiation exposure and is uniformly irreversible. Injury is predominantly to the white matter and is dose and volume dependent. The clinical manifestations are diverse and may vary from subtle deterioration in higher cognitive function and behavioural changes to gross neurological deficit associated with a space-occupying lesion. The latter is difficult to differentiate from a recurrent tumour.

Radiation necrosis is the most severe form of damage, appearing as an expansile mass within the white matter. Radiologically, it can mimic tumour recurrence since both processes may demonstrate areas of necrosis, contrast enhancement and associated oedema. Functional imaging (e.g., thallium-SPECT or FDG-PET) might be helpful in differentiating between the two. The risk of radionecrosis is low with doses of radiation below 65 Gy delivered in standard fractionation but rises precipitately thereafter.

The rate of onset and the severity of late radiation damage in brain depend strongly on fraction size and total dose. However, the dependence on overall treatment time is weak for treatments delivered more than 12 hours apart. A dose of 72 Gy in 36 fractions to partial brain is reported to be associated with an approximate 5% incidence of late radiation necrosis.  

Currently, the recommended dose for treating high-grade tumours is a relatively conservative 60 Gy in 30 fractions, although both total dose and fraction size are reduced in situations with better prognosis. To minimize late damage, fraction sizes for radical brain treatments should not exceed 2 Gy and modern complex delivery techniques such as VMAT should be considered to reduce normal brain exposure.

Other late complications of brain irradiation include hormonal (pituitary) failure and radiation-induced tumours (10% at 30 years, principally benign meningiomas). Although it is rare, damage to the optic nerve or chiasm can occur and the risk increases with doses above 55 Gy. No late events were reported after doses of 50 Gy or below in the recent QUANTEC analysis of radiation tolerances.  

Late radiation damage to the cord may be sudden or insidious in onset, with sensory or motor abnormalities, bowel and bladder disturbance and diaphragm dysfunction in higher cord lesions. The most severe form is complete transection of the cord at the affected level. As in the brain, the pathogenesis remains obscure, with both vasculature and oligodendrocytes identified as principal targets and the damage occurring in the white matter. There is no evidence that either the level or the length of the cord irradiated materially affects the incidence of myelitis in patients receiving standard doses of radiotherapy. Most recent evidence suggests that the cord is substantially more resistant to damage than it was previously thought to be with the estimated risk of myelopathy being <1% and <10% at 54 and 61 Gy, respectively, using standard fractionation. Re-irradiation data in both animals and humans suggest that partial repair of damage is evident from about 6 months post treatment and further repair occurs over the next 2 years.

Some chemotherapeutic drugs such as methotrexate and nitrosoureas can enhance radiation damage. These are drugs with measureable CNS penetration that can produce toxic damage in their own right. Others such as doxorubicin become toxic following disruption of the blood–brain barrier (BBB) after radiation exposure.

Other radiation morbidity resulting from irradiation of the central nervous system

Radiation side effects from brain treatments can include deafness, cataract, endocrine dysfunction, skin erythema and desquamation. Alopecia, which commonly occurs at doses above 30 Gy, can be permanent and is particularly distressing. It should be emphasized that with sophisticated radiotherapy techniques many of these effects can be avoided or minimized through dose reduction to the relevant organs. Lethargy following brain irradiation is very common, often reaching its peak a few weeks after the completion of treatment. It can be profound, especially in the elderly.

Chemotherapy

For a drug to be effective, it must be active against the disease and able to penetrate the protective BBB to reach the target. Drugs with a high partition coefficient (e.g., nitrosoureas) or that are small (temozolomide) can circumvent this barrier. Although in the vicinity of tumours the barrier is partially defective (as illustrated by the leakage of contrast scanning agents), large hydrophilic molecules remain largely excluded from the tumour and are not useful for therapy. However, some agents thought to be only modestly penetrating can be very effective, for example, platinum compounds in germ cell tumours and medulloblastomas.

Chemotherapy can be given as part of primary treatment in an attempt to influence disease behaviour and survival (neo-adjuvant, concomitant, or adjuvant) or in recurrent disease, essentially in a palliative setting. The common primary brain tumours are relatively (astrocytoma) or highly (meningioma) chemo-resistant. However, some rarer diseases show marked chemosensitivity. Thus, in medulloblastoma, germ cell cancer, CNS lymphoma and some oligodendrogliaomas systemic treatment contributes effectively to primary treatment and also can be very effective in prolonging and maintaining quality of life (QOL) at recurrence.

ACTIVE SINGLE AGENTS

The majority of active agents are alkylating agents, principally nitrosoureas, temozolomide and procarbazine.
The chloroethyl nitrosoureas, for example, carmustine (BCNU) and lomustine (CCNU), are highly lipid soluble, non-ionized drugs that rapidly cross the BBB. Most are oral agents, although BCNU is given intravenously. They have different pharmacokinetic properties while retaining the same basic chemical activity. None has proved more effective than any other. Adverse effects include gastrointestinal (GI) toxicity, lung fibrosis and delayed myelosuppression, which restricts the administration interval to 6 weeks. Permanent myelofibrosis is a feature of these agents, which restricts the total amount of drug that can be given.

Gliadel is a system comprising a biodegradable polymer wafer impregnated with carmustine. It is discussed under surgery (see the section 'Primary disease').

Procarbazine is a prodrug activated in the liver to an alkylating agent. It has a low single-agent response rate in glioma therapy and is usually used in combination with nitrosourea. It causes nausea, vomiting and myelosuppression and interacts adversely with alcohol and some smoked and preserved foods.

Temozolomide acts as an alkylating agent by adding methyl groups to sites on DNA bases, most importantly the O\(^{6}\) position of guanine. It has high oral bioavailability and is converted spontaneously into the active compound at physiological pH on entering the bloodstream. It penetrates readily into brain tumours. The O\(^{6}\)-methylguanine lesion is efficiently repaired by MGMT, a suicide enzyme that removes the methyl adducts. For this reason, protracted, fractionated delivery of temozolomide, which depletes the cell of MGMT, is likely to be more effective than short courses of the drug. Conversely, tumour cells with unmethylated MGMT gene promoter regions that express high levels of MGMT protein are relatively resistant to temozolomide. Temozolomide is active against astrocytic and oligodendrogial tumours and has a predictable and modest toxicity, principally myelosuppression.

Epidophyllotoxins and platinum compounds including VP-16, cisplatin and carboplatin are valuable for treating non-glial brain tumours such as medulloblastoma and germ cell tumours. However, they have only minor activity against gliomas. Topoisomerase inhibitors such as irinotecan can have shown activity against glial tumours, including GBM, both as single agents and in combination. All of these drugs require intravenous administration and have substantial adverse effect profiles. They are generally reserved for second- or third-line treatments.

**COMBINATION CHEMOTHERAPY**

Only a few effective combinations are available. Combination building follows the same rules as those for extra-cranial cancer. A standard treatment has been the combination PCV comprising procarbazine (100 mg/m\(^2\) po days 1–10), CCNU (100 mg/m\(^2\) po day 1) and vincristine (2 mg iv day1) repeated 6 weekly. However, evidence that it is superior to single-agent nitrosourea is very sparse,\(^{31}\) and it is equally acceptable to use single-agent nitrosourea in relapsed GBM. Combinations may be more successful for some less common tumours (see under Medulloblastoma, Germ Cell Tumour and Lymphoma).

**COMBINED CHEMO-RADIOThERAPY**

Because both chemotherapy and radiotherapy have some moderate activity in the treatment of intracranial tumours, a logical management approach is to combine the two agents. The combination of PCV and radiation has improved outcome in oligodendrogial tumours as has concomitant/ adjuvant treatment with temozolomide and radiation in GBM. Integration of combination chemotherapy with radiation is standard treatment in medulloblastoma and germ cell tumours. All are discussed in later sections under the relevant tumour type.

**NOVEL APPLICATIONS OF CHEMOTHERAPY**

Because many agents find access to the brain difficult, alternative strategies have been tried to increase the concentration of drug in the tumour. Arterial catheterization has been used to deliver agents such as the nitrosoureas directly into the tumour. Results have been disappointing and the complication rates high. Global BBB disruption has been achieved with high-dose mannitol prior to infusion of hydrophilic drugs. Again, this approach has proved to be unacceptably toxic.

Convection-enhanced delivery\(^{26}\) is a surgical technique in which a thin catheter is placed into the brain and connected to an extra-cranial, pump-driven syringe containing a compatible medium. By selecting an appropriate delivery rate, the medium can be made to 'flow' into the brain or tumour. The medium can be used to carry a variety of cytotoxic agents, including large molecules or even small viruses, to regions in the brain remote from the catheter tip. Randomized trials have failed to establish a role for this technique in glioma management, and the technique remains experimental.

**Targeted biological therapies**

As with other cancers, a number of key proliferation and survival signalling pathways are identified as being important to the growth of brain tumours. For example, abnormal EGF, PDGF, HGF, IGF and vascular endothelial growth factor (VEGF) signalling has been demonstrated in GBMs. Excess activity through over-expression, mutation or over-stimulation of receptors has been identified to lead to uncontrolled cellular proliferation, survival and invasion. In spite of there being intense exploration of inhibitors of these processes, little progress has been made in the management of CNS tumours.

