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Original article

Intensity modulated radiation therapy (IMRT) in the radiotherapy treatment of colo-rectal cancer: the influence of profile smoothing on the efficiency of delivery

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Abstract

Small bowel toxicity due to radiotherapy treatment of rectal cancer is common. The potential use of intensity modulated radiation therapy (IMRT) to reduce the volume of small bowel irradiated during radiation therapy (RT) for cancer has previously been reported. However, IMRT treatment implementation is relatively difficult for these patients. The PTV is large and has a concave shape, with the small bowel in very close proximity. Therefore, the intensity profile calculated by an inverse planning engine could be highly modulated and complicated to deliver.

In this study, two methods were used to optimise IMRT plans for rectal cancer patients. Scatter contribution when backprojecting dose values to fluence values and a smoothing function were only implemented in the optimisation searching of one method. A common arrangement of five beams, each separated by equal gantry angle, was adopted. With both methods used, the dose coverage of the PTV was satisfactory. Small bowel irradiated to a dose of 95 % was reduced by about 70% as compared to a 3D conformal 3-field treatment technique. However, incorporation of scatter contribution and a smoothing function in the iteration of optimisation searching greatly reduced the degree of modulation in the two-dimensional intensity profiles. Instead of 120–160 step-and-shoot MLC segments only 30–60 segments were necessary to deliver the five intensity profiles. The number of monitor units per fraction was reduced accordingly to about one half. Therefore, by controlling the smoothness of the intensity profiles during optimisation, the produced IMRT plans could be delivered more efficiently. Moreover, the possibility to account for overlap of organs was found to be very valuable to avoid hot spots in these regions and to get the full DVHs of all organs at the same time.

Keywords

Intensity modulated radiation therapy; colo-rectal cancer; small bowel toxicity

INTRODUCTION

For patients with rectal cancer, adjuvant post-operative radiotherapy and chemotherapy has been shown to significantly reduce the risk of both pelvic and distant failure, with an improved survival rate.[1] However, small bowel toxicity due to treatment of rectal cancer is common. About 30% of patients receiving adjuvant post-operative radiation therapy (RT) with 5-fluorouracil and leucovorin were found to have grade ≥ 3 acute diarrhoea,[2] leading to breaks and/or early termination of therapy. Increased long-term bowel disfunction, such as more frequent bowel movements and/or incontinence, has also been reported for both patients receiving adjuvant combined modality therapy as well as those treated with short course pre-operative RT alone.[3] Any reduction in the volume of small bowel irradiated may improve the tolerance to therapy.

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The potential use of intensity modulated radiation therapy (IMRT) to reduce the volume of small bowel irradiated during both post-operative and pre-operative RT for rectal cancer has recently been shown. The reduction was greatest for patients with abdominoperineal resection (APR) and low anterior resection (LAR).[4] However, IMRT treatment planning is difficult for those patients. In general, the shape of the planning target volume (PTV) is more or less concave and the small bowel is very close to the PTV. Compared to prostate cancer treatment plans, larger field sizes are necessary in most cases. Therefore, even if the goal to reduce the irradiated small bowel volume is achieved by the IMRT treatment planning system, the intensity profiles calculated from inverse planning could be highly modulated and complicated to deliver. As a consequence, the number of necessary field segments would be too high and therefore the time for treatment would be too long for delivery.

This study examines the impact of modulation, or smoothness, of intensity profiles on the applicability of IMRT for rectal cancer. We report the results of a comparison of two different inverse-planning methods used to create IMRT treatment plans for rectal cancer patients. Scatter contribution when backprojecting dose values to fluence values and a smoothing function were only implemented in the optimisation searching of one method. We demonstrate the importance of this new addition to IMRT planning engines. The quality of resulting treatment plans in this challenging clinical situation is considered with respect to the resulting dose-volume histograms (DVHs), the calculated dose distributions and the number of field segments necessary for 'step-and-shoot' delivery.

MATERIAL AND METHODS

Patient preparation and treatment planning

Treatment planning computer tomography (CT) scans were obtained for four patients with rectal cancer. All patients had CT compatible small bowel contrast. They were positioned prone in a rigid foam cradle with an abdominal cut-out area, and instructed to have a full bladder. The clinical target volume (CTV) and small bowel were outlined. The planning target volume (PTV) was defined as CTV + a 3 mm isotropic margin. Three plans were calculated for each patient: A conformal three-field plan with two lateral wedged fields (18 MV) and two IMRT plans with a common arrangement of five 18 MV beams, each separated by equal gantry angle. Two different methods were used to optimise IMRT plans for rectal cancer patients. Scatter contribution and a smoothing function were implemented only in the iteration of the optimisation searching of one method.[5] For each patient, identical PTV, critical structures, dose-volume objectives and constraints were employed.

After the optimisation procedure the calculated intensity profiles were translated into multi-leaf collimator (MLC) segments, deliverable on Elekta linear accelerators. A minimum beam resolution of 1x1cm in the isocentre plane was chosen for the translation. Tolerance levels of 5–7% were chosen for the maximum deviation between calculated intensity profiles and intensity profiles resulting from the translation into step-and-shoot fields.

These step-and-shoot fields were then used to create an IMRT-treatment plan in the planning system Pinnacle Version 4.2f (ADAC Laboratories, Milpitas, CA, USA), to recalculate the dose distribution and the according DVHs. Recalculations of dose distributions were performed with the adaptive-convolve method in Pinnacle, while the inverse planning engines used a finite-sized pencil-beam algorithm for dose calculation. Homogeneity was enforced for the Pinnacle computations to avoid the bowel contrast from falsely indicating density variations on the planning CT scan.

