Eur J Cancer, Vol. 26, No. 6, pp. 750–753, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

Feature Articles

Conformal Therapy

Diana M. Tait and Alan E. Nahum

INTRODUCTION

CONFORMAL THERAPY is external-beam radiotherapy in which the high-dose volume (i.e. the shape of the volume receiving at least 90% of the prescribed target dose) is made to conform closely to the target volume. In so doing, more normal tissue is excluded than in conventional radiotherapy so that it should be possible to increase the target dose without a parallel increase in toxicity. Although clinical dose–response data are scarce, this approach can be expected to result in better local control and, for certain tumours where local failure remains an important cause of death, improve survival [1]. With such a prospect, interest and activity in conformal therapy has accelerated as technology has made the method a possibility. However, there is an imbalance between the effort being put into technical development and that being directed at clinical evaluation.

TECHNICAL STATUS

What techniques have been used for conformal therapy and which ones offer the most promise? Conventional linear accelerators have, up to very recently, been able to deliver fixed rectangular fields only. This results in box-shaped high-dose volumes and tumours are anything but rectangular. One way of achieving more flexibility in the shape of the high-dose volume is to allow the gantry angle, the collimator jaws, and even the treatment couch to move during irradiation; this is known as dynamic therapy. The simplest form of dynamic therapy is rotation, which has been practised for many years. However, this technique can produce at best only cylindrical high-dose volumes. True dynamic therapy has been pursued vigorously at a few centres, notably at the Royal Free Hospital in London where a tracking cobalt unit [2] exploits couch movement and at the Joint Centre for Radiation Therapy (JCRT) where computer control has been extended to the four collimator jaws which all move independently. The JCRT team have reported spectacular examples of high-dose volumes conforming to very complicated target shapes with a slit-beam technique [3]. At both these centres the machines had to be modified in-house. Since the mid-1980s accelerators with the jaw and gantry movement under computer control have become commercially available. However, slow development of the accompanying software has so far prevented full exploitation of the possibilities offered by dynamic therapy.

The simplest way to shape radiation fields is to cast shielding blocks; this can be done in virtually every radiotherapy department. One of the most common examples is the shaped mantle field for the treatment of Hodgkin's lymphoma. There are now automatic block-cutting machines that make the process less time-consuming. However, shielding blocks are heavy and unwieldy; no practical radiotherapy technique would ever use them on more than three or four fields even though the sparing of normal tissue may be considerable [4]. An elegant solution is provided by the multileaf collimator, which consists of many (typically 80) narrow blades or leaves of thickness sufficient to transmit only a few per cent of the incident radiation [5]. The position of each leaf is controlled by a small motor and thus in principle an irregular field-outline can be achieved by remote control, removing the need to position heavy shielding blocks manually in the beam path. The major manufacturers of accelerators are currently designing such devices which will come into widespread use during the next few years. Several centres are working on software interfaces between three-dimensional treatment planning systems and the control systems of multileaf collimators (P.C. Williams, Christie Hospital, Manchester; R. Mohan, Memorial Sloan-Kettering Cancer Center, New York). The aim is to adjust the leaf positions automatically as a function of gantry angle, either statically or dynamically. Several Japanese centres have been using multileaf collimators with a fewer number of thicker leaves for several years [6].

Computer control of treatment machines opens up a range of possibilities because of the ability to deliver complex therapies without operator intervention. There is now no practical or technical reason why ten or even twenty fields, at different gantry angles, cannot be delivered under (remote) computer control. This greater flexibility of beam delivery has led to a revived interest in mathematical methods of planning the best treatment. Novel and interesting work by Brahme [7] and Webb [8] has shown that combining several beams with a non-uniform profile can result in dose distributions that conform to high-dose volumes of virtually any shape, including concave volumes that wrap around sensitive structures. The dose to such structures can be reduced to impressively low values. Advances are also being made in the quantification of normal tissue

Correspondence to D.M. Tait.
D.M. Tait is at the Department of Radiotherapy and Oncology, Royal Marsden Hospital, and A.E. Nahum is at the Joint Department of Physics, Institute of Cancer Research and Royal Marsden Hospital, Sutton, Surrey SM2 5PT, U.K.

complication probability via dose–volume histograms [9], which can be produced with modern three-dimensional planning systems based on computed tomography (CT) [10, 11]. These systems, which are a prerequisite for planning conformal therapy, are undergoing rapid development driven by the revolution in computer graphics and processing speed.