**INHIBITION OF ANGIOGENESIS**

Gliomas are highly vascular tumours that rely on an enhanced blood supply for their rapid growth. Stimulation of the vascular endothelial growth factor receptor (VEGFR) by VEGF underpins this angiogenesis, promoting endothelial cell migration and proliferation and leading to the formation of
new vessels. The vessels are abnormal, having large diameters, tortuous routes, decreased pericyte coverage, increased thickness of basement membrane and altered transport properties. Anti-VEGF agents induce endothelial cell apoptosis and inhibition of new vessel formation while normalizing existing tumour vessels and decreasing permeability.

Bevacizumab is a lead anti-angiogenic compound; it is a humanized monoclonal antibody that binds to and inhibits the activity of VEGF. When given to patients with relapsed GBM, it often produces rapid improvements in imaging appearances by abolishing contrast leakage and enhancing patient well-being by reducing vasogenic oedema. On the basis of two small studies, it was given accelerated Food and Drug Administration approval for use in recurrent GBM.\(^{32,33}\) However, improved survival has not been demonstrated when it was used either alone or in combination with cytotoxic drugs (commonly irinotecan) in relapsed disease or with standard chemo-radiotherapy in newly diagnosed GBMs (the Avaglio study). Within its limitations, it remains a useful adjunct to the treatment of relapsed disease in selected patients.

Many other agents with anti-angiogenic properties have been investigated for their value in patients with brain tumours (for a review, see the study by Grimm and Chamberlain\(^ {34}\)). None has found a routine place in their management.

**OTHER PATHWAY INHIBITORS**

EGFR is amplified in nearly half of all patients with GBM. Of these, approximately 30% demonstrate a mutant receptor (EGFRvIII) that has a deletion of exons 2–7. This defect results in constitutive, ligand-independent activation. Attempts to treat GBMs using EGFR blockade have not met with any success. However, the mutant EGFRvIII is a target for an immunotherapy approach that is currently in phase III trial. Other targets have included integrins, protein kinase C and histone deacetylase. None has shown any benefit.\(^ {34}\)

Everolimus is an inhibitor of the mammalian target of rapamycin (m-TOR), a serine-threonine kinase downstream of the PI3K/AKT pathway. This pathway is dysregulated in tuberous sclerosis and in some patients leads to the formation of subependymal giant cell astrocytomas. It has been shown that treatment with everolimus can produce shrinkage of these tumours, which are otherwise resistant to any form of therapy except surgery.\(^ {35}\)

**Adjunctive treatments**

Corticosteroids produce symptomatic benefit in patients with brain tumours, although the physiological basis for this is not clear. Dexamethasone is most frequently used, typically at a dose of 16 mg or less, which should be titrated down to the minimum needed to control symptoms. This will minimize the impact of severe side effects, which in the elderly are particularly proximal myopathy, diabetes and osteoporosis and in the young, acne and appetite stimulation. All patients may suffer from weight gain, sleep disturbance and disorders of mood and perception.

Epilepsy is common in patients with brain tumours. Anticonvulsants should be given in doses determined by the efficacy and toxicity of a drug in a particular patient and not by the measured plasma level. The established agents carbamazepine, phenytoin and sodium valproate are giving way to a newer generation of drugs including lamotrigine and levetracetam. The latter have the added advantage that they do not induce hepatic enzymes to the extent of some of the older drugs and thus do not interfere with the metabolism of other therapeutic agents, particularly chemotherapy and the newer small molecule agents.

Although headache is a common presenting symptom, severe pain is fortunately unusual in patients with treated brain tumours, even following recurrence. When pain is a problem, the same analgesic ladder should be used as for other malignant conditions. The liberal use of morphine in the later stages of the disease is entirely justified. Dexamethasone is an effective treatment for headache caused by raised intracranial pressure.

Nausea can be a particularly troublesome symptom and may have a variety of causes such as it being a part of posterior fossa syndrome or secondary to raised intracranial pressure. It is also associated with seizure, drug toxicity (particularly anticonvulsants) and peptic pathology. Limited-field brain irradiation uncommonly causes nausea, although this should be a diagnosis of exclusion. Clearly, the cause of the toxicity should be sought and, where possible, treated. When the usual anti-emetics fail to control nausea of intracranial origin, subcutaneous delivery of agents such as major tranquillisers or anti-histamines may be useful.

**Additional support**

Brain tumours are rare, but their effects are devastating. Cognitive decline and major physical disability often accompany the late stages. Because of their rarity, family doctors will have managed very few cases. Patients may require input from physiotherapists, speech therapists, social workers, palliative care workers, the general practitioner (GP) and the district nurse. The specialist ‘brain tumour support nurse’, who has knowledge of the patient’s current condition, needs and likely prognosis as well as the facilities available in a particular area, can provide invaluable support to all workers involved in care, particularly the GP. Even if a brain tumour is incurable, the quality of the patient’s life can be greatly enhanced by efforts to minimize the impact of their deficit. It is not acceptable to prolong the life of a patient without maximizing its quality.

Attention needs to be given to the often devastating functional and social consequences of CNS disease, including loss of driving licence, reduced employment prospects, loss of status in society and family, behavioural and personality change, and the prospect of limited life expectancy. The situation is further complicated by the side effects of the drugs used, particularly steroids and anticonvulsants. Clinical depression is more common in these patients than is generally recognized and merits early recognition and treatment.\(^ {36}\) Introduction of counselling and psychiatric,
pilocytic astrocytoma and ganglioglioma (regarded as grade 1), and those that infiltrate diffusely into cerebral tissue (grade 2 and above). However, this distinction may blur.

**Grade 1: Pilocytic astrocytoma**

Pilocytic astrocytomas are primarily tumours of children and young adults. They most commonly arise in the posterior fossa but are also found in the cerebral hemispheres, optic nerve and chiasm, thalamus and basal ganglia, brain stem and spinal cord. There is a strong association with neurofibromatosis type I.

On imaging, they appear as hyper-dense, well-delineated solid or solid/cystic tumours. They break the rule for low-grade tumours in that they frequently enhance with contrast. They are characterized by slow growth and may, without intervention, stop growing or even regress. Rarely, they progress relentlessly without change in low-grade histology or may seed in the CNS. Very rarely, pilocytic astrocytomas progress to a more malignant phenotype.

The histology is characterized by the presence of bipolar, GFAP-positive ‘pilocytes’ and eosinophilic hyaline masses known as Rosenthal fibres. They are often highly vascularized and may show endothelial hyperplasia identical to GBM. They do not demonstrate inactivation of p53. *BRAF-KIAA1549* fusion proteins (see the section ‘Molecular biology of brain tumours’) are present in the majority of paediatric pilocytic astrocytomas, less frequently in adults and not at all in diffuse astrocytomas, providing diagnostic differentiation in difficult cases.

The treatment of pilocytic astrocytoma is surgical. Maximal surgical resection (MSR) should be performed. Even if this is incomplete, further tumour progression may not occur. There is no evidence that post-operative radiation improves on surgery alone. If re-growth occurs, the treatment is again surgical. Should the second resection be incomplete, adjuvant radiotherapy can be tried (45–50 Gy), but there is no clear documentation that this is beneficial.

Overall, the prognosis for pilocytic astrocytoma is very good, with long-term control or cure rates of 80%–90%. The achievement of a complete resection is an important prognostic factor.

**Diffuse gliomas**

Diffuse gliomas are most common in the cerebral hemispheres. Irrespective of their histological grade, they infiltrate diffusely into adjacent and distant brain. Tumour grade is based on cytological features, mitotic activity and features of the microenvironment. The grade allocated is the highest seen in any part of the specimen. Appropriate treatment and prognosis depend not only on grade but also on the molecular detail of the specimen and clinical factors such as the patient’s age, performance status and mental status.

Lower grades of diffuse glioma progress to more malignant phenotypes. The rate of progression is very variable. Transformation from astrocytoma to GBM may be complete within 1 year or may not begin for 20 years or more. When transformation occurs, it is accompanied by the cumulative acquisition of genetic alterations.

**Grade 2: (Diffuse) astrocytoma**

Low-grade diffuse astrocytomas (LGAs) are well-differentiated, slow-growing tumours that are more frequent in young adults, although they can occur at any age. They most commonly present with seizure. LGAs are best seen on T2-weighted (or FLAIR) MRI sequences, where they appear as infiltrating hyper-intense lesions. They are hypo-intense, non-contrast enhancing on T1-weighted MRI sequences and CT (Figure 1.2).

Histologically, they are recognized to contain abnormal numbers of astrocytes, which show monotonous, minor degrees of anaplasia (nuclear pleomorphism and cytoplasmic changes). Mitoses are uncommon. The background may contain increased numbers of cellular processes and microcysts, which aid diagnosis. GFAP positivity is common. Somatic mutations of isocitrate dehydrogenase *IDH* genes 1 and 2 are common in LGA, particularly the *IDH1 R132* mutation (see the section ‘Molecular biology of brain tumours’). Patients with tumours demonstrating specific *IDH* mutations have a better prognosis than those with wild type *IDH*. However, the mutation has no predictive value.

The management of low-grade astrocytoma remains controversial. In many units, if a firm diagnosis is made on scanning, biopsy is delayed until the clinical situation demands it. Other units believe that an upfront biopsy is necessary for adequate management. Some surgeons believe that immediate surgical removal of all imaged tumour is associated with longer survival.

