Conformal Radiotherapy and Intensity-modulated Radiotherapy

Clinical Data

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Conformal radiotherapy (CRT) is based on three hypotheses: (i) a higher rate of local control can improve the survival rate; (ii) dose escalation can increase tumor control; and (iii) CRT allows the delivery of higher doses by decreasing the incidence of late effects. These postulates are now supported by several data. Three-dimensional conformal radiotherapy (3D-CRT) has markedly progressed since its introduction two decades ago. However, there are situations for which 3D-CRT cannot produce a satisfactory treatment plan because of complex target volume shapes or the close proximity of sensitive normal tissues. This is why intensity-modulated radiation therapy (IMRT) was introduced. Its aim is to overcome the limitations of 3D-CRT by adding modulators of beam intensity to beam shaping. IMRT can achieve nearly any dose distribution; however, the role of the planner remains crucial. CRT has been investigated mainly for prostate cancers and head and neck cancers. By and large, the clinical data, although still limited, seem to confirm the advantages of this type of radiotherapy. Dose escalation in prostate cancers improves the local control rate without increasing late effects and for this cancer site IMRT appears to be a significant advance over conventional 3D-CRT. In head and neck cancers the clinical data are still scarce but encouraging. CRT should be investigated in breast cancers with the aim of reducing the incidence of late effects. The available data underline the great potential for major progress in 3D-CRT and IMRT. The techniques are still costly and time consuming, nevertheless they merit investigation since their cost should decrease. Efforts should be concentrated on the specification of robust optimization criteria, taking into account clinical and radiobiological data.

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Progress in radiation therapy (RT) has been linked from its beginning to an increased selectivity of irradiation of the tumor and a decrease in the dose to the normal tissues. First attempts toward this aim were crossfire irradiation and increased x-ray depth dose ratios by means of filtration and higher kilovoltage. Later, x-rays of high energy were used and the advent of cobalt teletherapy and of megavoltage x-rays represented a great leap forward in the mid-1950s. In parallel, the greater accuracy of beam dosimetry and the introduction of isodose curves permitted full advantage to be taken of the lower attenuation of photon and electron beams.

Two major advances have been made over the past two decades. First, new techniques in medical imaging have greatly improved the three-dimensional (3D) delineation of the tumor. Secondly, 3D treatment planning and new technologies for beam delivery have made it possible to deliver a high radiation dose in a spatial distribution conforming to the tumor volume. This change has been driven in large part by the advances in computer hardware and software that have taken place.

The concept of three-dimensional conformal radiotherapy (3D-CRT) was introduced about two decades ago (1, 2). Its aim is to irradiate a target volume defined in a 3D imaging study, and hence to replace the 2D dose planning system with 3D treatment planning. The major change for the treatment planner is the task of determining target volumes and organs at risk on a slice-by-slice basis as opposed to drawing beam portals on a simulation radiograph. In conventional 3D-CRT, optimization of dose distribution is accomplished mainly by shaping the incident beam apertures so that the contour of the beams corresponds to the 'beam's eye' view of the target. The radiation beams are of uniform intensity across the field or modified by simple devices such as wedges or compensating filters. Multiple leaf collimators (MLC) can be used but they do not give any greater conformal dose distribution than customized blocks of low melting point alloys; however, they do save time and labor. The problem is that situations remain for which conventional 3D-CRT cannot produce a satisfactory treatment plan because of complex

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target volume shapes or close proximity of sensitive normal tissues. More recently, an advanced form of 3D-CRT, called intensity-modulated radiation therapy (IMRT), was developed. Its aim is to overcome these limitations by adding modulation of beam intensity to beam shaping. IMRT represented a second major paradigm shift which is introduced before conventional 3D-CRT is practised in a majority of RT departments. In this method, intensity modulators such as MLC, or other beam modifiers, divide the treatment beam into a set of small beamlets, the intensity of which can vary from 0 to 100% independent of all other beamlets. IMRT can achieve nearly any dose distribution, notably an abrupt decrease in the dose at the limit between the tumor volume and adjacent normal tissues in order to reduce both the volume of irradiated normal tissues and the dose delivered to them. The planner has to define the anatomical contours of the target volume, the desired dose and the degree of inhomogeneity which is acceptable in the tumor volume. Several target volumes can be distinguished (i.e. the primary tumor and the lymph nodes at risk of microscopic involvement). The total dose and the dose per session to each target volume can be modulated. The treatment planner introduces constraints, taking into account the tolerance of the various critical normal tissues. Simple IMRT has been optimized manually; however, in order to take full advantage of IMRT an automated optimization has to be carried out because of the potential number of beams involved and the large potential number of beamlets in each beam. 'Inverse treatment planning' is used for that purpose. In the traditional iterative forward planning approach, the physician defines the target volume, and various protocols are compared in order to select, on the basis of experience and by a process of trial and error, the one which gives a satisfactory dose distribution. In inverse treatment planning, the physician defines the target volume but also specifies the optimization criteria. Thereafter, an optimization search algorithm, according to the criteria which have been introduced in the program, generates the optimal location of ports, the shape of the ports, the relative beam weightings of the ports and beamlet weighting within a port. In this process, the optimization criteria therefore play a critical role. They should include the dose to the target volume and the degree of dose heterogeneity which is acceptable within it, as well as the following constraints: areas of avoidance, the delineation of the critical normal tissues, the proportion of tissues that may receive a dose higher than a given value, and the relative importance of the various structures. The system must be informed of the trade-off to be made when there is a conflict between the desired goals. The planning process for IMRT is labor intensive. Although most of it is performed by the computer, the role of the treatment planner remains important because the a priori constraints that are introduced in the program are often not sufficient to select the best plan in all clinical situations. Thus, at present, interaction between the planner and the system remains necessary.

