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Conformal Radiation Treatment: a Critical Appraisal

C.C. Ling and Z. Fuks

INTRODUCTION

IN THE last decade, advances in engineering and computer science have facilitated the implementation of high precision and high dose radiation treatment, the so-called 3-dimensional conformal radiotherapy (3DCRT). The advanced technology includes high-speed graphics workstations [1, 2], multileaf collimators [3, 4], computer-controlled treatment machines [5] and on-line portal imagers [6]. In conjunction, approaches and

algorithms have been developed, including beam's eye view [1, 2, 7 8], optimisation and inverse treatment planning [9–11], intensity modulation with multileaf (MLC) [12–14], image analysis and correlation [15, 16], and biophysical modeling of treatment results [17–20].

Based on the assumption that beams-eye view (BEV) planning with complete 3D volume-dose information, together with precise radiation delivery may minimise marginal misses, avoid in-field underdosage, and reduce the amount of irradiated normal tissue, dose-escalation studies have been initiated [21–24]. It is reasoned that the increased tumour dose and the decreased marginal misses will combine to enhance local control, and in turn decrease the incidence of metastasis stemming from tumour regrowth [22, 25–27]. While early results are promising, answers are unlikely to be definitive for some time [21, 24, 28]. However, potential problems exist which may moderate the theoretical benefit of 3DCRT. Primary among these are the uncertainty of the tumour extent, radiobiological resistance, and changes in tumour and organ location and shape, both during a treatment session and during the treatment course. Other challenges include the efficacious use of the abundant structure-specific dose-volume information and correlating it with clinical outcome, a better understanding of the dose-volume dependence of normal tissue complication, and the resolve to conduct phase III randomised study for demonstrating clinical efficacy [23, 26].

In this brief overview, we summarise the technical and physical developments and the clinical studies, and discuss the areas of difficulties and investigations. We suggest that improvements in our clinical and radiobiological knowledge is the key for the eventual success of this new modality.

PLANNING OF TREATMENT

The process of treatment design is the gatekeeper to improvements in radiotherapy. The new generation of planning systems with high-speed graphics workstations has provided more user-friendly interface, faster processors, and higher speed of image manipulation. However, the old-fashioned "planning by convention" philosophy and the inefficient trial-and-error process will persist for some time. In addition, the most time consuming task of outling the boundaries of critical structures and of the target, remains largely a tedious manual process.

Improvements in efficiency may be achieved by automating certain steps in the treatment planning process. An example is our "Autoplan", the semi-automated design of a six-field treatment for prostatic cancer [26]. Upon completion of the contours and selection of an isocentre, Autoplan automatically applies radiation ports in six gantry orientations, designs the field shape for each, calculates the dose distributions, displays isodose contours in three orthogonal planes and provides dose-volume histograms. The various parameters (e.g. gantry angles) and criteria (margins on aperture design) are user-selectable. This "class solution" approach can be used if the same planning steps can be applied repeatedly to patients with similar anatomical and tumour configurations.

The class solution approach, which permits semi-automated treatment design, fits nicely into the process of stepwise or sequential optimisation: finding a generic solution for each disease site, and further optimising for individual patients. For a specific disease site, complete optimisation is initially performed for a number of patients (say, 10) to identify the class solution, i.e. generic beam arrangement approximately appropriate for the majority of the test cases. Subsequently, for individual patients, one begins with the class solution and optimises user-selectable parameters. This strategy will work well for disease sites in which the geometry between the tumour and normal structure is similar among patients (e.g. prostate and nasopharynx), but will probably be ineffective for other sites (e.g. lung). Even for prostate, approximately 30% of T_2C and T_3 could not be treated by the class-solution until after adjuvant hormone administration. To identify the class solutions, a number of optimisation algorithms may be used. Two such methods are the simulated annealing technique and the BEV volumetric analysis with the so-called "Globe" display [1, 10, 11]. Given that this step of the optimisation is investigational, and not for routine clinical application, the speed and efficiency of the algorithm is not of crucial concern.

The so-called inverse method may further improve the conformality of the dose distribution [9, 29]. In addition, it is well suited to the class solution approach and can be integrated as one component of the process. The basic idea of the inverse method is that, given a number of incident beams, intensity modulation within each beam can be designed to generate the desired dose distribution. Thus, in the sequential optimisation process, after the class solution has been derived for a disease site, the inverse technique is invoked for individual patients, using the generic beam arrangements of the class solution as a starting point.

In part due to limitations of dose-based optimisation, the inverse method has recently been extended to include the specification of biological endpoints as criteria [30, 31]. Important for its success is the specification of an objective score function, comprised of appropriately weighted endpoints, upon which the optimisation process is based. It is likely that treatment plans designed using the inverse technique will be applied in clinical radiotherapy in the near future.