A treatment machine with enormous potential has been recently developed. The race-track microtron combines a multileaf collimator with a magnetically scanned electron beam with a maximum energy of 50 MeV [12]. Another novel feature is the use of helium in the sealed treatment head to reduce air-scattering of electrons, thereby making it possible to shape electron and photon beams with the multileaf collimator. Such a machine might make it practicable to deliver several deliberately non-uniform beams with software control of the scanning pattern, provided that the elementary beams are sufficiently narrow. These are indeed exciting times.

A conformal technique that is already in clinical use is stereotactic radiotherapy or radiosurgery: small lesions (either arterio-venous malformations or metastases) in the brain are irradiated by very many small circular fields, typically 20 or 30 mm in diameter. The patient's head is positioned precisely in the stereotactic frame that is used for the CT examination. This technique is now being successfully carried out on linear accelerators with several non-coplanar arcs [13]. Small spherical light-dose volumes surrounded by rapid dose fall-off have been achieved by several groups. Unfortunately, this almost perfect realization of conformal therapy is possible only for small lesions in a nearly spherical volume such as the head.

So far we have discussed high-energy photon radiation. In contrast to both photons and electrons, protons have a well-defined range in tissue and can thus provide a superior concentration or radiation dose in the tumour in certain situations [14]. However, high energies are required, e.g. the Harvard cyclotron laboratory accelerates protons to 160 MeV, giving a range of 15.9 cm in tissue. Approximately 200 MeV is required to reach deep-seated tumours. The extremely narrow Bragg Peak at the end of the particle range can be broadened to cover the extent of the tumour by beam modulation. Proton therapy is being investigated clinically at ten facilities worldwide. The first hospital-based proton-beam treatment centre, to be constructed at Loma Linda [15], will have a maximum energy of 250 MeV and one treatment room with a movable gantry enabling fields to be delivered at different angles.

Conformal therapy puts greater emphasis on the correct positioning of the patient. If the high-dose volume now conforms closely to the target volume, the consequences of any patient movement or set-up errors are potentially greater than those for the larger box-shaped volumes typical of conventional radiotherapy. The underdosing of even a small part of the tumour will lead unequivocally to local control failure. Much effort is going into the development of devices that use the therapy beam itself to image the patient on the treatment couch (so-called megavoltage imaging [16]). These devices are superior to conventional portal radiographs since they provide instant digital images that can be compared to both the simulator films and to radiographs digitally reconstructed from the CT data used to plan the treatment. Thus any discrepancies should be revealed. The clinical evaluation of the various technological approaches to this problem (such as one- and two-dimensional detector arrays of liquid-ionization chambers and photodiodes) is proceeding in parallel with the development of conformal therapy techniques.

CLINICAL EVALUTION

Against this background, how is the speciality ensuring that the technical innovations on offer can provide real improvement in radiotherapy in terms of effectiveness, safety and efficiency? Unfortunately, little is being done. As a result, although there are compelling arguments in favour of the use of conformal therapy, the impact on patients remains to be proven. It must be borne in mind by clinicians that, in the long term, conformal therapy might be self-defeating in that local control rates could worsen. This might occur, for example, if the margins around visible tumour were inadequate to account for the inherent limitations of the imaging technique. The problems of ensuring precision in delivery of treatment and positioning of patients could compound this error and result in underdosing of an area of tumour. It is therefore crucial that sytematic clinical investigation be done as soon as possible to prevent an experimental technique becoming an unwarranted new orthodoxy. If this were to happen, the credibility of radiotherapy as a clinical science would be seriously jeopardised and the future of the discipline compromised. It would be a shame if conformal therapy were to follow the course of other attempts to improve local control of radiation, such as the addition of hyperthermia, which remains of unproven value despite routine use in several centres.

Proper clinical evaluation of conformal therapy involves two major issues: the size of the real benefits, both short and long term, and the costs. In other words, can the available techniques spare sufficient normal tissue to influence the occurrence and/or severity of side-effects so that the target dose can be safely escalated and an improvement in local tumour control detected? In addition, can the situations in which conformal therapy proves to be inferior to conventional treatment be established and the contributing factors identified? Only when this analysis has been completed can the role of conformal therapy be defined and an assessment made of whether the investment in money and manpower is justified [17]. The present clinical work can be looked at under four headings.