This new method of radiotherapy was made possible by the decreasing cost and increasing power of computers, but is also the result of many technological advances. To take full advantage of IMRT, a computer-driven linear accelerator is required in order to use a large number of beams without increasing the duration of the session or the labor costs. Moreover, the intensity of the radiation beam and beamlets should be modulated during delivery, for example by means of computer-controlled MLC.

Thus IMRT can achieve very sophisticated dose distribution, but it requires an experienced team, up-to-date equipment and adequate quality-assurance programmers. It is currently time consuming and costly, but despite its increasing complexity its cost will gradually decrease and when fully automated may become lower than that of conventional radiotherapy.

The aim of this paper is to consider the therapeutic progress that has resulted from these techniques as well as their prospects. However, it should be emphasized that 3D-CRT and IMRT encompass several methods of varying sophistication and which are rapidly evolving. Therefore, many of the clinical data have been obtained with methods that are to some extent obsolete.

CRT raised three main questions:

Does a higher rate of local control of the primary tumor improve the survival rate?

During the 1970s and 1980s, when there was a rivalry between medical oncologists and radiation oncologists, it was claimed that improvements in RT, which achieve higher local control probabilities, will fail to yield gains in survival because ultimately the new local control patients will develop distant metastases. This thesis was mainly based on breast cancer patients. For these patients, it was claimed that postoperative therapy increased local control rates but failed to increase long-term survival. The hypothesis was therefore proposed that local failure represents a marker of the highly malignant nature of the tumor and that these patients had already established occult distant metastases at the time of initial treatment (3). The conclusion of many oncologists was therefore that emphasis should be placed on adjuvant chemotherapy (CT) or hormonal therapy and not on local control.

Two series of criticisms were made against this thesis. First, analysis of the natural history of human tumors, in particular of breast cancer, has shown that there is a clear relationship between the size of the primary tumor and the probability of distant dissemination. For each tumor subtype there is a critical volume below which distant dissemination very seldom occurs, and above which it becomes frequent (4). Moreover, it was also shown that for breast

tumors (5) residual tumors represent a nidus for distant dissemination. The same conclusion appears to be valid for prostate (6) or tumors of the upper respiratory and digestive tract (URDT) (7). Indeed, local recurrences are strongly associated with an excess of distant metastases and these additional metastases become detectable significantly later than in patients with tumors of the same type in whom the primary tumor has been locally controlled (5, 6, 8).

Secondly, other authorities, in particular Suit (9, 10), have shown that the probability of distant dissemination at the time of treatment is independent from the local response of the primary tumor. These clinical findings are consistent with laboratory studies which have not shown any correlation between radiation resistance and propensity to distant dissemination (10, 11). Moreover, the outcome of the disease depends on local control in human as well as in experimental tumors (5, 10, 11). For example, during the history of RT, better treatment planning systems, use of modern imaging for the delineation of the tumor, combination of surgery and RT, or even the use of surgery instead of radiation for radioresistant tumors, have improved survival rates (10). In T3 tumors of the bladder, Bloom et al. (12) reported that 5-year survival rates were 24% and 44% for 60 Gy and 40 Gy plus cystectomy, respectively. For stage II of the endometrium, Grisby et al. (13) reported that the disease-free survival rate was 54% and 77% for radiation alone and radiation combined with surgery, respectively. Furthermore, long-term disease-free survivors are obtained by salvage therapy for local failures after RT in a significant proportion of patients for many tumor categories (10). This shows that higher local control rates are often translated into higher survival rates (5, 8, 14–16).

Even in tumor types with high rates of metastatic dissemination, such as Ewing tumor (12) or small cell lung carcinoma (SCLC), improvement of local control increases survival. In a meta-analysis carried out on over 2140 patients with limited SCLC included in 13 trials, the long-term survival was slightly but significantly higher in patients treated by RT plus CT than in those treated by CT alone. The relative risk of death was reduced by 14% and the benefit in terms of survival at 3 years was $5.4 \pm 1.4\%$ (17). Conversely, in the first controlled clinical trial on conservative surgery for stage II breast cancer, in which the radiation dose was far too low by present standards, the incidence of both local recurrence and distant metastases was significantly increased (18). Moreover, meta-analyses carried out on head and neck tumors or the combination of RT with CT showed no evidence of a benefit in survival for adjuvant or neoadjuvant chemotherapy. The survival was significantly improved only when CT was delivered concomitantly with radiation or alternated with it. This observation strongly suggests that for these cancers the beneficial effect of CT is not to control occult distant metastases (which is the aim of adjuvant CT) but rather to improve local control (19).

Do higher doses increase tumor control and long-term survival?