LGG patients presenting with controllable seizures as their only symptom and who show non-distorting, non-enhancing lesions on scanning may remain well for many years without active intervention. Adverse prognostic factors for patients with these tumours have been defined and include tumour size (>6 cm), lesions crossing the midline, presence of neurological symptoms, age above 40 years and wild type *IDH*. There is no evidence that early radiotherapy intervention in good-prognosis patients improves survival, compared to treatment that is delayed until required.
in spite of there being an improvement in time to progression. Nor is it clear whether radiotherapy or chemotherapy represents the best choice of initial treatment.

Patients who certainly require treatment are those with poor prognostic features, those whose tumours show marked progression on scanning and those who develop neurological deficit or possibly loss of seizure control. If most of the tumour mass is accessible, MSR is usually recommended. If minimal tumour remains and the entire resected tumour is low grade, an observation policy can be reinstated. Otherwise, radiotherapy is recommended usually within 4–8 weeks of surgery. Patients are planned using CT/MRI fusion. The tumour is defined as the high signal region on the T2 or FLAIR sequences. This is expanded by 1 to 2 cm to create the clinical target volume (CTV). The additional margin required to create the planning target volume is determined by local facilities and techniques. Conformation of the treatment volume to the target is essential, and the condition lends itself well to IMRT or VMAT techniques (Figure 1.6). A total of 45–50 Gy is delivered in 1.8 Gy fractions, depending on the size of the irradiated volume. Two randomized trials inform us that doses beyond 45–50 Gy are not necessary. If resective surgery is not thought to be useful, then radiotherapy as described can be used as primary treatment.

Chemotherapy as primary treatment is a potential alternative to radiotherapy. Temozolomide, nitrosoureas and combinations have all been shown to have activity. An EORTC trial to examine the relative values of primary radiotherapy and chemotherapy in this setting has completed recruitment and results are awaited.

The outcome of this form of management is variable. The majority of patients will relapse, with ultimate tumour transformation, progression and death. Overall, the median survival is about 5–8 years. However, some patients continue well without progression for 20 years or more after treatment. Salvage treatment at relapse can be performed with any of the aforementioned modalities.

**Grade 3: Anaplastic Astrocytoma**

AA is a diffusely infiltrating, astrocytic tumour typified by increasing cellularity, increasing nuclear size and variation and the presence of mitoses (growth fraction around 5%–10%). In the WHO classification, tumour necrosis must not be present. Tumours in this category that carry co-deletions on chromosomes 1p and 19q are best regarded as AOs and treated as such. Mutations of *IDH* are common and, when present, indicate a better prognosis.

AA is primarily a tumour appearing during middle age. It appears with variable density on CT or signal on MRI. There is usually enhancement with contrast, but this may be diffuse or patchy and is rarely of the classical ‘ring’ type seen in GBM. Unlike LGA, rapid growth in AA is the rule. Treatment must include maximal safe surgery and high-dose radiotherapy, as for GBMs leading to a median survival of 2–5 years. Although many now include concomitant/adjuvant chemotherapy, there is no proof of its benefit and it is difficult to justify the added toxicity in routine practice. For this reason, the CATNON Intergroup trial is examining the role of concurrent and/or adjuvant temozolomide in patients with non-1p/19q-deleted anaplastic glioma.

Virtually all patients with AA will recur following treatment and should be actively treated. Chemotherapy with or without prior surgery is the usual approach, although repeat, highly conformed radiotherapy is an option in selected cases.

**Grade 4: Glioblastoma**

GBM is a poorly differentiated, extensively invasive, highly mitotic and pathologically heterogeneous astrocytic tumour. It can arise at any age but is most common in the sixth and seventh decades. It occurs preferentially in the cerebral hemispheres, from where it extends into adjacent structures such as basal ganglia and across the corpus callosum to form the classic butterfly tumour. It can arise, rarely, in the cerebellum, brain stem and spinal cord. It is universally fatal.

Macroscopically, the tumours appear as grey masses with areas of haemorrhage, yellow necrosis and sometimes cysts. Any apparent capsule is always an artefact of rapidly growing tumour and compressed brain. Peri-tumoural oedema is common and tends to spread along the white-matter tracts to form a conduit for clonogenic, migratory tumour cells, which can be found many centimetres from the main tumour. These cells may form secondary masses, giving the appearance of multifocality.

GBM is highly heterogeneous at the cellular level, with almost any size and shape of cell being seen, including multinucleated giant cells, which are a hallmark. Secondary GBM is more likely to have areas comprising lower grade astrocytoma. Immunohistochemical staining with GFAP, S-100 and vimentin is also heterogeneous. Recognized GBM variants are giant-cell GBM and gliosarcoma, the natural histories of which are similar to that of classical GBM.

Micro-vascular proliferation and tumour necrosis are histological characteristics of GBM. Angiogenic tyrosine receptors (e.g., VEGFR-1 and 2) are up-regulated in proliferating tumour vessels, and the ligands (e.g., VEGF) are found in the GBM cells themselves, leading to paracrine stimulation of angiogenesis. There are two types of tumour necrosis: large-scale coagulation necrosis, which is usually visible on imaging studies, and microscopic serpiginous foci of necrosis, which form the pseudo-palisading pattern typical of GBMs. The molecular biological changes are discussed in the section ‘Glioblastoma’.

The typical imaging appearance of a GBM is a rim-enhancing, irregular tumour with a low-density (necrotic/cystic) centre and surrounding low-density oedematous brain situated in the deep white matter (Figure 1.1). The brain is often distorted, with evidence of raised intracranial pressure.

The overall strategy of management will depend on the likely prognosis, and several published guidelines are available. A diagnosis of GBM will be suspected from the imaging in the majority of cases. The very elderly, or patients with severe, steroid-resistant symptoms, may need only...
symptomatic care, as their outlook will be little changed by provision of the precise diagnosis and treatment. All other patients need a minimum of biopsy proof of diagnosis, and in many patients an attempt at resection is appropriate (see the section ‘Primary disease’). It is common clinical experience that patients tolerate subsequent treatment, particularly radiotherapy, better when their tumours have been decompressed. Maximal safe tumour removal for patients with resectable tumours is now the standard of care, even in older patients.

The use of Gliadel (BCNU-impregnated biodegradable) wafers is supported by the National Institute for Health and Care Excellence (NICE) in newly diagnosed patients whose tumours have had at least 90% resection. Unfortunately, the combination of Gliadel and chemo-radiotherapy has not been adequately evaluated in clinical studies and therefore was not assessed by NICE. An important study is underway to examine this combination in patients who have undergone optimal, 5-ALA-guided resection. Until results are available, combination treatment must be regarded to be still experimental and overall the place of Gliadel in newly diagnosed disease remains uncertain.

Multiple studies have shown that treatment with radiation improves survival in patients with malignant glioma compared to best supportive care alone. Surgery followed by limited-volume radiation therapy is established in the standard treatment for this disease. The choice of treatment volume recognizes that when GBMs relapse they do so within 2 cm of the original enhancing rim in 85% of cases. The treatment volume is defined on a post-operative MRI scan, which is fused with the planning CT scan. The gross tumour volume (GTV) comprises the enhancing tumour margin or the resection margin, whichever is greater. The CTV increases the GTV by 2 to 3 cm but must take into account natural boundaries. Planning should use conformal techniques.

The standard dose for a radical treatment is 60 Gy in 30 fractions over 6 weeks, or the equivalent in 1.8 Gy fractions. Not all patients merit a radical approach with radiotherapy. For those with a poor performance status (e.g., WHO 2 or greater) or for the very elderly, shorter courses of radiotherapy (40 Gy in 15 fractions or 30 Gy in 6 fractions on alternate days) are recommended. Simpler planning techniques may be used in this situation (see the section ‘Conformal/partial brain irradiation’).

Patients thought suitable for radical radiotherapy following surgery should now in addition be offered concomitant/adjunctive chemo-radiotherapy as the standard of care, unless there is a specific contraindication. In 2005, the EORTC/NCIC (NCIC stands for National Cancer Institute of Canada) published the results of a randomized trial in which a regime of standard radiotherapy with concomitant daily temozolomide (75 mg/m²) followed by monthly temozolomide (200 mg/m² × 6) produced a survival advantage of 16% (from 10% to 26%) at 2 years. Furthermore, the QOL was maintained and the toxicity was modest. Benefit was greatest in well-resected patients with a WHO performance status of 0 or 1. These results have been reproduced many times since the publication of this study. Further follow-up to 5 years has demonstrated an ongoing survival advantage to combined chemo-radiotherapy (Figure 1.8).

Further intensification of the chemotheraphy regime has not improved outcome. Benefit from the addition of chemotherapy was most evident in patients whose tumour demonstrated methylation of the MGMT gene; however, combined chemo-radiotherapy remains the standard of care in all patients eligible for radical treatment irrespective of MGMT status.

The optimal management of elderly patients with GBM has been recently reviewed. Patients with poor performance require only supportive care. In contrast, fit patients merit active management with radiotherapy, chemotherapy or a combination of the two following surgery. Randomized studies show no benefit of 6 weeks of radiotherapy over shorter hypo-fractionated treatments. Also, in some patients, particularly those with MGMT methylated tumours, primary chemotherapy may be preferred to radiotherapy. Whether combined short-course chemo-radiotherapy will improve on short-course radiotherapy is the subject of an NCIC/EORTC trial.

When patients relapse, around 30% of those with good prognostic factors may enjoy a further brief improvement with chemotherapy. Single-agent CCNU (or other nitrosourea), PCV and temozolomide can all be given as outpatient treatment and produce about the same level of response in chemo-naive patients with only modest acute toxicity. Patients previously exposed to temozolomide can be re-challenged or treated with alternative chemotherapy. Carboplatin with or without etoposide can be used as second-line chemotherapy.