Planning studies

These studies usually involve a comparison of the dose distribution for conformal and conventional therapy plans at a particular treatment site. Analysis of the data with, for example, dose–volume histograms allows some assessment of the extent to which normal tissues can be spared with a conformal technique and, by inference, the size of the potential clinical benefit can be estimated. For instance, in a series of patients with invasive bladder cancer, the use of a simple conformal technique reduced the volume of rectum irradiated to at least 90% of the isocentric dose by more than 30% in most patients [4]. A similar analysis has been done on patients with parotid tumours where, by normal tissue complication probability functions, it was estimated that for a tumour dose of 70 Gy there would be a reduction in the probability of bone necrosis from 8.4% without beam-blocking to 4.1% if customized blocks were to be used (R. Keus, Netherlands Cancer Institute, Amsterdam).

In an investigation with a head phantom, the optimum beam arrangement and target sizes for stereotactic radiotherapy were established from dose–volume distributions. This analysis showed that there was little advantage in using an arrangement of more than three non-coplanar arcs in terms of sparing of normal tissues to high dose irradiation (J.D. Graham, Royal Marsden Hospital, Sutton).

Studies of this sort compare radiotherapy techniques at any

treatment site. Their main value probably lies in indicating the treatment areas where conformal therapy might have the best chance of achieving its goal. However, this approach can only define a potential benefit and, of course, goes no way toward exploring the practical outcome of applying these techniques.

Phase I and II studies

Several centres have started single-arm dose-escalation studies to find what target dose a conformal technique will permit for the same level of normal tissue injury. At the Netherlands Cancer Institute, customized, partial transmission blocks are being used to deliver 1.6 Gy daily fractions to the whole pelvis with 2 Gy daily fractions to the prostate itself. With this technique, the prostate dose has been escalated to 70 Gy and it is planned to proceed 80 and then 85 Gy, depending on the normal tissue reaction at each dose level (H. Bartelink). A similar study is underway at the University of Michigan where, with customized blocks, 76 Gy is delivered to the prostate with plans to raise the dose to 80 Gy, provided the acute normal tissue reaction is acceptable at the lower dose level. This centre has also a dose escalation programme for adult brain tumours aiming to deliver 76 Gy, in 1.8 Gy daily fractions, to the conformal target volume.

As well as using dose-escalation, the Netherlands Cancer Institute is using the same sort of study to see to what extent overall treatment time can be shortened while keeping normal tissue reaction within tolerable limits. This is being done with a conformal technique for invasive bladder cancer.

In a study of intra-arterial 5-fluorouracil and focal radiotherapy in primary and metastatic liver tumours, dose–volume histograms are being used to fix the dose prescription (A.S. Lichter, University of Michigan, Ann Arbor). For example, depending on the percentage volume of normal liver spared, as defined by the 50% isodose, the prescribed dose is either 36, 48 or 66 Gy. This is, to our knowledge, the first study involving the use of a patient's individual dose–volume distribution to decide the target dose. It represents the start of an exciting development in cutomized radiotherapy planning.

It is encouraging to see conformal techniques being applied to common radiotherapy situations. However, as interesting and innovative as these studies are, they are open to the well-recognized criticisms of phase I and II studies, especially the likelihood of patient selection and the reliance on historical controls. Therefore this type of study can never establish the superiority of a conformal technique over the best available conventional therapy.

Phase III

The value of a conformal technique can only be established in a prospective randomized trial where a comparison with the best available conventional technique is made. Large patient numbers are required, which obviously focuses attention on the common radiotherapy treatment sites; even so, collaboration between centres may be necessary. Unfortunately, this sort of programme requires much time and effort to start and maintain and is slow to yield results.

At the Royal Marsden Hospital a programme of evaluation is underway in which sequential randomized trials have been designed to test the hypothesis that conformal therapy can improve local control rates. All patients receiving CT-planned pelvic irradiation are eligible for the programme. The first trial, in progress, is addressing the question of whether a conformal technique can bring about sufficient reduction in normal tissue irradiation to alter the frequency and/or severity of toxicity. The conformal technique involves using customized blocks designed from three-dimensional 'beam's eye view' planning, while in the conventional arm standard-shaped lead blocks are employed. All patients are planned by both methods before randomization to reduce bias that might enter the planning process. The initial acute toxicity is determined by self-assessment questionnaires. If a difference in toxicity is detected, in a second trial all patients will be treated by the conformal technique but the randomization will be to different dose levels.