Over the past 100 years of the history of radiotherapy, it has been observed that advances in techniques and equipment have permitted higher doses to be delivered to tumors and that these higher doses have resulted in higher tumor control rates (8, 10). A few prospective studies and a large number of retrospective analyses have documented an increase in the percentage of tumor control with the dose (20–26) and a relationship between dose and local control, in particular for prostate cancer (27). The cure probability is minimal below a threshold dose; it increases progressively with dose and may reach a value close to 100% for some tumors. In some clinical studies, there is no clear evidence of higher local control rates with higher doses (28, 29); however, other studies carried out on the same type of tumor show a relationship between dose and local control probability (30, 31). In fact, clinical response is influenced by several factors, in particular tumor bulk, pathological subtype and tumor cell radiosensitivity, and in retrospective studies the patients who are treated with different doses might not be comparable. Moreover, high doses were in the past often restricted to a smaller volume on account of the limit imposed by the tolerance of normal tissues on the dose and size of the irradiated volume.

The typical dose–response is a sigmoid-shaped curve which is characterized in experimental and clinical studies by the median tumor control dose 50 (TCD_{50}) and the median slope (26). Assuming that all the tumors have the same radiosensitivity, calculations show that the dose must be increased by approximately five sessions of 2 Gy to increase cure rates from 10% to 90%. However, the steepness of the curve relating the variation of tumor control probability with dose depends on the range of radiosensitivity among the tumors of a particular type. The slope can be estimated by the mean dose increment corresponding to a given increase in probability of local control. In the review by Moore et al. (22), the mean dose increment corresponding to a 34% increase in probability of local control was equal to 20% of the TCD but varied from 10 to 30%. Williams et al. (32) analyzed 26 series of patients in whom local control values of 40% and 60% were reported. In half of these studies the dose increment was about 12%, which is only slightly greater than the theoretical value for uniform sensitivities in all tumor cell populations. However, in several series the required dose increment was markedly higher, e.g. it was about 25% in Morrison's prospective study on bladder tumors (23). A likely interpretation is that such tumor series with a shallow slope comprise tumors of different radiosensitivities (33). When the control probability increases slowly with dose,

the dose increment required to obtain a high proportion of controls (85 or 90%) can be much higher than that controlling 60 or 70% of the tumors of that series and the value of the dose increment cannot be predicted.

Clinical tumor radiosensitivity is influenced by several factors such as intrinsic radiosensitivity of clonogenic tumor cells, hypoxia and better repair of potentially lethal damage due to a large proportion of quiescent cells. The radioresistance of large tumors is greater than that of small tumors and the increase is greater than that corresponding to a larger number of cells (26). Moreover, for large tumors the slope of the dose–effect relationship is shallower than for small ones, suggesting a greater variability in response from one tumor to another, which might be due to the presence of radioresistant subclones in some of the large tumors. It is therefore not surprising that for stage IV tumors some authors did not find a dose–effect relationship for local regional control (34) in tumor types for which a dose effect had been found for less advanced tumors (28). Thus multivariate analysis is recommended in retrospective studies. For example, for breast cancer (20) and nasopharyngeal carcinoma (30), multivariate analyses evidenced a dose–effect relationship for local control. However, such a relationship was not observed in other studies, possibly because of inaccuracy in the assessment of the dose effectively delivered to the tumor (28).

Does conformal radiotherapy allow the delivery of higher doses by decreasing the incidence of late effects?

The rate of normal tissue complications after radiotherapy is also dose dependent and the corresponding dose–response relationships are also usually sigmoid, but for a given dose the probability of complications depends also critically on the volume of irradiated normal tissues (26). For normal tissues, variations in radiosensitivity from one subject to another seem to be smaller than for tumors, but the occurrence of late effects strongly depends on the dose per session. Therefore, a reduction in the dose per session will reduce their incidence and severity.

The impact of dose per session and dose rate explains the relatively good tolerance of brachytherapy. The development of 3D-CRT has triggered quantitative studies relating the amount of normal tissue irradiated and the dose received by those tissues with the probability of late effects. However, quantitative studies were difficult without the evaluation of the dose received by each area of the normal tissue and the dose–volume relationship specified by histograms. Several new dosimetric parameters have been proposed which take into account the proportion of the tissue (e.g. the lung) which has been irradiated at various dose levels. Follow-up of the patients will help to select those parameters which best predict the sequelae of irradiation (35–38).

In several types of cancer, the beneficial effect of radiotherapy is partly or totally outweighed by its adverse effects on normal tissues which cause lethal complications. The reduction in the volume of normal tissue receiving high doses could therefore have a critical importance. Thus, a better dose distribution could diminish the late effects in normal tissues and improve the long-term overall survival. It was previously often felt that since tumor control doses are usually lower than those which cause serious normal tissue toxicity, the effect on normal tissues does not interfere with the probability of long-term survival as long as proper fractionation (dose by session) and protraction are used. Follow-up of patients whose primary tumor was cured by radiotherapy shows, however, that irradiation of some normal tissues, such as the heart and the lung, at doses that are apparently well tolerated could induce late effects which impair long-term survival (39).

CLINICAL DATA

During the past few years, treatments using 3D-CRT or IMRT have been investigated for a large number of tumor sites, including prostate cancer, head and neck cancer, and breast cancer. However, most studies to date have been either comparisons of dose distribution or non-randomized cohorts of patients treated by CRT, which are compared with historical control groups treated with conventional techniques. It is only for patients with prostate cancer that the preliminary data of controlled clinical trials are available.