RADIATION DELIVERY

Computer-controlled radiation treatment machines with multileaf collimators are becoming increasingly available and most likely will become the standard of radiotherapy. Fully computerised machines (e.g. the Scandintronix MM50) can automatically set-up and deliver a sequence of fields in succession without human intervention [5, 32]. The multileaf collimation system, also under computer control, shapes each of the radiation fields in the sequence. These capabilities can increase the efficiency of treatment delivery and patient throughput, with improved or equal precision relative to that achieved with conventional units and cerrobend apertures [3, 33]. It is most likely that multileaf will become a standard feature of treatment machines in the near future.

Computer-controlled multileaf collimation also permits the modulation of radiation intensity across the treatment field, and thus holds the key to producing dose distribution designed by the inverse method. One approach is the so-called "move and shoot" technique: variable increments of radiation are successively delivered, in sequence with MLC movement to the specified positions [12]. Alternatively, intensity modulation can be achieved with dynamic multileaf collimator during radiation delivery [13, 14]. Whichever the method, assurance of radiation delivery according to plan is crucial, and is a subject of a current

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study. For this capability of 3DCRT as well, it is likely that implementation may occur in the near future.

ASSURANCE OF TREATMENT

The technical requirements of 3DCRT, discussed above, increase the overall complexity of the treatment. Although computer-aided automation can alleviate the quotidian chores in treatment delivery, the verification of treatment is more difficult. In this regard, the coming on-line of commercial on-line radiographic imaging devices is a welcome fortuitousness [6]. Ongoing developments will produce improved and clinically efficacious systems such that adequate verification of conformal radiotherapy can be achieved in real time.

In addition to treatment verification, the on-line imager is a convenient tool for quantifying treatment uncertainties stemming from anatomical changes, organ motion, and day-to-day set-up variations. In fact, treatment uncertainty is a subject under intensive investigation [34]. The derived results may lead to improved set-up procedures and provide patient-specific and population-averaged frequency distributions of set-up errors. The population-average data increases our understanding of the magnitude and effect of anatomical motions and alterations, and renders a more realistic estimation of the dosimetric characteristics of the treatment plan. The patient-specific information can be used retrospectively to generate the actually delivered radiation distribution for the entire treatment course. Such improved dosimetric information may prove useful in patient follow-up studies and in outcome evaluation.

CLINICAL STUDIES

A number of phase I dose escalation studies are in progress. These studies have so far been designed to assess toxicity rather than to demonstrate clinical efficacy of higher doses. In the treatment of prostate, 46 patients have been treated to a prescription dose of 81 Gy at the Memorial Sloan Kettering Cancer Center (New York, U.S.A.), with a median follow-up time of 19 months (range 6–25). Similarly, our colleagues at the University of Michigan (U.S.A.) are accruing patients at 80 Gy, following their experience of 31 stage C (T3) patients at 76 Gy [24, 28].

The dose escalation study of high-grade glioma at Ann Arbor (Michigan, U.S.A.) has accrued 20 patients at 80 Gy, with no severe complication, prompting a further increase to 86 Gy [28]. Similarly, they have performed dose escalation for liver tumours to 70 Gy, and for lung carcinoma to 84 Gy (6 patients) [28]. At the Memorial Sloan Kettering Cancer Center, our lung study involving stage II and III patients has accrued 35 cases at 70.2 Gy, and escalation to 75.6 Gy has recently been implemented.

Taken together, the preliminary results of these studies show that dose escalation is possible in the disease sites tested, and that the tolerance dose may even be higher than the highest dose currently used. However, once the tolerance dose has been identified, will clinical trials be conducted to definitively demonstrate that high-dose 3DCRT increases local control and cancer cure relative to conventional approaches? On the necessity and the nature of the clinical trials, opinions vary [23, 26]. To unequivocally prove a dose–response relationship, clinical studies are required, randomising patients into a high-dose arm and a lower dose control arm and using the same 3DCRT techniques. Alternatively, the randomisation should be between traditional treatment (at conventional dose and with non-3DCRT techniques) and high-dose 3DCRT, in order to show the increased efficacy of the latter. But given the ability to safely and more precisely deliver a higher dose, would it be ethical to conduct a randomised trial, whatever its nature? Conversely, in the light of the socio-economic aspects of high-technology medical costs, shouldn't the benefits of this modality be demonstrated before its acceptance and promulgation? In addition, clinical problems exist (e.g. treatment uncertainties, ambiguity in tumour extent, etc.) which might compromise the potential of 3DCRT. Considering all these factors, one may suggest that phase III trials may be needed but may not be ethically feasible, and if they were, considerable difficulties need to be overcome [23, 26].

CHALLENGES

The technical advances in anatomical imaging, plan optimisation, radiation delivery and treatment assurance perhaps have outpaced the clinical and biological aspects of radiation oncology. This section briefly discusses the key challenges for clinical radiotherapy, if the full technical capabilities of 3DCRT are to be meaningful in terms of clinical outcome.

Target volume delineation

For a number of disease sites (e.g. brain), the extent of the tumour and its microscopic extentions are not precisely known, due primarily to the limitation of diagnostic modalities in pinpointing small volumes of disease. A breakthrough in this area would be most significant, although there is nothing of great promise on the horizon.