There have not been any reports of prospective randomized trials designed to evaluate the worth of conformal therapy, and we are not aware of any other trials that are on-going.

Technical verification

Conformal therapy means more complex treatments which, in turn, means a greater chance of errors being made. Furthermore, errors in patient set-up and/or movement may have a greater consequence in terms of tumour control. Thus verification of both these aspects is important.

Megavoltage imaging attempts to address the patient position issue, but firm results have not yet emerged from the studies underway in Amsterdam, at the Royal Marsden and at several other centres. The Royal Free Hospital have, for many years, paid particular attention to the accuracy of automatic execution of the treatment machine prescription by performing a 'dummy run' before each treatment and comparing the prescribed machine movements with those actually carried out [2]. The JRCT performed two dose calculations, one for the patient and one for a phantom containing dosimeters. The phantom was irradiated and the measurements compared with the computed dose values before each irradiation [3]. Such approaches will have to be developed whenever conformal treatments are complex.

There is an enormous difference in the time and effort required for these approaches to the clinical evaluation of conformal therapy. The least demanding are the theoretical planning studies, the most demanding the randomized clinical trials, with technical verification and phase I/II studies being intermediate. However, to compensate, the value of the information derived is proportional to the effort involved.

CONCLUSION

We have the technology but how much do we need it? The relevant questions have not yet been answered and this situation is unlikely to change in the near future. Although the results of several planning and phase I/II studies are available, and more work is in progress, almost none of the crucial phase III trials are even at the planning stage. This situation needs to be rectified.

Is technology leading the science rather than vice versa? Computer-controlled linear accelerators equipped with multileaf collimators are now commercially available. This sharpens the dilemma for many radiotherapy departments. Will the extra cost of this technology buy better treatment for patients?

1. Suit HD, Becht J, Leong J *et al.* Potential for improvement in radiation therapy. *Int J Radiat Oncol Biol Phys* 1988, **14**, 777–786.
2. Davy T. Physical aspects of conformation therapy using computer-controlled tracking units. In: Orton CG, ed. *Progress in Medical Radiation Physics II*. New York, Plenum Press, 1985, 45–94.
3. Chin LM, Kijewski PK, Svensson GK, Chaffey JT, Levene MG, Bjarngard BE. A computer-controlled radiation therapy machine for pelvic and para-aortic nodal areas. *Int J Radiat Oncol Biol Phys* 1981, **7**, 61–70.
4. Tait DM, Nahum A, Southall C, Chow M, Yarnold JR. Benefits

expected from simple conformal radiotherapy in the treatment of pelvic tumours. *Radiother Oncol* 1988, **13**, 23–30.
5. Boesecke R, Doll J, Bauer B, Schlegel W, Pastyr O, Lorenz WJ. Treatment planning for conformation therapy using a multi-leaf collimator. *Strahlentherapie Onkologie* 1988, **164**, 151–154.
6. Matsuda T. Clinical significance of computer controlled conformation radiotherapy—from seven years experience. Proc. 8th ICCR, Toronto, 1984, 474–478.
7. Brahme A. Optimisation of stationary and moving beam radiation therapy techniques. *Radiother Oncol* 1988, **12**, 129–140.
8. Webb S. Optimisation of conformal radiotherapy dose distributions by simulated annealing. *Phys Med Biol* 1989, **34**, 1349–1370.
9. Kutcher GH, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. *Int J Radiat Oncol Biol Phys* 1989, **16**, 1623–1630.
10. Goitein M, Abrams M. Multi-dimensional treatment planning I(1). Delineation of anatomy. *Int J Radiat Oncol Biol Phys* 1983, **9**, 777–787.
11. Goitein M, Abrams M. Multi-dimensional treatment planning II. Beam's eye view, back projection and projection through CT sections. *Int J Radiat Oncol Biol Phys* 1983, **9**, 789–797.
12. Brahme A. Design principles and clinical possibilities with a new generation of radiation therapy equipment. *Acta Oncol* 1987, **26**, 403–412.
13. Podgorsak EB, Pike GB, Loivier A, Pla M, Souhami L. Radiosurgery with high-energy photon beams: a comparison among techniques. *Int J Radiat Oncol Biol Phys* 1989, **16**, 857–865.
14. Austin-Seymour M, Urie M, Munzenrider J *et al.* Considerations in fractionated proton radiation therapy: clinical potential and results. *Radiother Oncol* 1990, **17**, 29–35.
15. Slater JM, Diller DW, Archambeau JO. Development of a hospital-based proton beam treatment center. *Int J Radiat Oncol Biol Phys* 1988, **14**, 761–775.
16. van Herk M, Meertens H. A matrix ionisation chamber imaging device for on-line patient set-up verification during radiotherapy. *Radiother Oncol* 1988, **11**, 369–378.
17. Smith AR. Evaluation of new radiation oncology technology. *Int J Radiat Oncol Biol Phys* 1990, **18**, 701–703.