3D-CRT has two main goals: the increase of local control and the reduction of side effects.

Increase of local control

Dose escalation and local control for prostate cancer. Since Del Regato's paper in 1979 (40) and the seminal work of Bagshaw (41), radiotherapy of prostate cancer has become the treatment of choice when the disease is localized. However, when conventional radiotherapeutic techniques are used, the proximity of the prostate to the rectum and the bladder has limited the ability to deliver to the whole prostate doses higher than 70 Gy. While this dose is effective in most prostate cancers, it was recognized that a significant proportion of tumors is not controlled. Several hypotheses were put forward to explain these failures: underdosage of some regions of the tumor due to inadequate definition of the target volume, insufficient accuracy of treatment planning, or errors in the calculation of dose distribution or the set-up of the patient. However, the most likely explanation is that 70 Gy is insufficient to sterilize some prostate cancers, either due to the relative radioresistance of some tumor cancerous clones or to local conditions such as poor vascularization and local hypoxia. Since the fear of severe side effects made it difficult to deliver doses higher than 70 Gy to the entire tumor with

conventional beam therapy, it was logical to use 3D-CRT for investigating dose escalation.

Several groups undertook such studies in the late 1980s and early 1990s (42–48). The aims of the studies were: to improve local control by dose escalation, and/or to reduce the incidence or the severity of side effects. Feasibility studies were carried out to investigate patient positioning accuracy and organ movement (49–56), precision of tumor delineation (48) and cost (44). New techniques were developed in order to improve treatment accuracy and quality assurance.

The groups of the Memorial Hospital in New York and the Royal Marsden in London have recently reported and updated results of their controlled clinical studies, and they are summarized briefly here. In London (56, 57), the trial compared 114 patients treated with conformal therapy with 114 treated with conventional therapy. A dose of 64 Gy was delivered in daily 2 Gy fractions. Baseline characteristics of the two groups were similar in terms of age, tumor stage and grade. Significantly fewer men developed radiation-induced proctitis and bleeding in the conformal group than in the conventional group (37% vs. 56% RTOG grade 1, $p = 0.004$; and 5% vs. 15% RTOG grade 2, $p = 0.01$). There were no differences between groups in the bladder function after treatment or any difference in local tumor control. The authors concluded that conformal techniques are appropriate and they will use these data as the basis for dose-escalation studies to improve local control.

At Memorial, New York, a first series of patients was treated using a six-field coplanar conformal technique (3D-CRT) with daily fractions of 1.8 Gy (58–60). A first group of patients received usual dose levels of 65 and 70 Gy to test for acute tolerance and late complications at these doses with the 3D-CRT approach. Subsequently, a dose-escalation program was implemented, beginning at an initial level of 75.6 Gy (April 1991 to May 1992) for patients with T2b–T3. The treatment volume included the entire prostate and seminal vesicles but did not encompass the regional lymph nodes. Neoadjuvant androgen deprivation therapy was given to patients with exceptionally large volume prostate glands to decrease the target volume for irradiation in order to reduce side effects. When no late toxicity was observed at 75.6 Gy after a minimum follow-up, this dose was delivered to patients with lower stage disease. Concomitantly, the dose for patients with T2b–T3 was escalated to 81 Gy (October 1992 to December 1993). A restriction imposed in designing the treatment plan for 81 Gy limited the rectal dose to no more than 75.6 Gy. To meet this requirement, the last 9 Gy was delivered using a separate multifield coplanar arrangement with the rectum completely blocked in each field. Nevertheless, the occurrence of a grade 2 rectal bleeding toxicity was markedly increased (17% of the patients instead of 6% for lower doses) and the grade 2 urinary toxicity slightly increased (13% vs. 8%).

These data suggested the usefulness of developing IMRT for prostate cancer in order to improve the conformality relative to the tumor and reduce the side effects in normal tissues. The intensity profiles were determined for each field, and beams of non-uniform intensities were generated by multileaf dynamic collimation. Six such fields were combined isocentrically. Not only was the high dose distribution more tightly confined to the prostate but also the dose to normal tissues was given in smaller dose fractions. Twenty randomly selected patients were planned concomitantly with 3D-CRT and IMRT and compared for various dosimetric parameters. Analysis of the dose volume histograms indicated that while $98 \pm 2\%$ of the clinical target volume would receive 81 Gy with IMRT, only $95 \pm 2\%$ would receive the same dose with conventional 3D-CRT. With regard to the rectal wall, $9 \pm 3\%$ of it would receive 75 Gy with the IMRT plan, whereas $14 \pm 3\%$ would be exposed to this dose with 3D-CRT (59–61). This improvement is promising but it remains to be seen whether these differences are of clinical significance.

