# TREATMENT *of* CANCER

edited by Keith E. Halnan

J. L. Boak, D. Crowther, C. F. von Essen, J. S. Orr, M. J. Peckham

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# Preface

Attainment of the best treatment of cancer will continue to be of paramount importance for the foreseeable future. One of the current dogmas, almost a cliché, is the importance of integration and of team work, of the main methods – surgery, radiotherapy, and chemotherapy. Yet this is still often much more precept than practice. This book is an attempt towards achieving this important goal. It describes *cancer treatment of all kinds*, everyday and esoteric, so that anyone interested in the optimum management of cancer can read sufficiently to know something sensible and up to date about the particular tumour or particular treatment method that concerns him, whatever his specialty. This is meant to be an international textbook, considerably based on distinguished British authors but with contributors also from North America, Asia and the continent of Europe.

Like Gaul, the book is divided into three parts – principles, practice and techniques. The first part – Principles of Treatment – reviews the roles and rationales of Surgery, Radiotherapy (with a section on the newest radiations – nuclear particles), Chemotherapy, Endocrine treatment, and Immunotherapy. The second main part – Clinical Practice – is an extensive series of chapters in every individual class of tumour. Some of these chapters are purposely more expansive then others, to allow world authorities, such as John Ho on nasopharyngeal cancer, to let us all have the benefit of much wider experience than most of us can hope to achieve, and others to give space for the very interesting newly described tumours such as the apudomas. Some are comprehensive summaries mainly based on the outstanding experience of one particular centre, such as the unique experience of the Christie Hospital in cancer of the mouth. Others are on tumours only now beginning to be attacked by the modern combined approach, such as tumours of the liver and pancreas. All should give a guide sufficient to point the way to the best contemporary treatment protocols. The final part – Methods and Techniques – gives more essential detail which will be of value in deciding on technique including medical management; the extremely important practical and psychological handling of patients (sometimes terminal) and of their relatives; and radiation equipment and treatment planning. Lastly, there are two essential chapters on statistics and trial protocols.

I have been greatly helped, not only by the authors, usually working in teams of two or three, but especially by five associate editors who have given advice on their areas of expertise: James Boak on surgery, Carl von Essen on particle radiotherapy and the American viewpoint, Derek Crowther on chemotherapy, Stewart Orr on physics and science, and Michael Peckham on radiotherapy. Barry Shurlock and the publishing staff of Chapman and Hall have been most helpful and tolerant. Finally, I wish to urge all doctors (surgical, medical and radiation) to read about all that can be done by their colleagues with even more attention than they give to their own roles.

London Keith E. Halnan

# A note on radiation units

In this book the current units the rad, curie and rem are used. New SI (Systeme Internationale) units are about to come in; in Britain they will be legally authorized from 1981 and will be in sole use by 1986. Their introduction in the European Economic Community (EEC) had been authorized since 1978. In many other parts of the world there are no plans yet for change. Tables of the new units are given below.

| *Quantity* | *New named unit and symbol* | *In other SI units* | *Old special unit and symbol* | *Relationship old to new units* |
|---|---|---|---|---|
| Exposure | – | C/kg | röntgen (R) | 1 R = $2.58 \times 10^{-4}$ C/kg |
| Absorbed dose | gray (Gy) | J/kg | rad (rad) | 1 rad = 0.01 Gy |
| Dose equivalent | sievert (Sv) | J/kg | rem (rem) | 1 rem = 0.01 Sv |
| Activity | becquerel (Bq) | $s^{-1}$ | curie (Ci) | 1 Ci = $3.7 \times 10^{10}$ Bq |