Eur J Cancer, Vol. 26, No. 6, pp. 753–755, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

Adjuvant Therapy for Colon and Rectal Cancer

NIH Consensus Development Conference

U. Metzger

INTRODUCTION

COLORECTAL CANCER is a major public health problem in Western industrialized countries. More than a quarter of a million people are newly affected each year. Over the past 30 years, the population-adjusted incidence has remained constant at 45–50 cases per 100,000, and thus the number of cases has increased due to population growth and increasing age. About three-quarters of patients with these cancers will have a primary surgical resection but, despite the high resectability rate and a general improvement in surgical therapy, nearly half of all patients with colorectal cancer die from metastatic tumour. Adjuvant therapy is administered in addition to resection. Options include chemotherapy, radiation therapy and immunotherapy. Over the past three decades, many studies have failed to demonstrate benefits from adjuvant therapy. Claims of efficacy have been viewed with scepticism. New data from several studies have demonstrated delays in recurrence and increases in survival for specific groups of patients.

Although the history of adjuvant therapy for colorectal cancer spans 30 years, only in the past 5–8 years have several trials yielded reproducible positive results. To evaluate this information and to resolve issues about adjuvant therapy for patients with colon and rectal cancer, the National Cancer Institute and the Office of Medical Applications of Research of the National Institutes of Health convened a consensus development conference on 16–18 April 1990. After presentations by experts and discussion by the audience, a panel considered the evidence and agreed on answers to the following key questions.

WHO IS AT RISK FOR RECURRENCE?

Clarification of the role of adjuvant therapy for colon and rectal cancer and maximization of the benefit of adjuvant regimens require identification of those individuals most likely to develop recurrent disease. Patients should undergo evaluation of the remainder of the large bowel for synchronous lesions. The presence of inflammatory bowel disease, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer or more subtle familial associations should be assessed. Abdominal computed tomography (CT) or ultrasound for liver metastases should be done and carcinoembryonic antigen (CEA) should be measured preoperatively.

At laparotomy, complete surgical exploration is mandatory. Colon lesions should be resected with contiguous and regional lymph nodes. Adequate radial margins must be obtained to minimize local recurrence in rectal lesions. The pathologist should specify the gross and microscopic extent of all surgical margins, the depth of penetration, the number of nodes removed, the number involved and whether the apical node (highest level) is positive. The disease should be defined by TNM stage [1]. Characteristics such as venous or lymphatic invasion, perineural invasion, histological subtype and grade should be documented.

There are several possible prognostic factors in defining subgroups of patients at risk for recurrence. Pathological stage is the most important determinant of risk of recurrence. The degree of penetration of the primary lesion, the lymph-node involvement, and the number of involved nodes are all significant independent risk factors. There are differences in the natural history and patterns of failure between colon and rectal cancer that require the testing of distinct adjuvant strategies for lesions in the two sites. Elevation of preoperative CEA (over 5 ng/ml) indicates increased risk for recurrence. Raised CEA correlates with stage and histology. Normal preoperative CEA does not obviate the need for adjuvant therapy in node-positive patients. However, elevated CEA may indicate a high-risk subset with node-negative colon cancer. It is premature to use certain cellular or molecular characteristics as standard determinants of

Correspondence to: U. Metzger, Department of Surgery, City Hospital Triemli, CH-8063 Zurich, Switzerland.