A total of 1050 prostate patients was treated by 3D-CRT between 1988 and 1998 with doses ranging from 64.8 Gy to 70.2, 75.6, 81 and 86.4 Gy. The follow-up of patients with 86.4 Gy is too short, but for the others the data show that both the clinical response and the long-term tumor control are dose dependent. The incidence of an initial complete response (prostate-specific antigen (PSA) decreasing to ≤ 1 ng/ml) was 90% in patients receiving 75.6 Gy or 81 Gy compared with 76 and 56% for those treated with 70.2 and 64.8 Gy, respectively ($p < 0.001$). The 5-year actuarial PSA relapse-free survival for patients with intermediate or unfavorable prognosis receiving ≥ 75.6 Gy was 78 and 53, respectively, compared with 54 and 17% for the patients treated with ≤ 70.2 Gy ($p < 0.05$). Biopsies carried out at 2.5 years after RT found evidence of residual tumor in only 4% of patients receiving 81 Gy, compared with 27, 36 and 57% for those receiving 75.6, 70.2 and 64.8 Gy, respectively ($p < 0.05$). Thus, these data show that an increase in dose is possible with CRT and that it should improve local control. They also suggest that it can reduce the incidence of acute and late effects, although a longer follow-up would be of great interest in confirming this point (58–61).

Two other groups in the USA have reported phase I and II dose-escalation studies which delivered doses up to 80 Gy (43, 62).

In breast cancer, it has been clearly shown that residual tissue and local recurrence are a nidus for distant dissemination (5). It is probable that this statement is also valid for prostate cancer (6, 43) and it can be expected that the increase in local control will reduce the incidence of distant metastatic dissemination.

Most data, and in particular those of the Memorial Hospital, support the notion that rectal and bladder toxicities after radiotherapy exhibit both a dose and a volume

effect (57, 60–64). The combined rates of acute grade 1 and 2 rectal toxicities and the incidence of late grade 2 rectal bleeding were significantly lower among the IMRT patients (the 2-year actuarial risk of grade 2 bleeding was 2% instead of 10% in 3D-CRT patients). This was probably because, as discussed above, IMRT resulted in a significantly lower rectal wall volume exposed to 75 Gy (61). This volume effect is consistent with the data reported by the Royal Marsden discussed above (57). In a randomized study of 150 patients, Pollack et al. (65, 66) showed no differences in acute toxic effect between conformal therapy to 76 Gy and conventional techniques to 68 Gy, and the preliminary analysis of late toxic effects has shown a low and similar frequency of complications in both groups. Lee et al. (64) reported that the addition of rectal shielding for the last 10 Gy in patients treated with 3D-CRT to ≥ 74 Gy reduced the actuarial incidence of grade 2 and 3 rectal toxicities from 18 to 9% ($p = 0.003$). Boersma et al. (63) did not find any correlation between rectal volume and grade 2 bleeding in 130 prostate cancer patients; however, they reported a higher incidence of severe rectal bleeding among patients with more than 40% of the rectal volume receiving more than 65 Gy ($p = 0.02$), a rectal volume of 30% receiving at least 70 Gy ($p = 0.008$), or a rectal volume of 5% receiving more than 75 Gy ($p = 0.02$). The impact of the rectal volume on the incidence of acute and late effects is encouraging since CRT offers a possibility for reducing it (67).

In summary, the data reported for prostate cancer seem to confirm the beneficial effect of the paradigm of CRT: a higher dose to the tumor, and a lower dose to a smaller volume of normal tissue. However, the data also show that a large number of prerequisites has to be studied and solved before attempting dose escalation with 3D-CRT or IMRT: the assessment of combined errors of positioning variability (68) and organ motion, and the size of the margin of safety around the tumor volume. Moreover, the data show that even with IMRT, increasing the tumor dose without increasing the incidence of complications is a difficult endeavor and requires sophisticated techniques. Even with these it is difficult to avoid heterogeneity of the dose to the tumor and the impact of these inhomogeneities on the probability of tumor control is not yet known. Great caution is therefore needed before such techniques could be advocated in all radiotherapy departments. Dose escalation must be slow and cautious since there is no parallelism between acute and late effects (57). Moreover, the patients who would benefit from such techniques will have to be selected in light of the results of ongoing studies. Thus far, higher doses have not affected PSA outcome in the favorable risk group, but have been beneficial for tumors in intermediate and unfavorable risk patients. However, in unfavorable groups the incidence of metastatic disease remains relatively high, probably because distant dissemination had occurred prior to treatment in most of them. Thus, these sophisticated methods will achieve better survival mainly in patients belonging to the intermediate group, and it can be hoped that the ongoing studies will better identify the subsets of patients who will benefit from the them.

Head and neck cancers. Dose escalation by the use of 3D-CRT or IMRT deserves to be studied for several other cancer sites in which the rate of tumor control and survival could be improved by the delivery of higher doses to patients with radioresistant tumors. Long ago, Fletcher and others showed that, for these cancers, increasing the dose can increase the probability of local control and that large tumors require high doses (69). Moreover, data strongly suggest that locoregional control has an impact on the occurrence of distant dissemination (7, 14). Preliminary studies have been reported for endometrial and pelvic cancers, and head and neck cancers (30). For these cancer sites, IMRT will improve the dose distribution (70, 71) but statistical data demonstrating a clinical benefit are still scarce.