The use of bevacizumab in the relapsed setting, either alone or in combination with irinotecan, remains...
controversial. Although its use does appear to improve symptoms and scan appearance, survival is unaffected. In Europe, it is not recommended as routine practice but may be applicable in selected cases.

OLIGODENDROGLIOMAS

Oligodendrogliomas are diffusely infiltrating glial tumours, believed to arise from oligodendrocytes or their progenitor cells. They account for around 5%–10% of gliomas and have a peak age incidence between 30 and 50 years. They arise in white matter, with a predilection for the frontal and parietal lobes.

Low-grade oligodendrogliomas (LGOs) are WHO grade 2, slow-growing tumours that most commonly present with seizure. Their imaging characteristics are similar to those of low-grade astrocytoma, but calcification is more frequent (approximately 50%) (Figure 1.9). Long-standing tumours in the frontal brain may extend across the corpus callosum to affect the contralateral lobe, even when the tumour is low grade.

Macroscopically, the tumours usually appear as grey/pink masses, often well demarcated and with calcium frequently evident to the naked eye. Microscopically, the tumour comprises abundant uniform, small cells with round nuclei and a fine chromatin pattern – often referred to as ‘chicken wire’.

Although the majority of oligodendrogliomas are low grade, a substantial minority are more aggressive. These are AOs (WHO grade 3), which harbour the high-grade features of increased cellularity, mitotic activity, pleomorphism and vascular proliferation. In addition, they demonstrate mutations of IDH, a hypermethylation phenotype, and, in a significant percentage, loss of heterozygosity on one or both chromosomes 1p and 19q (see the section ‘Molecular biology of brain tumours’). This latter co-deletion is known to be associated with a good response to chemotherapy.

The management of LGOs is similar to that of low-grade astrocytoma. However, transformation to the high-grade phenotype generally occurs later and overall survival is longer. Also, because the LOH 1p19q genotype tends to predict good response to chemotherapy this may be preferred to radiotherapy as initial treatment.

The importance of the 1p19q co-deleted genotype in AO is shown by the recent analysis of two trials begun in the 1990s. Both demonstrate that adding PCV chemotherapy to initial treatment with surgery and radiotherapy prolongs survival in co-deleted patients only (Figure 1.10). As a result, many regard the standard treatment for 1p19q co-deleted oligodendrogliomas to comprise maximal surgical resection, followed by conformal radiotherapy, and to add PCV chemotherapy either prior to or following the radiation treatment. Others argue that chemotherapy alone has not been formally tested in this setting and might offer an alternative with lesser toxicity, reserving radiation until needed for recurrence. Another major unanswered question is whether temozolomide can replace PCV with equal efficacy. For the time being, treatment of co-deleted AO should be guided by the available evidence.

Patients with AO that is not co-deleted should be treated as AA including being considered for the CATNON trial.

Many patients with AO will do well for many years following primary treatment. Further treatment at recurrence should be offered in the majority of cases using any of the aforementioned agents.

EPENDYMOMA

Ependymoma is a glioma arising from the ependymal cells that normally line the cerebral ventricles and the central canal of the spinal cord. They can arise at any site, usually in association with the ventricular system, but are most common in the posterior fossa, where they present with obstruction or with posterior fossa syndrome. The incidence of intracranial tumours is greatest in young children. Imaging usually shows a well-circumscribed tumour with variable contrast enhancement in the characteristic location.

Ependymomas are soft, grey/pink tumours that often show their ependymal origin. Histologically, perivascular pseudo-rosettes and ependymal rosettes interrupt a monotonous cellular background. Anaplastic tumours may also show pleomorphism, disorganized cyto-architecture, increased mitosis and necrosis. The 2007 WHO classification recognizes three grades and six histological variants of ependymoma: subependymoma, myxopapillary, cellular, papillary, clear cell, and tanycytic.

Ependymomas spread via the CSF, but the influence of spinal seeding on outcome has probably been over-estimated. Although post-mortem series have shown up to
30% spinal seeding, in life it is detected in around only 10% and is symptomatic in less than 5%. Spread is more likely with infra-tentorial high-grade tumours.

All patients should be staged with neuraxis imaging. Maximal tumour resection should be attempted regardless of site, as extent of resection is a major predictor of outcome.\(^5^8\) Gross total removal of posterior fossa tumours is achieved in only 50% or so. Post-operative imaging is strongly recommended and the option of second operation for incompletely resected tumours is considered.

The role of radiotherapy is more controversial and cannot be clearly determined from published studies. A reasonable policy is to deliver post-operative irradiation (54 Gy in 1.8 Gy fractions) to the tumour site using a modest margin (~2cm) for all incompletely resected low-grade tumours. Where the surgeon believes a macroscopic complete removal of a low-grade tumour has been achieved and this is confirmed on MRI, there is a case for a careful observation policy with radiation if recurrence is identified. This policy is supported in major publications in Europe and the United States.\(^5^9\),\(^6^0\) Whole-brain or whole-CNS radiotherapy is reserved for patients with evidence of dissemination. Supra-tentorial high-grade tumours should be treated as GBMs and carry a similar prognosis.

The 5-year survival for patients with low-grade tumours is greater than 50%, although it is worse for young children. Most series show lower survival for patients with high-grade tumours. Treatment failure is most commonly due to local recurrence. Chemotherapy is of minimal value for low- or high-grade tumours in the newly diagnosed or relapsed setting.

Myxopapillary ependymoma is a variant most commonly found in the sacral region. It is of low grade (grade 1) and may often be watched, following resection even if removal is incomplete. The rare subependymoma is a very-low-grade lesion that should be treated with surgery alone.

**RARE NEURO-EPITHELIAL TUMOURS**

**Astroblastoma**

This unusual, probably astrocytic, tumour is regarded by some as a growth pattern rather than a separate pathological entity. The lesion comprises prominent elongated tumour cells that form pseudo-rosettes around blood vessels. The tumours are often superficial, well circumscribed and amenable to surgical resection. The role of radiation and chemotherapy is not established but may be appropriate for patients with poorly resected or recurrent tumours.\(^6^1\)

**Pleomorphic xanthoastrocytoma**

This is usually a cystic and peripherally located tumour in children and young adults, characterized by a mixture of spindle-like cells and mono-nucleated or multi-nucleated giant cells. There is often intracellular lipid accumulation and the marked presence of reticulin fibres. It is normally a low-grade tumour. The major treatment modality is surgery, and complete excision is associated with the best outcome. However, higher grade tumours are found and low-grade tumours can transform to higher grade ones. Radiation treatment may be of value in the management of more aggressive tumours or those that recur after surgery.\(^6^2\)

**Subependymal giant-cell astrocytoma**

This very-slow-growing tumour is frequently associated with tuberous sclerosis. Treatment is with surgery or observation only. There is no role for either radiotherapy or chemotherapy in this condition, although recently the m-TOR inhibitor everolimus was licensed for use in difficult circumstances (see the section ‘Other Pathway Inhibitors’).

**Brain-stem glioma**

Gliomas of all types may arise in the brain stem, most commonly in the pons. Biopsy can be very dangerous, and it is acceptable in these cases to treat on the basis of imaging appearances and clinical features alone. Treatment is usually with radiotherapy (54 Gy for high-grade and 45–50 Gy for low-grade tumours). Studies of hyper-fractionation and adjuvant chemotherapy have not improved outcome. The majority of patients have high-grade tumours, and their outlook is very poor. Patients with lower grade gliomas may survive for years after treatment. Chemotherapy can produce a further response in patients with low-grade tumours who relapse after radiotherapy. In addition to the familiar prognostic factors, patients with exophytic tumours appear to do better.

**Optic nerve glioma**

This tumour, which is most common in children and young adults, is usually low grade and very slow growing. Because of its position, it causes devastating symptoms of visual and hormonal disturbance. Management is controversial. Surgery (for unilateral disease), radiotherapy and sometimes chemotherapy have been advocated, but the timing is crucial and some tumours will spontaneously cease to progress. Simple guidelines to management cannot be offered, and the reader is referred to more detailed approaches.\(^6^3\)

**Gliomatosis cerebri**

This is a pattern of presentation for a variety of glial tumours in which the brain is diffusely affected. Multiple lobes are involved, and sometimes the disease extends infra-tentorially, even into the spine. Imaging appearances, although abnormal, are frequently non-specific, and biopsy is often non-diagnostic. Surgery has almost no therapeutic role in this condition. Chemotherapy or whole-brain radiotherapy (WBRT) may delay the disease process and prolong survival in some patients, particularly those with the \(IDH1\) mutation. For most, however, the outlook is dismal; many patients die within months of presentation.

**Dyssembryoplastic neuro-epithelial tumour**

This is a benign tumour that arises predominantly in the temporal lobes of children and young adults. Histopathologically, these tumours are characterized by a specific glioneuronal element, often with a nodular
component and associated cortical dysplasia. Treatment is by surgical excision; there is no evidence for the value of either radiotherapy or chemotherapy.

**Gangliocytoma and ganglioglioma**

These tumours comprise neoplastic ganglion cells alone (gangliocytoma) or in association with neoplastic glial cells (ganglioglioma). Most patients are under 30 years of age, and a great majority present with seizure. The primary treatment of both tumours is surgery. Radiotherapy is now usually withheld from these lesions, which are regarded as WHO class 1, even if resection is incomplete. However, anaplastic transformation may occur in the glial component, when the outcome becomes much more sinister and treatment more aggressive.