In terms of uniformity in nomenclature, the definitions of GTV (gross target volume), CTV (clinical target volume) and PTV (planning target volume) established by ICRU50 are useful in establishing a common language and convention among investigators [35]. However, the criteria for delineating these volumes are not well-defined for many disease sites, leading to significant differences in the outlining of the various targets among institutions, and among physicians in the same institution [36]. Inconsistencies in the identification of these volumes among studies will introduce tremendous difficulties in comparing 3DCRT treatment outcome from different centres. It is most important to standardise the delineation of these volumes, and collaborative studies among institutions for this purpose are urged.

Analysis of clinical outcome and dose-volume data

Conformal therapy planning avails 3D volume-dose data (dose-volume histogram or DVH), which together with clinical data and knowledge of the biological basis of radiation-induced injury, may lead to a better understanding and potential circumvention of radiation-induced morbidity [37]. In the next decade, a substantial body of data is likely to emerge on the analysis of outcome based on organ-specific DVHs [38–41], and as the physicians accumulate experience, the challenge will be to relate dose-volume information to treatment results, and subsequently, in translating such clinical expertise into improved treatment. Such endeavours on normal tissue damage are already beginning, aided by the development of mathematical models [17–20]. Conversely, model development may also benefit from clinical data, and may in turn benefit clinical practice. In parallel, studies using animal systems are needed to provide complementary data on the nature of the target cells, the associated tissue architecture, and their influence on the partial volume effect of the different endpoints [37, 42].

Recognition and reduction of treatment uncertainty

The organ-specific DVHs derived from treatment planning are only approximations, as the volume-dose pattern will be affected by set-up uncertainties and organ motion during each treatment session, and by anatomical changes during the treatment course [43]. These uncertainties must be reduced as much as possible since otherwise the high precision attribute of 3DCRT would be compromised. In this regard, on-line correction of patient set-up is a possibility that is under investigation. The remaining uncertainties should be quantified, and when not exactly known, estimated and explicitly acknowledged as confidence limits of the DVH [43]. Without this recognition and quantification, treatment decision and outcome analysis based on DVH may engender inconsistencies.

Patient selection and predictive assay

In terms of cancer cure, high-dose 3DCRT will benefit only a subset of patients, those without occult metastasis and for whom a higher dose translates to a meaningful increase in tumour control probability. Given its high cost, it would be wasteful to apply 3DCRT to patients who have little chance of benefiting from the higher dose and increased precision. Techniques to identify patients with a high propensity for occult metastasis using molecular biological probes are being developed [22, 26, 44]. Distinct, but in parallel, are efforts to assess tumour radiosensitivity as predictive assays for individual patients [45–47]; tumours with either exquisite radiosensitivity or extreme radioresistance would not be optimal candidates for 3DCRT. Successes in both these areas would benefit clinical trials and enhance the usefulness of this modality.

SUMMARY

Significant technical advances have improved the precision of radiation treatment of human malignancies and permitted dose-escalation studies. However, a number of challenges remain, particularly in the clinical and radiobiological aspects of radiotherapy. Even with these deficiencies, it is likely that improved overall treatment results will be forthcoming with 3DCRT. Nevertheless, the cost-effectiveness of this approach needs to be assessed, based on the magnitude of the improvement in the treatment of various disease sites.

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Pergamon

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EORTC Report

The Present Role of Laparoscopy in Gynaecological Oncology; the EORTC Point of View

J.B. Trimbos and P. Zola

INTRODUCTION

THE HISTORY of laparoscopy began in Europe. Pioneers like Raoul Palmer developed relevant methods that made diagnostic laparoscopy feasible and safe. In the years after World War II, the pneumoperitoneum and the Trendelenburg position became an integral part of clinical laparoscopy.

For decades, gynaecological laparoscopy remained a diagnostic tool for infertility and pelvic pain and it was used for sterilisation. Recently, there has been a new interest in laparoscopic surgery (LS) by the general surgeons exploring laparoscopic gallbladder removal and colonic procedures. With this revival, new applications in fertility surgery and benign gynaecology have been developed and at present a new procedure in gynaecological laparoscopy seems to emerge every few months. Laparoscopic procedures have also been undertaken in the field of gynaecological oncology, but "the proliferation of endoscopic procedures seems haphazard, uncontrolled and dominated by a few endoscopic virtuosos, with more interest in the technical development of new instrumentation and capabilities for operative laparoscopy than in the methodical integration of this exciting technology into the discipline of gynaecology" [1]. This integration is difficult by its very nature because survival is ultimately at stake in oncology, and a jeopardised survival is an unrealistically high price for decreased morbidity.

The present situation is that laparoscopic procedures in gynaecological oncology are being conducted by pioneering experts in a few laparoscopy centres, and that gynaecological oncologists as a group are trying to define their position regarding the integrated role of laparoscopic surgery for oncology means.

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