Head and neck tumors will be used here as an example for illustrating the problems that must be overcome during the development of these new techniques. 3D-CRT and, even better, IMRT techniques are well matched to the complexity of head and neck cancer management. Doses higher than 70 Gy are commonly required for tumor control and aggressive radiotherapy can be planned because imaging techniques can identify accurately the target volume and the normal structures. The tolerance to the dose to neighboring normal tissues should be taken into account. That of the spinal cord is well known. However, other normal tissues (salivary glands, brain stem, optic chiasm, larynx, auditory structure) should also be spared and a dose limit must be assigned to each of them. Parotid gland volume may have nodal penetration and its avoidance requires careful attention. It already appears that conformal therapy allows high doses to the whole of the target volume or the target volumes, and offers new potentialities for dose escalation to the highest risk region because the degree of normal tissue sparing is greater than is possible with conventional radiotherapy. Thus. these new methods can both increase local control, even for patients who have experienced local recurrence, and/or improve quality of life by reducing side effects.

However, several problems need to be solved. The reproducibility of patient fixation requires reliable immobilization systems because a high precision is needed (72). The accuracy of dose delivery compared with planned dose must be checked since tissue heterogeneity and air cavities can introduce dosimetric errors. Studies on phantoms are necessary but not sufficient (73). IMRT has allowed the introduction of new concepts such as simultaneous modulated accelerated radiation therapy (SMART), with the aim of shortening the overall treatment time in order to overcome accelerated repopulation and to increase the

efficacy on tumors by increasing the dose per fraction (2.4 Gy). This is achieved while delivering a conventional dose per fraction to normal tissue at risk for microscopic disease (2 Gy per fraction) and significantly lower doses per fraction to adjacent normal tissue (< 2 Gy per fraction to the spinal cord) or to the parotid gland (74). IMRT has a great potential for sparing the parotid and therefore avoiding or reducing the incidence of xerostomia (74, 75). For head and neck tumors, IMRT appears to achieve more satisfactory dose distribution than 3D-CRT (75). The Baylor College Group has reported encouraging results (73). Recently, the Mallinckrodt Institute of Radiology has described its technique (76) and has reported the preliminary results of 17 patients with head and neck tumors (including seven nasopharyngeal carcinomas, seven oropharyngeal carcinomas and one supraglottic carcinoma). Only about 3% of the target volume received less than 95% of the prescribed dose, whereas only 30% of the parotid gland volume received more than 30 Gy (77). Acute side effects were comparable to those of patients treated with conventional beam arrangements during that period, although higher control rates and lower late effects can be expected.

Full advantage of IMRT for head and neck tumors will be obtained only when the anatomy of the pathways of disease spread (by contiguity in the fascial spaces and along lymphatic and perineural spaces) is known. They must be taken into account in the delineation of the target volume and of the areas at risk of subclinical disease involvement. This goal requires a better understanding of the natural history of the disease as a function of its site size and histological characteristics. Increasing the dose to the ipsilateral high jugular nodes (near the base of the skull) and the retropharyngeal nodes in patients at risk has been suggested (78).

Nasopharyngeal carcinoma appears to be a good candidate for this new technique in view of the severity of the lesions which could be caused to the adjacent normal critical tissues (28). Preliminary data show that IMRT provides improved tumor target coverage with excellent local control and significant sparing of normal tissues. It may represent a major advance in the treatment of these lesions (79).

Pediatric brain and head and neck tumors. Brain tumors are logically the best site for 3D-CRT because the tumor movement is minimum as it is encased in the cranium. IMRT can be used as a boost or preferably for full course, with the aim of modulating the dose per session, i.e. differential daily fraction sizes to different targets. It may enable dose escalation. Sixty-one children with brain and head and neck tumors have been irradiated at Baylor (80) with encouraging results; however, more clinical data are needed to confirm the potential promise.

Brain tumors and meningiomas. A few studies have explored the use of conformal therapy for meningiomas (81). Attempts at dose escalation for brain tumors are ongoing (82).

Reduction of the late effects of radiation therapy

Besides dose escalation and an increase in tumor control, the other potential advantage of CRT is a diminution in the incidence of late effects.

Analysis of long-term survival of patients whose cancer has been cured demonstrated the impact of treatment toxic effects even for relatively moderate doses when they are delivered to large volumes of critical normal tissues. Two examples are presented to illustrate this point: cancer of the breast and Hodgkin's disease.

Cancer of the breast. A recent overview of the favorable and unfavorable effect on long-term survival of radiotherapy has recently been carried out on nearly 20000 patients based on the analysis of 40 controlled clinical trials (39). It clearly demonstrated that breast cancer mortality is reduced in patients treated by radiotherapy compared with control groups who have not been irradiated. The incidence of local recurrence is markedly reduced in irradiated patients, from 27.4% in control patients to 8.9% in irradiated patients at 10-year follow-up and from 30.5% to 10.6% at 20-year follow-up. Cancer mortality has been assessed by the difference between the total mortality rate minus non-breast cancer mortality. The improvement is modest but highly significant ($2p = 0.0001$). Specific survival at 10 years is 63.8% compared with 60.9% in control non-irradiated patients, and at 20 years is 53.7% and 49.2, respectively. The benefit from RT increases with the duration of the follow-up and at 20 years is about 4.5%. Unfortunately, non-breast cancer mortality is also increased. At a 10-year follow-up survival is 90.1% and 88.5% for control patients and irradiated patients, respectively, and at 20 years 69.0 and 73.7%, respectively. Thus, in this meta-analysis the increase of mortality due to toxic effects of RT nearly outweighs its beneficial effects. Analysis of the data shows that more than half of the excess mortality is due to cardiovascular disease and to a smaller extent to respiratory disease. Secondary cancers account for about 20% of the excess mortality (39).