**Central neurocytoma**

This is a rare tumour that arises within the ventricles of young adults. Histological features are of small round cells with neuronal differentiation. Treatment is mainly surgical, and the outcome, even after incomplete resection, can be good. However, troublesome recurrence can occur; at that time, radiotherapy and even chemotherapy may be of value.

**Choroid-plexus tumours**

Choroid-plexus papillomas are rare intra-ventricular tumours derived from the choroid-plexus epithelium. They are predominantly found in children. The malignant choroid-plexus carcinoma is even less common. Treatment is surgical, and the outcome is highly dependent on the completeness of resection. Radiotherapy is reserved for incompletely removed tumours and malignant lesions. CSF spread can occur, even in low-grade lesions.

**EMBRYONAL TUMOURS**

Embryonal tumours are the largest group of malignant paediatric brain tumours. They include medulloblastoma, AT/RT and CNS PNETs. Despite a superficial resemblance to medulloblastoma, patients with CNS PNET and AT/RT fare poorly in comparison.

**Medulloblastoma**

Medulloblastomas are malignant (WHO grade 4) tumours arising in the posterior fossa, usually in the midline (vermis). They spread by local invasion into the cerebellar hemispheres and rostrally into the fourth ventricle and project into the brain stem. They readily spread via CSF to produce metastases on the leptomeninges of the brain and cord, a process that defines their treatment.

It is found that 70% of medulloblastomas occur in children under the age of 16 years (peak 7 years), and they are rare after the age of 40 years. The European annual incidence rate is approximately 6.5 per million in children aged under 14 years. There is a slight male predominance.

The tumours may be soft or firm and are frequently haemorrhagic. The 2007 WHO classification separates medulloblastomas into five types on the basis of their histopathological features: the classic tumour (~70%), desmoplastic/nodular, medulloblastoma with extensive nodularity, anaplastic medulloblastoma and large cell medulloblastoma. Differentiation along neuronal, astrocytic, ependymal, muscular and melanotic pathways may be present, but the significance is not known.

Clinically, medulloblastoma presents with a cerebellar syndrome or with raised intracranial pressure due to CSF outflow obstruction. The characteristic imaging appearance is of a solid, often uniformly enhancing mass with a discrete edge (Figure 1.11). Sometimes, the tumour is more irregular, inhomogeneous and occasionally cystic.

The diagnosis will usually be suspected from the clinical presentation and the imaging appearances. Hydrocephalus might constitute an emergency and require prompt ventricular drainage and steroids prior to a definitive operative procedure, although some surgeons undertake both the drainage and the tumour decompression simultaneously. Full neuraxis imaging (gadolinium-MRI) should be done pre-operatively to look for metastatic spread before blood is introduced into the CSF at operation. If this is not possible, the investigation should be done within 48 hours following surgery. The CSF should be sampled and examined for malignant cells before manipulation of the tumour. Complete tumour removal is associated with a better prognosis and should be attempted wherever possible. In some situations, for example, involvement of the brain stem, total excision may not be possible. Post-operative imaging should be done within 48 hours of surgery to assess the amount of residual disease.

Figure 1.13 (See colour insert.) A contrast-enhanced CT scan showing a patient with a primary central nervous system lymphoma. Note the characteristic features of periventricular location and uniform enhancement. Primary central nervous system lymphoma (PCNSL) is often multifocal and can appear to resolve rapidly with steroids (ghost tumour).
Risk stratification in medulloblastoma is currently based on age, metastatic status, extent of surgical resection and histopathology. Standard-risk patients are aged >3 years with well-resected, localized disease and without anaplastic subtype. All other patients are considered high risk.

CSI remains essential for all patients with medulloblastoma aged over 3 years [see the section ‘Whole-neuraxis radiotherapy (craniospinal irradiation)’]. In children with standard-risk disease, 23.4 Gy are delivered to the entire craniospinal axis (brain and spinal cord with the meningeal coverings) with a further 30.6 Gy (total 54 Gy) delivered to the whole posterior fossa in 30 daily fractions over 6 weeks. There is no advantage to using hyper-fractionated radiotherapy. The radiotherapy is accompanied by eight weekly doses of concomitant vincristine (1.5 mg/m²: maximum 2 mg). Adjuvant chemotherapy begins 6 weeks after the end of radiotherapy and comprises eight cycles of cisplatin 70 mg/m² iv and lomustine 75 mg/m² po on day 1, and vincristine 1.5 mg/m² iv on days 1, 8 and 15, with a 6-week interval between cycles. Following this regime, a 5-year event-free survival of around 80% can be expected. High-risk patients should be treated with high-dose CSI (see later in this section), but the outlook is much less good. Attempts at improving this through the use of neo-adjuvant chemotherapy or intensified chemotherapy including autologous stem cell rescue have been made. None is in routine clinical use. For children under 3 years, chemotherapy is used to avoid or delay the use of radiotherapy. A review of this topic can be found in the study by Massimino and others.

For adults with medulloblastoma, because they tolerate the extensive myelosuppressive and neurotoxic chemotherapy less well and the late consequences of CSI are less severe than for children who are still growing, this ‘standard’ chemo-radiation regime has not been adopted. Rather, full-dose CSI comprising 35 Gy in 20 fractions, with a posterior fossa boost of 19.8 Gy in 11 fractions, is given. Modified adjuvant chemotherapy has been explored, but its value has not been established.

CSI is accompanied by acute and late toxic effects. Acute toxicity includes nausea and vomiting, requiring anti-emetics, and the exit dose from a spinal x-ray field may produce radiation oesophagitis. Myelosuppression is common but rarely requires support or interruption of treatment. Some degree of alopecia is universal. Later consequences are ongoing nausea (especially in teenagers), deafness, loss of intelligence quotient, hormonal deficits, loss of height due to direct and indirect (growth-hormone) effects on bone and cataracts from scattered radiation dose. The principal toxic effects of the chemotherapy are myelosuppression, GI upset and neurotoxicity.

The overall 5-year survival is around 60%–80%, depending on the prognostic mix, although patients may still relapse even many years after primary treatment. Because of the severe physical and psychological effects caused by the disease and its treatment, young people who develop the condition need extensive support during treatment and for many years following its completion.

Patients who relapse should be treated aggressively with a mixture of chemotherapy, further surgery, focal radiotherapy and high-dose therapy. Durable remissions can be induced using a variety of chemotherapy regimes, which include alkylating agents such as temozolomide, epidophyllotoxins and platinum-containing compounds among others.

Very recently, it was recognized that medulloblastoma comprises at least four molecularly distinct subgroups, which exhibit distinct clinical behaviours (see the section ‘Medulloblastomas’). Future trials are likely to incorporate molecular grouping into their design.

**Atypical teratoid rhabdoid tumor**

ATRTs are rare, malignant embryonal tumours usually arising in the posterior fossa of children, especially infants. Histopathologically, they show rhabdoid cells, often together with cells resembling PNET. In the great majority of cases, alterations of the locus of the tumour suppressor gene SMARCB1 on the chromosome band 22q11.2 can be demonstrated.

The standard approach to treatment is with maximal resection followed by intensive chemotherapy and irradiation as allowed by the age of the patient. However, the outcome is very poor, particularly in patients aged less than 3 years where the 2-year survival is under 20%.

**Central nervous system primitive neuro-ectodermal tumour**

CNS PNETs are predominantly hemispheric tumours that make up around 3%–5% of all paediatric brain tumours and are occasionally found in adults. These undifferentiated, highly proliferative embryonal neoplasms are extremely challenging to diagnose pathologically and are divided, by some, into categories such as CNS PNET not otherwise specified, CNS neuroblastoma, CNS ganglioneuroblastoma, medulloepithelioma and ependymoblastoma. Attempts to improve the understanding of the disease and its classification using genomic methods are being made. Irrespective of the variant, it is a highly aggressive tumour with poor survival in spite of intensive therapy with surgery, chemotherapy and irradiation.

**Tumours of the meninges**

**MENINGIOMAS**

A variety of tumours develops in the meninges; but the most common by far are meningiomas, which arise from the meningotheelial cells themselves. They are usually benign. They occur most commonly on the convexity or falcaline brain regions, but they may arise anywhere that meninges are present and cause particular difficulties in sites around the base of the skull. Spinal meningiomas are most common in the thoracic region.

Meningiomas present most commonly in middle age, more often in women (female: male = 3:2). They rarely occur in children, when they tend to be more aggressive.
They can be induced by radiation and are associated with some genetic syndromes, particularly NF2. A majority of tumours shows the presence of progesterone receptor, and a minority is oestrogen receptor positive. Whether this is important in the aetiology is not established. Loss of chromosome 22 is a consistent finding in meningioma and is particularly prominent in the atypical form (see the section ‘Meningiomas’).

Most meningiomas are round or lobulated, smooth, firm and well-delineated tumours, often indenting and compressing the brain but rarely attached to or invading it. More commonly, they invade into or through the dura and induce hyperostosis in the overlying skull. In the base of the skull, they may grow as plaque-like tumours. Meningiomas derive their blood supply from the adjacent meningeal artery and are highly vascular. Identification and embolization of this artery can be therapeutic in its own right and can aid surgical removal.