The table below gives the prefixes to be used with SI units

| *Multiples* | | | *Sub-multiples* | | |
|---|---|---|---|---|---|
| *Factor* | *Prefix* | *Symbol* | *Factor* | *Prefix* | *Symbol* |
| $10^{18}$ | exa | E | $10^{-1}$ | deci | d |
| $10^{15}$ | peta | P | $10^{-2}$ | centi | c |
| $10^{12}$ | tera | T | $10^{-3}$ | milli | m |
| $10^{9}$ | giga | G | $10^{-6}$ | micro | $\mu$ |
| $10^{6}$ | mega | M | $10^{-9}$ | nano | n |
| $10^{3}$ | kilo | k | $10^{-12}$ | pico | p |
| $10^{2}$ | hecto | h | $10^{-15}$ | femto | f |
| $10^{1}$ | deca | da | $10^{-18}$ | atto | a |

# Contents

# Part One: Principles of Treatment

# 1 Introduction
# An approach to the treatment of cancer: past, present and future

Keith E. Halnan

This book is written by many authors with one common theme – the optimal treatment of cancer. Sir George Pickering has discussed the aims of treatment, and his views on hypertension can equally well be applied to cancer. Doctors have different attitudes to treatment. Some treat their patients as human individuals; some treat the labels which they have fixed to their patients, perhaps as cases in a scientific randomly controlled trial protocol; some treat the patient's relatives and a few treat the doctor himself. *The main object of treatment should be that expressed by the American Declaration of Independence in 1776, namely: 'Life, liberty and the pursuit of happiness'.* Many oncologists may too easily concentrate on the first, at the expense of the second and third – the quality of life must not be disregarded.

### Basic concepts: the nature, growth and spread of cancer

> Cancers can arise in any organ of the body, but some sites are more frequent than others. Each cancer is descended from a single cell that at some stage became free from its normal territorial restraints and so was able to form a family of cells that could multiply without limit. (Cairns, 1978)

There are about $10^{13}$ cells in the human body and from start to finish, from the fertilized egg to death in old age, a human being is the product of about $10^{16}$ cell divisions.

The layman often thinks that cancer is a single incurable disease that can begin anywhere in the body, and that it spreads throughout the body, causing much pain and other unpleasant symptoms before inevitable death. Similarly, it may be thought that surgery is unpleasant and mutilating, that radiotherapy burns the patient and makes him sick, and that chemotherapy not only makes him sick but does this repeatedly and interminably, usually removing all his hair also. This is the main cause of unnecessary fear and of the highly undesirable delay before diagnosis.

In fact the definition of cancer or 'malignancy' is extremely difficult. Firstly, perhaps one should state that cancer is a disease in which a family of cells will grow progressively, with permanent impairment of normal growth control, resulting in spread of the primary group of tumour cells – the primary tumour – which penetrates the capsule of the parent organ. Secondly, the cancer cells will penetrate the walls of either lymphatic or blood vessels, and will be capable of implantation and growth in secondary or metastatic sites, especially in lymph nodes from lymphatic spread, and in any organ from blood-borne spread, especially lungs, bones, liver and brain.

Either of these criteria can be sufficient. For example a basal cell carcinoma of skin or a glioma of the brain will be capable of killing the patient without any distant metastasis, lymphatic or blood-borne. Similarly, there may be widespread distant metastases from a tiny thyroid carcinoma or a small cell bronchial carcinoma while the primary carcinoma is still small and well confined to the primary organ. The histologist or cytologist will then recognize criteria for malignancy in individual cells: abnormal nuclei, frequent abnormal mitoses and changes in the ultrastructure. There may

also be changes in the structure and arrangement of the tumour compared with normal parent tissue.

It is this last kind of diagnosis that is more debatable, when the transition occurs between a papilloma and carcinoma of the bladder, or a malignant or benign ovarian cyst. Pre-malignancy or carcinoma-in-situ is one very arguable field; good examples are carcinoma *in situ* of the uterine cervix which may not become invasive at all, or tiny latent carcinomas of the prostate, apparently present in a majority of very elderly men and often never causing any symptoms at all.