The main question, therefore, is whether with better techniques the gain could be kept while the detriment could be reduced. In fact, this is what is observed in some series of patients, in particular in the most recent trials (83, 84) in which great efforts have been made to limit cardiac and lung irradiation.

Moreover, non-breast cancer mortality is higher in patients treated on the internal mammary chain to a dose up to 40 Gy than in those who received 40–55 Gy (39). It could be expected that in the latter series RT was more carefully performed, which supports the hypothesis that a carefully planned RT could reduce the late side effects. Similarly, the annual death rate in trials that started after 1975 or were large trials, in which more than 1000 patients were accrued, is smaller than in older or smaller series (39).

These data (39) support the concept that a reduction in the dose to the normal tissue and a reduction in the volume of the irradiated lung or heart might further diminish non-breast cancer mortality. There is no direct evidence in favor of this thesis but attempts have been made to improve dose distribution in the breast and the thoracic wall by the use of modulators. More limited irradiation of normal tissues also seems achievable during irradiation of the internal mammary chain. It has been shown that intensity modulation with a standard tangential beam arrangement can significantly reduce the dose to the coronary arteries, ipsilateral lung, contralateral breast and surrounding soft tissues (85, 86). It remains to be seen whether these dosimetric improvements will lead to better outcome.

Hodgkin's disease

Hodgkin's disease (HD) was formerly a fatal malignancy. Currently, more than three-quarters of all patients are cured of their disease. Since the treatment is often aggressive, in particular in patients who have relapsed and have been rescued by polychemotherapy, it was of interest to follow them over a long period. These studies (87–91) have shown that even when they are cured (survival without evidence of disease at 10 years or more after last treatment), their survival rates are significantly lower than in an age-matched general population. The main causes of death (secondary malignancies, cardiac disease, pulmonary late effects and infections) may be attributable to treatment and often exceed mortality as a result of HD. However, a part of this excess mortality may be due to the genetic predisposition of patients with HD or to the immunodeficiency associated with the disease. Nevertheless, it appears that the late effects of intervention (such as staging laparotomy) and treatment (radiotherapy, polychemotherapy) contribute significantly to the overall mortality.

Cardiac mortality is the third cause of premature death contributing to approximately 10–15% of all causes of mortality (90–94). Besides acute myocardial infarction, secondary to coronary disease, other cardiac complications have been reported, including pericarditis, pericardial effusions and congestive heart failure (95–97). Some data suggest that improvement in radiotherapy techniques may reduce the incidence of cardiac mortality. It is therefore justifiable to search for techniques of mediastinal irradiation in which the volume of the heart irradiated and the dose to the heart could be significantly reduced. This would be particularly important for patients older than 50 years of age. Thus, it might be advisable to protect a large part of the heart during the irradiation of mediastinal adenopathy. 3D-CRT may contribute to this aim. Similarly, a limitation of lung radiation field size, especially when radiotherapy is given in conjunction with CT, might be beneficial.

DISCUSSION AND CONCLUSION

In radiotherapy, as in other medical fields, each new technical advance solves many problems but raises new ones (98–101). In the 1950s, the introduction of telecobalt and megavoltage suppressed the limitations associated with acute skin effects, but made a much more precise determination of dose distribution necessary because the radiotherapist could no longer rely on skin reaction, which with 200 kV x-rays had been a fairly reliable indicator of normal tissue tolerance. 3D-CRT and IMRT already appear to be a highly significant development in radiotherapy and certainly have a great potential for major progress. They have opened a new chapter in radiation oncology for several tumor sites (102). However, it should be recognized that currently IMRT is costly and time consuming. It will require great efforts before it is perfected. Nevertheless, in the long run there is no doubt that systems integrating 3D planning and treatment delivery systems will become faster, more accurate and easier to use. Thus, even from an economic point of view, they will have many advantages: they will bring higher productivity and, for some tumors, lower costs (98–100).

Of course, some radiotherapy centers may, at this time, choose a 'wait and see' policy because there exist so many IMRT methods and commercial systems that a selection is difficult (100, 101). For some tumor sites the 'step and shoot' technique, in which a number of fixed beams is added, might be preferable. In others it might be dynamic methods, such as the 'sliding window' technique, in which the beam-shaping devices move during beam delivery, or fan beams, tomotherapy, scanned photon or electron beams, or therapy with the Peacock systems (100, 101). It is not the purpose of this paper to discuss their respective advantages and drawbacks, which have been analysed in several review papers (100–102). One thing is certain: we are only at the first generation of IMRT systems. Progress in instrumentation is needed. Intensity modulators must have finer resolution, less leakage and increased field size; they must be fully integrated in terms of both hardware and software in the acceleration. Rotational or fixed delivery should be available. Nevertheless, we feel that a 'wait and see' policy would be a mistake for the advanced centers. The great lesson learned from the 1950s when telecobalt units and betatron were introduced is that it is those who pioneered this new field who made the most useful contributions to its progress and who obtained the best results. This is not surprising since they were able at an early stage to acknowledge its limitations and deal with them, and appreciate its possibilities, which were then rapidly exploited. The same will probably be true for 3D technologies.