WHO grade 1 tumours comprise a variety of histological variants, all with similar behaviour.

Atypical meningioma (WHO grade 2) is identified when tumours show increased cellularity, a sheet-like growth pattern, increased mitosis, high nuclear:cytoplasmic ratio, geographic necrosis and brain invasion. Malignant meningioma (WHO grade 3) is said to be present when these features become increasingly prominent (very high mitotic rates). It is clear that these definitions are not precise, and they are subject to variation between pathologists.

The rare chordoid subtype is always regarded as WHO grade 2 and the rhabdoid and papillary forms are graded 3 and are associated with a high rate of invasion and recurrence.

Patients with meningioma have diverse presentations. Although headache is very common, seizure and functional deficit are also frequent. CT or MRI usually reveals an iso- to hyper-dense/intense lesion, with a meningeal base, enhancing strongly with contrast (Figure 1.12). Angiography may add further diagnostic information.

Surgery dominates the treatment of meningioma. The aim is to remove the entire tumour and any involved adjacent structure (dura, soft tissue and bone) to maximize the prospect for enduring local control. Pre-operative embolization of the main feeder vessel is often performed as an aid to surgical removal. The site of the tumour determines the surgical procedure. Convexity meningiomas have the best chance of total excision. Removal of parasagittal tumours risks damage to the sagittal sinus and its draining veins. Tumours of the base of the skull are particularly problematic because of the difficult access and the proximity of sensitive structures.

The outcome following surgery strongly depends on the extent of resection. Re-growth varies from less than 10% for patients with complete excision to over 40% for patients undergoing partial resection. It follows that patients with tumours in the most accessible regions have better prospects than patients with tumours in difficult areas such as the sphenoid ridge. A second operation for recurrence is possible in the majority of patients.

Radiotherapy is effective in the management of meningioma. It is usually given in the adjuvant setting following an incomplete resection where further surgery might prove to be difficult, after multiple relapses following surgery or when the histology is unfavourable.

The GTV will include any imageable residual or recurrent tumour. The CTV will include a margin for spread into adjacent structures. Some recommend treating the entire dural base along with the tumour, whereas others recommend treating just the imaged tumour. Neither approach has been demonstrated to be superior. For malignant tumours, the brain and overlying bone must also be considered at risk. Typically, doses between 50 and 55 Gy in 1.8 Gy fractions are used for grade 1 lesions, whereas 60 Gy in 30 fractions is recommended where possible for higher grade tumours. Sophisticated immobilization, localization and beam-conforming techniques should be used to minimize the irradiated normal tissue, especially in sensitive areas around the skull base where stereotactic radiotherapy can be used to advantage.58 Stereotactic radiosurgery has also been used to treat meningiomas, but the tendency for dural spread and the damaging effect of large single doses may limit the success of this approach.

Chemotherapy is of no proven value in benign meningioma, although sarcoma regimes may be tried for palliation of the malignant form. The identification of hormone receptors in the majority of meningiomas has led to the use of anti-androgen hormone therapy, but with little success. The use of interferons has been tried, but any benefit is minor and short-lived.

Not all patients with meningioma require immediate surgery. Small lesions may be found serendipitously. Particularly in the elderly, these tumours may be so slow growing that they pose no threat during the patient’s lifetime. They can be managed with follow-up and observation, needing intervention only if the clinical or imaging situation deteriorates.

**HAEMANGIOPERICYTOMA (SOLITARY FIBROUS TUMOUR)**

Previously thought of as a variant of meningioma, this tumour is now believed to be indistinguishable from haemangiopericytoma in other sites where it is usually designated as solitary fibrous tumour. It has been thought to derive from the meningeal capillary pericyte, although the true histiogenesis remains uncertain.69 It is a rare tumour that tends to arise in a younger age group than meningioma and is more common in men. They arise in the dura as highly vascular, lobulated masses. They are densely cellular and often highly mitotic and may be graded WHO 2 or 3 on this basis. Haemangiopericytomas have a marked tendency to recur after surgery alone and to metastasize within and outside the CNS, particularly to bone. Maximal surgery is essential treatment, but post-operative high-dose radiotherapy (55–60 Gy) is often recommended to reduce local recurrence and metastasis. Median survival is around 5 years.
Primary central nervous system lymphoma

PCNSL is defined as the lymphoma arising in the CNS (including the eyes) in the absence of obvious lymphoma elsewhere at the time of diagnosis. Its development is strongly related to immunosuppression due to either disease or therapy. There is a high incidence of PCNSL in patients with AIDS, following organ transplantation, and possibly in rheumatoid disease. The incidence in both immune-compotent and immune-compromised patients appears to be rising. PCNSL may occur at any age, but in immune-compotent patients it is most common in middle age. It is slightly more common in men.

PCNSL arises preferentially in peri-ventricular regions of the brain. On imaging, they appear as iso- or hyper-dense lesions that usually enhance uniformly. Approximately 20%–60% are multiple at presentation. Characteristically, they respond rapidly to treatment with steroids and may ‘disappear’ within 48 hours of starting treatment, leading to PCNSLs being described as ‘ghost tumours’. Ocular disease is present in 15%–20% of cases. Clinically, they usually present as mass lesions, although more subtle symptoms, such as personality change, are not uncommon. CSF cytology is positive in 10%–20%. Primary spinal lymphoma is extremely rare.

The pathology is much the same as for systemic extranodal lymphomas. The great majority of PCNSLs are diffuse large B-cell tumours that express the usual pan B markers (e.g., CD20). Only 2% are T-cell tumours. A striking feature is the extremely high proliferative activity.

When primary Hodgkin’s disease and plasmacytoma occur in the CNS, they are usually dural based. Both are extremely rare.

Although imaging may suggest PCNSL, histological proof is essential for adequate management. Surgical resection does not improve outcome, and a biopsy alone is needed. Steroids should be avoided prior to biopsy as this can impair diagnostic yield. Whether these patients need full lymphoma staging is controversial, as the pickup for systemic disease is low. However, most agree that a full ophthalmologic examination; a lumbar puncture with cytological evaluation and flow cytometry (where possible); whole-neuraxis MRI; CT of chest abdomen and pelvis; bone marrow examination; and an immunological screen, including human immunodeficiency virus (HIV) test, are important.

In the past, patients with confirmed PCNSL were treated with radiotherapy alone. Although response rates were high, survival was dismal, 10%–20% at 5 years. Modern management comprises primary chemotherapy for most patients. The role of additional radiotherapy is unclear.

The chemotherapeutic treatment of PCNSLs is dominated by high-dose methotrexate (HDMTX). A dose of at least 3 g/m² by rapid infusion (~3 hours) is considered necessary to achieve adequate levels in the CNS. Other agents that can produce a response include cytosine arabinoside (cytarabine), procarbazine, temozolomide, epiphthylotoxins and nitrosoureas. Only high-dose cytarabine has been the subject of a randomized trial. In this study, patients were treated with HDMTX (3.5 g/m² on day 1) plus cytarabine (2 g/m² on days 2 and 3). Compared to patients treated with HDMTX alone, there was a statistically significant improvement in progression-free survival and response rate with a strong trend to improved 3-year overall survival, which did not reach statistical significance (P = .07). This combination has become the standard of care in PCNSL.

Other approaches including immunotherapy (rituximab), intra-thecal therapy and high-dose chemotherapy have all been tried, but none has gained general acceptance.

WBRT for PCNSL is associated with a high response rate and was routinely used following HDMTX. The high incidence of severe neurotoxicity, particularly in the elderly, led to the practice being questioned. In the only large study of its kind, patients with a complete response to HDMTX-based chemotherapy were randomized to 45 Gy of WBRT or observation. Consolidation WBRT resulted in a significantly better progression-free survival (median of 18 vs. 12 months) but no overall survival benefit (median 32 vs. 37 months). However, poor study design and execution limit the usefulness of the study. Given the uncertainty, it seems reasonable to withhold irradiation in patients who achieve a complete response to chemotherapy but to offer 40–45 Gy in 20–25 fractions of WBRT in those who do not.

Following aggressive chemotherapy, complete response rates of around 50% are typical. Unusually, prolonged survival can occur, particularly in younger, fitter patients and those who receive an early and complete response to chemotherapy. However, relapse is far more common and median survival is only between 2 and 4 years. In 10% of cases, relapse outside the CNS will occur. Following relapse, alternative chemotherapy, salvage radiotherapy, high-dose chemotherapy and immunotherapy can be tried, but responses are usually short-lived.

The treatment of HIV-positive patients is even less well defined. If their condition allows it, an aggressive approach, as for the immune-competent patient, can be followed. For patients who are less well, radiotherapy alone can be given. It is important to continue antiviral therapy. Very elderly patients or those not fit for other approaches can do quite well with an initial course of high-dose steroid alone, which can be tapered down as the tumour responds.

Tumours of the pineal region

Whereas pineal cell and germ cell tumours are particularly associated with the pineal region of the brain, other tumour types, including gliomas, meningiomas, benign tumours and metastases, also occur. Presentation is most commonly with hydrocephalus and is often accompanied by complete or partial Parinaud’s syndrome.

PINEAL PARENCHYMAL TUMOURS

These are uncommon tumours of the pineocytes. They always arise in the pineal gland but may disseminate in the CSF. They occur in children and adults and show no gender
of this is variably reported, but it is probably around 15%. Systemic spread, either blood borne or via ventriculo-peritoneal shunts, can also occur. Presentation is as for other mass lesions in the pineal region (or other sites).