The cancer may sometimes be multicentric but will more often be considered to arise from mutations of one cell into a new permanently malignant cell. The tumour may grow exponentially or more likely at decreasing rate as a 'Gompertz' growth curve. A just perceptible tumour of 1 g contains $10^9$ cells, and $10^{12}$ cells or 1 kg will often be more than enough to kill the patient (dependent upon patterns of spread). It becomes clear that many cancers must have originated for a substantial period, certainly months and often years before becoming clinically detectable or before causing symptoms and becoming apparent to the patient last of all. It also becomes obvious that latent microscopic metastases may well be present in very many patients and that treatment must be far more vigorous or must continue for much longer than needed to induce a 'complete remission', i.e. result in no clinical evidence of disease (Fig. 1.1).

### Epidemiology: present and future

The total incidence of cancer seems from past experience unlikely to change very much over the next ten years, particularly if one is considering incidence on an age-corrected basis. Most cancers have a steep increase in incidence with age; in most parts of the world the proportion of elderly people is itself increasing, as population control methods become so widely available and because of increasing success in treatment of disease, infectious especially, other than cancer and cardiovascular disease.

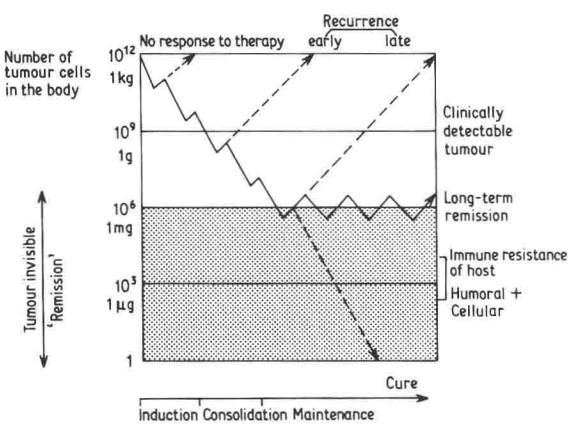


*Fig. 1.1* This diagram shows the successive response of a tumour to cycles of chemotherapy but the reduction in numbers from 'induction' therapy might well have been caused by surgery, the 'consolidation' by post-operative radiotherapy, with final reduction for long-term cure being caused by chemotherapy.

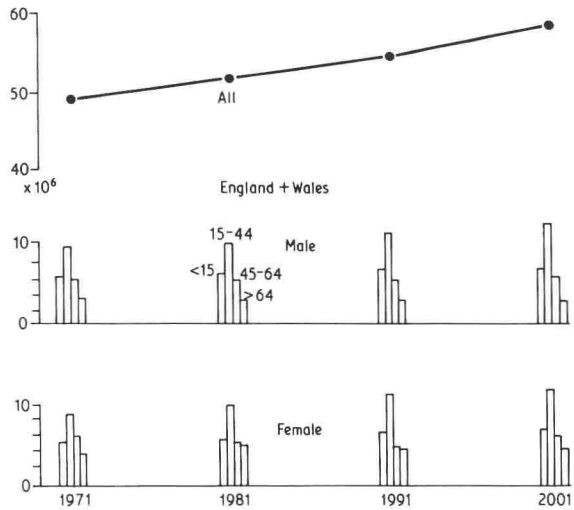


*Fig. 1.2* Population projection for England and Wales, with histograms showing age distribution.

Population changes will vary considerably but most 'developed' or Western countries are now only expanding relatively slowly as shown in Fig. 1.2 for England and Wales. The population group aged 75 and over is likely to increase by over 25%, and will have a considerable incidence of cancer.

Past experience (in Scotland as an example) will show us how these changes will alter the incidence of cancer. Over the last 50 years cancer has been increasing, this has mainly been occuring in the elderly (Fig. 1.3) as well as in the numerically very small group of children.

Major differences are occurring in different sites, the most important being the lung, responsible for most of the last 30 years' increase in cancer in men and likely to do the same for women if present trends continue and smoking continues unabated.

Detailed very interesting analyses for world trends are given in the recent report *Cancer Services in Scotland* from the Scottish Health Service Planning Council (1980). In Scotland itself the size of change expected in registration by 1991 is given in Table 1.1 based both on

*Table 1.1.* Projected change in cancer registration to 1991 in Scotland.