Of course, it would be preferable to have more clinical data and we are awaiting with great interest the results of the ongoing clinical trials. However, progress will be slow

and gradual, and thus, even if some of the results are disappointing these efforts must be pursued because the scientific bases of CRT are as sound as were those of the megavoltage endeavor. It must be recalled that with high energy it took more than a decade to prove rigorously the clinical superiority of this new type of radiotherapy. Fortunately, few radiotherapy centers waited that long before adopting the new technique. Moreover, it should be realized that since controlled clinical trials require a large number of patients, when the results are available the techniques that were used may already be obsolete since technical progress is rapid. Carefully planned phase II studies may be more informative at this stage; this is the strategy that has been chosen at Memorial Hospital for prostate cancer (59).

Progress must be made in several directions (98). First, a great accuracy in dose distribution and beam delivery would be meaningless without a parallel effort in the delineation of the tumor volume (103) and of the target volume which is presumed to include subclinical disease. The complementary information provided by magnetic resonance and position emission tomography must be incorporated. The width of the margin of safety that should surround the contour of the tumor should take into account the clinical and biological characteristics of the tumor. The pathways of disease spread and the areas at risk should be better known, and displays of small anatomical details and nodal chains should be available for the treatment planner (78, 102, 103). Secondly, one should also account for organ movement (54, 55), and the errors related to patient set-up and movement should be reduced (55, 72, 104). Thirdly, another important research goal is to compute dose distribution accurately in all situations, taking into account tissue heterogeneity (98, 105).

Treatment plan optimization is another research area (98, 100, 106). Algorithms need to be developed in order to increase the selectivity of the irradiation (96) and overcome the present limitations of the techniques (107–109). As already discussed, there are two components in this optimization.

1. Specification of robust optimization criteria that satisfy a large proportion of clinicians, and their mathematical expression. A score should include figures of merit and sets of constraints. Ideally, the algorithm should be able to rank a set of rival treatment plans without the involvement of the treatment planner. However, it should be recognized that there is still a long way to go before reaching this goal. The planning process should provide advanced tools for an easier definition of targets and structures. For each target the planner should be able easily to enter minimum and maximum doses, a minimal and maximal dose per session and the per cent volume that is allowed to be underdosed. For critical structures, the planner should specify what percentage of the structures can receive a given dose, which implies that he or she knows above what dose to what volume the function is compromised.
2. Progress in optimization algorithms, which are used for the selection of the treatment plan. A variety of optimization search algorithms has been investigated. Research should continue, but with the rapid increase in computer power, this problem should not be too difficult to solve (98). A score function should in the future assess how well the proposed plan compares to the desired result for each target volume.

Fourthly, treatment verification imaging and quality assurance of this new sophisticated radiotherapy technique need to be developed and criteria for quality assurance should be defined.

Finally, as already mentioned, IMRT provides a unique opportunity to introduce more radiobiology into radiotherapy by the modulation of the dose per session in the various tissues. This problem is fully discussed in the papers by Brahme and Withers in this issue. However, the paramount importance of clinical investigation must be emphasized here. There have been moments in the history of radiotherapy when progress is associated with technical advances and others in which progress depends on the careful study of the patients treated with these new techniques. CRT is entering this second phase, although the first one is not yet completed. Therefore, all pertinent clinical information must be collected. The first goal should be to assess the improvement in local control, even if it is modest, associated with dose escalation (110) and the clinical consequences of tumor dose inhomogeneities, both lower doses and hot spots. The concept of a uniform tumor dose should probably be abandoned. In many instances, the dose should be higher to the bulk of the tumor and lower to regions at risk of microscopic involvement. There are great variations in radiosensitivity among tumors located in the same site and of similar pathological types. The factors associated with these variations should be investigated in order to modulate the dose accordingly. Is lack of local control associated with hypoxia, or with differences in the proliferative rate? These parameters will, in the future, be explored by new functional imaging techniques. Similarly, the impact should be estimated of the biological characteristics of the tumor on the width of the safety margin around the tumor limit as defined by the imaging technique. From a radiobiological point of view, it will be of great importance to assess the relationship between the late effects and two variables that can now be measured: the volume of normal tissue irradiated and the distribution of dose per session. Technical progress enables us to achieve a large array of dose distributions, but it is the critical analysis of the clinical data that will determine the most appropriate criteria that the algorithm has to use

for selecting the optimal protocol. Thus, progress in CRT requires the collection of data which will enable the optimization of dose distribution on the basis of radiobiological objective functions (109, 111). The emphasis in the next few years may move from controlled clinical trials to the setting up of the well-organized databases which are required to provide the information necessary for developing such functions.

IMRT is not an end, but a means. It has paved the way but only clinical research will be able to take full advantage of it. In the meantime, we need to identify those tumor sites for which 3D-CRT and IMRT bring significant clinical progress and are advisable or mandatory, either because they enable the delivery of higher tumor doses without increasing the incidence of late effects or because they reduce the sequelae of treatment. These endeavors will require decades of multicenter cooperative studies but, in view of the importance of the goal, these efforts are highly justified. We have never been nearer to the old dream of the first radiotherapists: irradiating the entire tumor and only the tumor, but this is not the end of a process, this is the beginning of a new era.

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