The testicular tumour markers hCG and AFP can often be detected in the serum and CSF of these patients and can be a useful guide to response to treatment. Decay of the markers may be delayed by the presence of cysts, which act as reservoirs. The CSF to serum marker ratio is normally >1. If the ratio is reversed, systemic disease is more likely. The detection of serum AFP is diagnostic of teratoma and may obviate the need for biopsy.

**Gadolinium-enhanced MRI** is the imaging modality of choice and is essential for planning surgery. Germinomas tend to be homogeneous and enhance uniformly with contrast. Calcification is common, and cystic areas may be present. Teratomas, benign and malignant, are notably heterogeneous with variable signal characteristics and irregular contrast enhancement. The whole neuraxis should be imaged. All patients presenting with a suspicion of a germ cell tumour require serum estimation for AFP and hCG. The CSF levels should also be evaluated.

The management of germ cell tumours is complex and dependent on the precise histology of the lesion. Tissue (or marker) diagnosis is essential; however, the extent of surgery required is a matter of debate. Biopsy of this region using stereotaxy, although it is possible, may be hazardous. An open procedure may be considered the safest and also provides the opportunity for therapeutic resection. Ventriculoscopy and biopsy can be valuable in difficult cases. Surgical excision is usually curative for differentiated teratoma but offers no advantage over biopsy alone in germinoma. Surgical resection of NGGCTs may be valuable, but with the increasing success of non-surgical treatment the risk of complications should be considered in each case.

It is difficult to give simple guidelines for the treatment of these diseases. In the past, the standard treatment for localized germinoma was whole-neuraxis radiotherapy with a boost to the primary lesion. Although the cure rate was very high (>90%), the treatment was associated with substantial early and late toxicity. Most practitioners now advocate initial treatment with a combination of carboplatin and etoposide (two to four cycles) followed by radiation limited to the primary site plus the whole of the ventricular system (24 Gy in 15 fractions) and a boost to the primary site (16 Gy in 10 fractions). Cure rate is much the same but with reduced toxicity.

Although a standard management for patients with poor-prognosis, malignant NGGCT has not been established, it is agreed that they require aggressive multimodality treatment. Chemotherapy regimes may be up to six cycles and are usually platinum based (cisplatin or carboplatin) combined with agents such as etoposide, bleomycin and ifosfamide. Radiotherapy is an accepted element of management; but there is disagreement as to whether this should be craniospinal or localized, based on a sound knowledge of the disease distribution. However, the need for higher doses (>45 Gy) to the primary site
is agreed on. Surgery also has a more prominent role in this disease, as more extensive removal is associated with better outcome.

The outcome following these approaches is varied. In pure germinoma, 5-year disease-free survivals of 85%–100% can be expected. Radiotherapy alone for NGGCT produces only around 20% long-term survivors; but the introduction of platinum-based chemotherapy has improved this to around 50% or better, although radiation remains an important element of treatment in all patients. As in gonadal germ cell tumours, it is not uncommon to image residual abnormality in the tumour site following treatment. In the absence of evidence of progression, this may just need observation. However, if there is doubt concerning the completeness of treatment surgery may be indicated.

The functional outcome following treatment is often good, although the same complications of treatment experienced by medulloblastoma survivors occur. Patients presenting with severe Parinaud’s syndrome often suffer from persistence of deficit and require the input of a neuro-ophthalmologist. Patients with supra-sellar tumours may suffer from long-term endocrine problems.

Other Tumours

CRANIOPHARYNGIOMA

Craniopharyngioma is a benign epithelial tumour of the sellar region, thought to arise from a remnant of Rathke’s pouch. It is most common in children and young adults. It grows slowly and presents with pressure symptoms, endocrine and visual disturbances. Hydrocephalus may be present. The typical imaging properties of an enhancing solid and cystic lesion, often with calcification in a supra-sellar site, strongly suggest the diagnosis.

Two forms are recognized histologically, papillary and adamantinomatous. Both are slow growing and excite intense gliosis in neighbouring brain. Tongues of the tumour also extend into adjacent brain tissue and may be very difficult to remove surgically. Single or multiple cysts are very common and contain a thick, cholesterol-rich fluid. The fluid in the adamantinomatous tumour is often oilier than that in the papillary type and calcification is much more common.

Optimal management of these tumours is controversial. A common approach in the United Kingdom is to attempt maximal surgical removal. If this is shown to be complete, routine follow-up with interval imaging is sufficient. Because of the growth pattern, however, total excision may not be possible and the recurrence rate then is higher. In these cases, radiotherapy can be given. The volume should be minimized using accurate CT localization and conforming techniques, as a dose of 50–54 Gy in 1.8 Gy fractions is needed. This treatment restores the level of tumour control to that of complete excision. In very young children, in whom radiotherapy might produce high levels of morbidity, observation may be appropriate, even after partial resection. Follow-up in all cases includes endocrine assessment, neuro-ophthalmology and neuro-psychology, as well as tumour surveillance.

Treatment of recurrence is difficult as re-operation is hazardous. Radiotherapy-naive patients can be irradiated, and re-irradiation is possible in some situations if stereotactic techniques (SRS or SRT) are used.

Although the 10-year survival is around 90%, fewer patients are free from disease. There is no clear difference in outcome between the histological subtypes.

CHORDOMA

Chordomas are malignant, embryonal tumours that arise from the notochordal remnant. They are found predominantly in the region of the clivus and at the sacrococcygeous, in the extradural space, but they grow slowly and may invade the dura as they do so. Histologically, the identifying features are ‘physaliferous’ cells, which contain large mucus-filled vacuoles, and immunoreactivity for S-100 and epithelial markers such as the epithelial membrane antigen (MUC1) and cytokeratins. They are arranged in lobules and are usually surrounded by extracellular mucus.

The management of these tumours is complex. The best possibility for cure probably results from aggressive surgical resection within the constraint of preserved neurological function. However, even after apparent complete resection local recurrence can be a problem. Conventional high-dose radiotherapy is often given in the post-operative setting, although its value is not proved. Dose escalation to highly conformed target volumes using proton beam facilities or stereotactically localized, intensity-modulated x-ray techniques appears to produce better results. Median survival is around 6 years, and 20-year survival is just 13%.77

Spinal tumours

A similar spectrum of tumours arises in the spine as in the brain, although the frequency of occurrence is different and some types are absent. Tumours may be grouped according to their site of occurrence into extra-dural (metastasis, chordoma, and sarcoma), intra-dural/extra-medullary (meningioma and neurofibroma) and intra-medullary (astrocytomas, ependymomas and benign tumours) tumours.

For all sites, the commonest presentation is with pain and/or loss of function at and below the level of the lesion. Tumours cause functional loss by direct pressure, generation of spinal oedema, spinal infarction, invasion into spinal tissue and growth along nerve roots. Almost any pattern of motor deficit may occur. Combinations of complete and partial upper and lower motor neuron lesions arise as the tumour develops. Likewise, sensory deficits may be complex.

Plain spinal x-rays still play an important role in the early evaluation of a patient suspected of having metastatic disease, but the widespread availability of MRI scanning has revolutionized the investigation of spinal tumours (Figure 1.14). The clear identification of the tumour and its
boundaries allows surgeons to plan their operations accurately and radiotherapists to make rational judgements about field size and placement.

Surgery is the mainstay of treatment for many low-grade spinal tumours. Good results can be expected from the complete excision of meningiomas, neurofibromas, pilocytic astrocytomas and ependymomas. However, surgical decompression of spinal metastases, fibrillary astrocytomas and AAs and high-grade ependymomas should usually be followed by post-operative radiotherapy. Spinal cord compression due to an intra-medullary tumour nearly always requires urgent decompression.

Radiotherapy may be given with palliative or radical intent. For palliation, either direct posterior or opposed fields are used to deliver short courses of treatment. Doses of 30 Gy in 10 fractions and 20 Gy in 5 fractions are common in metastatic disease. Higher doses for radical treatments are often delivered using a technique based on a wedged pair of fields (Figure 1.15), although more complex delivery techniques such as IMRT can be used if available. Optimal planning will involve the use of CT. For treatments to low-grade tumours doses of 45–50 Gy in 1.8 Gy fractions are usual, but for highly malignant tumours doses up to 60 Gy may be appropriate. Although the risk to the spinal cord from the radiation is increased at these doses, it may not be as high as previously thought, provided megavoltage x-rays are used and the dose per fraction is kept below 2 Gy. This risk must be balanced against the risk of under-treating the tumour and the consequences of early re-growth.

**SPINAL ASTROCYTOMAS**

The majority of spinal astrocytomas are low grade, but the precise histology is important. If the tumour is pilocytic, the outcome following surgery is usually good and the value of adjuvant radiotherapy is doubtful. Diffuse astrocytoma, usually fibrillary, has a less good prospect. It is difficult for

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**Figure 1.14** A sagittal MRI showing a patient with an ependymoma of the filum. Note the well-delineated lesion lying between lumbar vertebrae 3 and 4.

**Figure 1.15** A stylized diagram of a wedged pair treatment planned on CT for a spinal tumour. Treatment to intramedullary tumours would use smaller field widths (~4 cm). If doses to vital structures (here, lungs) are excessive, the plan can be modified by using a posterior field together with the wedged pair.
the surgeon to find any plane between tumour and normal tissue, and there is less argument about the need for additional radiotherapy. Most patients are dead within 5 years.\(^7\) AAs and GBMs occur rarely in the spine, but when they do they should be treated as their cerebral counterparts with surgery and radiotherapy. The prognosis is very poor.