*All sites*: + 4–5%
*Specific sites*:

| *− 8–10%* | *Little change* | *+ 1–3%* | *+ 3–5%* | *+ 5–7%* |
|---|---|---|---|---|
| Cervix uteri | Ovary<br>Lymphatic system | Stomach | Breast<br>Leukaemia | Lung<br>Colon and rectum<br>Pancreas<br>Bladder<br>Prostate |

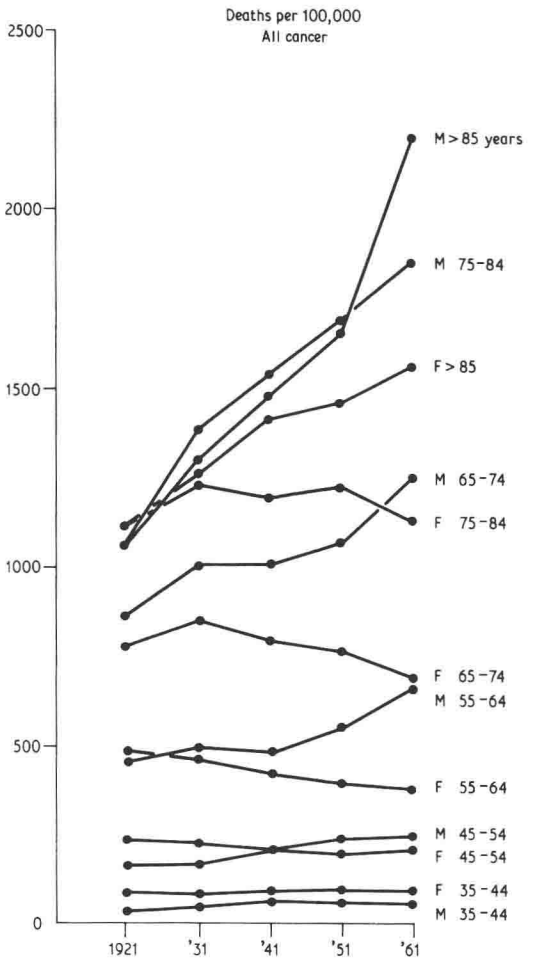


*Fig. 1.3* Cancer death rates in age groups in Scotland for men (M) and women (F).

recent trends and on population change.

Changing death rates in England and Wales make an interesting comparison with those from the USA given below. They show that the overall age-standardized death rate for all cancers is apparently not changing significantly, though there are very steep increases in death rates in both sexes for lung cancer, and reduction in cancer of the stomach, and cervix uteri. There has been a reduction in deaths from cancers of the colon and rectum also, possibly now levelling off, with similar increase in the pancreas, prostate and ovary. It should be stressed that these are age-corrected and that population changes, especially increase in the elderly, can still cause considerable overall increase (Fig. 1.4*a, b,* (Kemp and Toms, 1979)).

Changes in the USA are well summarized in the American Cancer Society's *Cancer Facts and Figures* (1978), they are similar to those seen in Britain, and likely in Europe (Figs. 1.4, 1.5*a, b*).

Estimates in 1978 of both incidence and death rates also make the position very clear (Figs 1.6, 1.7).

Estimates for other countries can similarly be made. In general, populations will often be increasing much more rapidly, such as in Egypt or Sri Lanka. Cancer incidence may at present be much lower but is likely to increase similarly. There are of course major site differences such as the increased prevalence of nasopharyngeal cancer in parts of China, the liver in parts of Africa, the stomach in Japan, the skin in Australia and New Zealand, and so on (see Table 1.7 below). Treatment itself may not need to be different.

### Diagnosis and referral

Many patients will come to the clinical oncologist with a ready-made diagnosis and more or less complete investigation or 'staging'. It is wise to be sceptical and iconoclastic; *no diagnosis should be taken for granted and this is more true the more eminent the physician or surgeon from whom the patient has come.*

The histology should be reviewed in all cases if pos-