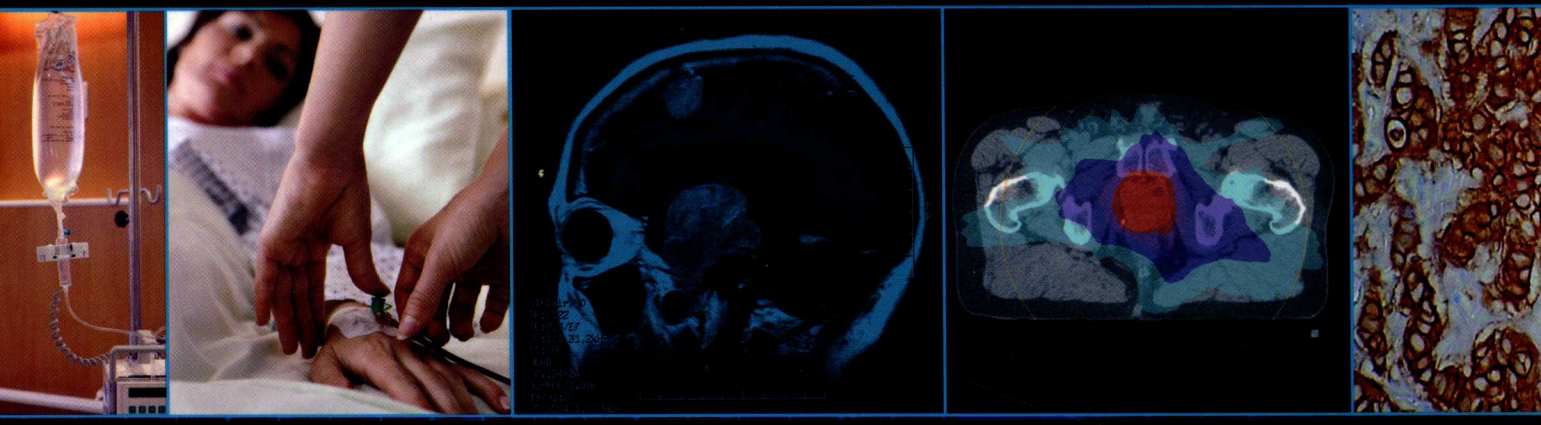
Sixth Edition

TREATMENT OF CANCER



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TREATMENT OF CANCER

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Sixth Edition

TREATMENT OF CANCER

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
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Preface

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).

Table 1 Cancer's timeline

• 3000 BC	First recorded description of breast cancer in the Smith Papyrus
• 400 BC	Hippocrates describes six cancer types
• 1880	Successful radical mastectomy
• 1896	Oophorectomy for breast cancer
• 1898	Discovery of radium
• 1899	Discovery of x-rays
• 1946	First publication on successful chemotherapy for cancer
• 1953	Double-helical structure of DNA elucidated
• 1958	Successful use of combination chemotherapy
• 1999	First molecularly targeted therapy approved for use
• 2000	Human genome mapped
• 2006	More than ten targeted therapies available
• 2008	Radiotherapy with IMRT (Intensity Modulated) and IGRT (Image Guidance)
• 2014	Personalized medicine for certain cancers

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 massive profits generated by the industry, usually achieves the desired endpoint. Advertising blatantly exploits the young of the developing world, associating images of sex, success and wealth with cigarettes as a lifestyle marker. The solutions are complex and require considerable political will. But with forceful and concerted international action against cigarette promotion, we could reduce cancer incidence by 20% by the year 2020.

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

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 could, 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

neoplasia. 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 natural history of many cancers (including incidence and mortality) may change over time for reasons that are poorly understood. In Europe, the incidence of stomach cancer has decreased dramatically over the last few decades, whereas breast cancer deaths reached a peak in the United Kingdom in 1989 and have decreased slightly each year since then.

Lobby groups often exercise political pressure to implement screening programmes (even when their effectiveness is undemonstrated), and manufacturers of equipment or suppliers of reagents may exercise commercial pressure. In fee-for-service-based provider systems, there is a financial inducement for doctors to investigate because doing nothing earns no money. The launch of the NHS breast screening service by the U.K. government in 1989 was viewed by many as a pre-election vote-winning exercise rather than a rational public health intervention, and there are now similar pressures to introduce prostate cancer screening, though uncertainty remains about the management of men with slightly elevated prostate-specific antigen (PSA).

Many groups (e.g. governmental organizations, medical charities, health maintenance organizations, professional bodies) have produced guidelines on cancer screening. These guidelines vary widely between countries, reflecting bias in the interpretation of evidence and cultural values in the practice of medicine. For example, annual PSA testing and digital rectal examination in men over 50 years of age are recommended by the American Cancer Society, but are not advocated in most other countries. The incidence of a particular cancer in a particular country and the economics of screening must be considered carefully – the cost of the technology required must correspond with the gain. Low-cost, direct inspection techniques for oral and cervical cancer by non-professional health workers seem attractive in achieving tumour downstaging and hence better survival results, but cervicoscopy programmes in India and China have shown surprisingly poor overall effectiveness. It is unclear whether intravital staining with acetic acid can enhance specificity at little extra cost.

A major cost in instituting any screening procedure is informing the public and then developing the logistics, often under difficult geographical conditions. Cultural barriers may be insurmountable without better education, particularly of girls, who as mothers will become responsible for family health.

Low-technology tests have low specificity; as a result, hard-pressed secondary care facilities are inundated with patients with non-life-threatening abnormalities. Detailed field assessment, preferably in a randomized setting, is essential before firm recommendations can be made, but political factors often interfere with this process. The well-meaning charitable donation of second-hand mammography units to some African countries has led to haphazard introduction of breast screening in populations in which the incidence of breast cancer is low and where there are few resources to deal with abnormal results.

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.

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

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.

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 fractionated treatment
- Movement of the tumour between treatments

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.

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 methylomics 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.

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?

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.

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.

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.

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

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