**SPINAL EPENDYOMOMAS**

Ependymomas may arise anywhere in the spine but have a predilection for the lower end around the conus. Ectopic extra-spinal tumours may develop in the pre-sacral region. Most are low grade. A clear operative plane is often found, and complete excision may be possible. In this situation, only follow-up is required. If complete excision is not obtained, adjuvant radiotherapy is often given, but clear evidence of its value is lacking. For low-grade tumours, this would comprise local radiotherapy only. High-grade tumours can rarely be excised completely, and post-operative radiotherapy is required.

The variant myxopapillary ependymoma is found almost exclusively in the conus/cauda equina region. It is treated surgically and has a particularly favourable prognosis.

**Malignancy metastatic to the brain**

Metastasis to the brain from systemic malignancy is common. Further, the incidence appears to be increasing, not only from common primaries such as breast,\(^7\) lungs and kidney and melanoma but also from those thought rarely to give rise to brain metastasis such as prostate.\(^8\)

The outlook for most patients remains poor, and treatment is symptomatic and palliative. However, a minority, although still rarely curable, has a better outlook and merits a more aggressive approach to management. The principal prognostic factors are age; performance status; presence of uncontrolled systemic disease; primary histology; and, importantly, the number of metastases present. Scoring systems to aid decision making and trial stratification such as the graded prognostic assessment tool\(^9\) are available. In general, only those with small-volume oligo-metastatic disease, or those with chemosensitive disease, are thought worthy of aggressive treatment.

The majority of patients will present with symptomatic disease, and the first step in management is to offer symptomatic care, which usually includes corticosteroids. Thereafter, the patient should be assessed for possible further treatment.

**WHOLE-BRAIN RADIOTHERAPY**

Until recently, WBRT was the standard of care for the great majority of patients with brain metastasis. However, its role in palliation is now much less certain. Much of the literature claiming a survival advantage is flawed, with selection bias being a common problem. Symptomatic improvement and reduced steroid requirement may be observed clinically following irradiation, but this is at the expense of hair loss and, frequently, debilitating lethargy. Overall, the benefit is unclear. The Medical Research Council (MRC) has been running a unique clinical trial (QUARTZ) comparing best standard of care (BSC) to BSC plus WBRT\(^10\) for patients with brain metastases from non-small-cell lung cancer. Interim results have shown no difference in either survival or QOL between the two arms, but it is emphasized that this is an indication to continue the trial rather than to change practice.

For patients with large-volume disease or multiple metastases and poor performance status after steroid use, there is little to be gained from WBRT. For those with Karnofsky performance status (KPS) 70 or greater, it is reasonable to discuss WBRT and the possibility of some degree of tumour control, but with the aforementioned drawbacks. There is little to suggest that regimes other than 20 Gy in five fractions to opposed fields have any worthwhile advantage. Entry into clinical trials, where available, is probably the best option.

**MANAGEMENT OF OLIGO-METASTATIC DISEASE**

Oligo-metastatic disease is defined as one to three metastases in the brain. Microsurgery and stereotactic radiosurgery have become standard tools in this condition. Both techniques have demonstrated a survival advantage for patients with single metastases.\(^8,4\) Where more than one metastasis is present, a survival advantage has not been demonstrated, but focal therapy can still achieve symptomatic control with less morbidity compared to WBRT. Not all patients are suitable for this, and selection for treatment should include recognition of other prognostic factors including age and performance status.

Pragmatism determines the choice of treatment modality. Larger lesions associated with brain distortion are best treated with surgery to relieve pressure. Smaller lesions, multiple lesions and lesions in inaccessible sites or adjacent to eloquent regions are best treated with SRS, which is also likely to be the less expensive option.\(^5\)

The value of adjuvant WBRT after localized treatment remains controversial. Although studies consistently demonstrate an improvement in local control, paradoxically there is no measureable impact on either survival or (surrogate) measures of QOL.\(^6\) Hence, it is unclear whether patients should be offered immediate WBRT or surveillance, with WBRT at relapse. Following surgery, there is a relatively high incidence of early relapse at the resection site; hence, a further option might be to offer small-field radiotherapy following surgical excision to reduce this phenomenon while still avoiding the ill effects of WBRT.

**ROLE OF CHEMOTHERAPY**

There is increasing awareness that for patients with chemosensitive disease systemic therapy might offer a reasonable first-line option for intracranial metastases. Small-cell lung cancer, ovarian cancer, germ cell tumours and even breast cancer can respond well to regimens containing agents possessing some degree of BBB penetration such as platinum.\(^7\) Although this offers an alternative to WBRT, it must be remembered that most patients have a poor prognosis and best support may remain the optimal care for them.
Chemotherapy, given as an adjunct to WBRT, has been disappointing and is not currently recommended outside clinical trials.88

PROPHYLACTIC CRANIAL IRRADIATION

Some cancers have a marked predisposition to produce intracerebral metastases. It has been demonstrated in small-cell lung cancer that prophylactic cranial irradiation (PCI) can reduce the incidence of cerebral metastases and improve survival,89 and this principle is now being explored in other high-risk diseases such as her-2 positive breast cancer and non-small-cell lung cancer. The drawback of this approach is the risk of radiation-induced neuro-cognitive damage following PCI. The use of complex radiotherapy delivery systems (IMRT and VMAT) to spare the limbic system, where the incidence of metastases is low, while maintaining radiation dose to the rest of the brain may help to reduce this side effect.

KEY LEARNING POINTS

• Tumours of the brain are characterized by their histological variety.
• Accurate histological diagnosis1 and molecular analysis are essential for appropriate management.
• Surgery and radio therapy remain the predominate treatments for the majority of tumour types.
• Surgical and radio-therapeutic techniques must be individualized to the specific tumour.
• Conventional chemotherapy plays an increasing role in the primary treatment of CNS tumours and at relapse.
• Although the biological and molecular processes involved in the development and maintenance of brain tumours are increasingly understood, this has not led to new therapies for routine practice.
• Cure can be obtained for some patients with brain tumours (particularly children), and there can be useful extension of life in the majority.

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Treatment of cancer


**USEFUL WEBSITES**


http://www.cancer.gov/cancertopics/types/cancersbodylocation/neurologic

http://www.cancer.gov/cancertopics/types/brain

http://www.cancer.gov/cancertopics/pdq/treatment/adultbrain/Health Professional/

- Fully comprehensive guide to the incidence, presentation and management of cancers of the brain and spine. Offers the opportunity to access information on current clinical trials. Inevitably biased to a U.S. perspective.


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2203994/


These are links to the charity funded American Brain Tumour Association. They provide a wealth of information for the lay person and the professional. The adult clinical practice pdf is a link to a document describing current American practice in managing brain cancer.

http://www.braintumouraction.org.uk

These are links to the charity funded American Brain Tumour Association. They provide a wealth of information for the lay person and the professional. The adult clinical practice pdf is a link to a document describing current American practice in managing brain cancer.

http://www.thebraintumourcharity.org/about-brain-tumours/adult-brain-tumours

This site is directed at the lay browser but has some useful information particularly about services available in the United Kingdom. The best and most informative U.K. site covering most aspects of brain tumours for lay and professional browsers.

http://www.braintumour.org.uk/

http://www.braintumourcharity.org/about-brain-tumours/adult-brain-tumours

http://www.nhs.uk/conditions/brain-tumours/Pages/Introduction.aspx

This NHS choices website gives good lay information and useful links for further information and sources of support.

http://www.abta.org/


Rather old now but this document still sets the standard of care recommended for patients in the United Kingdom. An update is expected imminently.

http://www.nhs.uk/conditions/brain-tumours/Pages/Introduction.aspx

http://www.btaa.org/

http://www.braintumour.org.uk/

http://www.braintumourcharity.org/about-brain-tumours/adult-brain-tumours

These are links to the charity funded American Brain Tumour Association. They provide a wealth of information for the lay person and the professional. The adult clinical practice pdf is a link to a document describing current American practice in managing brain cancer.

http://www.braintumour.action.org.uk

United Kingdom-based emotional and practical support for brain tumour patients and families. Brain Tumour Action provides trained counsellors, information and coordinates a U.K. network of support groups.

http://www.braintumour.ca

Help for Canadians dealing with a brain tumour diagnosis. Family-founded Brain Tumour Foundation of Canada supplies a range of publications, including a family handbook, free of charge. There is a toll free phone line for one-to-one support, access to a network of adult and child brain tumour support groups, online networking and personal story posts.

http://www.braintumourfoundation.org.au/

A free US handbook – The Primer of Brain Tumors – can be downloaded from Brain Tumour Alliance Australia as well as a load of information and links. Free handbook.

http://braintumourfoundation.org.au/

The Brain Foundation hosts a forum, an A to Z of disorders and general information about brain tumours and cancers.

**Ocular and adnexal tumours**


Head and neck cancer


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Breast cancer


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Lung cancer


Oesophageal cancer


Hepatocellular carcinoma


Biliary tract cancer


Gastric cancer


Bladder cancer


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Prostate cancer


Germ-cell cancer of the testis and related neoplasms


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Renal cell cancer


Ovarian and fallopian tube cancer


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Endometrial cancer


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Cervical cancer


Carcinoma of the vagina and vulva


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Primary bone tumours


Soft tissue sarcomas


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