The inverse-planning methods

The isocentre of treatment plans was specified to receive 100% of the prescription dose of 45 Gy, with the 95% isodose line encompassing the PTV and no more than 110% inhomogeneity within the target volume. To secure that these conditions are fulfilled for the PTV within some tolerance and to limit the small bowel and normal tissue dose at the same time as much as possible, eligible parameters must be set for optimisations in inverse-planning systems.

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Like most commercial inverse planning engines, one of the two optimisation methods used in this study (method 1) uses the steepest descent method to find the minimum of a quadratic objective function.[6] This function measures the goodness of the treatment plan. Optimisations are stopped as soon as the value of this function drops below a defined threshold. The objective function is given by:

$$f = \frac{1}{N} \cdot \sum_{i=1}^{N} w_{organ} \left(D_{calc.}(i) - D_{prescr.}(i) \right)^2$$

where N is the number of voxels, w_{organ} is the weighting factor that controls the relative importance of an organ, $D_{calc.}$ and $D_{prescr.}$ are calculated and prescribed dose. Typical objectives (quadratic underdose or overdose constraints, DVH constraints) used in this study for the IMRT treatment planning of rectal cancer with this method are listed below:

PTV:

- $D_{prescr.}$(max.) = 48 Gy with w_{organ} = 2–4 and
- $D_{prescr.}$(min.) = 43 Gy with w_{organ} = 2–5

Small bowel:

- $D_{prescr.}$(max.) = 43 Gy with w_{organ} = 1 and
- DVH constraints (100% of volume ≤ 45 Gy, 85–95% of volume ≤ 40 Gy and 50–70% of volume ≤ 30 Gy).

Rest of normal tissues (to avoid hot spots):

- $D_{prescr.}$(max.) = 45 Gy with w_{organ} = 0.5

One disadvantage of the used quadratic objective function is that the solution that results from the optimisation strongly depends on the chosen weighting factors. Several optimisations are necessary for almost every patient to find suitable optimisation parameters.[7] Another disadvantage of the used quadratic objective function is that even if one uses high values for the weighting factors of an organ, the given constraints for this organ are not necessarily completely fulfilled ("soft" constraints). This is, for example, why it was necessary to define $D_{prescr.}$(max.) = 43 Gy for small bowel and a DVH constraint for high doses (100% of volume ≤ 45 Gy) in order to avoid high doses in small bowel volume. Moreover, if organs overlap (which often happens between PTV defined as CTV + 3 mm margin and critical structures in the treatment planning of rectal cancer) voxels of this overlap region automatically do only belong to the organ with the highest priority in most inverse planning systems. Therefore, it is sometimes necessary to change the priority of organs and to restart the optimisation process, because DVHs have changed unexpectedly. Altogether it must be perceived that optimisations with quadratic objective functions need a lot of experience and probably never really result in the optimal solution. Nevertheless, they mostly result in an acceptable and improved dose distribution when compared to conventional 3D treatment plans.

Scatter contribution and a smoothing function are implemented in the second optimisation method used in this study (method 2). The method uses the conjugate gradient method and a target function where physical and "biological" objectives can be applied for the optimisation process.[5] The "biological" constraints (as there are "serial" and "parallel" constraints) allow users to increase the exponent of the objective function to values higher than two, as in quadratic objective functions.[8] In addition, the "parallel" constraint allows the definition of a volume (e.g. in lung) that the planner is willing to sacrifice for an improvement of the homogeneity in the PTV or to reduce dose in other areas of organs at risk. All constraints are automatically defined as "hard" constraints, which means that all constraints have to be nearly completely fulfilled before the optimisation stops. At the same time no constraints need to be defined for the PTV, because under the given constraints the optimisation algorithm always tries to find the solution with the highest dose values in the PTV. However, in most cases overdose limitations are given for the PTV. Compared to optimisations without overdose constraints for the PTV, optimisations may then potentially result in higher dose values in the critical structures and with larger areas of underdosage in the PTV. It was found that the result of optimisations can be more easily controlled with "hard" constraints than with "soft" constraints, if realistic constraints are chosen by an experienced user. Moreover, the possibility to define "biological" constraints was found to make it easier to find optimisation parameters which can be used for different patients with the same

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indication (class solutions). The objectives used for the IMRT treatment plans created in this study are listed below:

PTV:
- $D_{max.}$ = 49 Gy

Small bowel:
- $D_{isoeff} \leq$ 33–35 Gy (isoeffective dose), weight 8

Rest of normal tissues (to avoid hot spots):
- $D_{isoeff} \leq$ 45 Gy (isoeffective dose), weight 12

For different patients it was only necessary to change the allowed isoeffective dose of small bowel to find the optimal compromise between a slight underdosage in the PTV and a dose limitation of the small bowel structure. Because method 2 can account for overlap, it was not necessary to change the priority of organs and to restart optimisations because DVHs had changed. Instead, method 2 allows voxels of overlap regions to belong to several different structures at the same time. The optimisation process will then for example try to limit the dose of the overlap region because it belongs to an organ at risk and to maximise the dose, because it belongs to the PTV. The resulting solution will then be the best compromise under the given constraints, e.g. a dose distribution with a slight underdosage of the PTV in the overlap region.

It is possible to make treatment plans with the two above mentioned inverse-planning methods, which result in very similar DVHs and only small differences in the calculated dose distributions. Nevertheless, method 2 will always produce intensity profiles with a reduced degree of modulation, because its inverse optimisation incorporates scatter contribution when backprojecting dose values to fluence values and a smoothing method to limit the unevenness of local intensity values. These two additions are equally important to limit the unevenness of intensity profiles and are therefore never applied separately in this paper. To introduce the smoothing constraint in the optimisation searching, the fluence profile becomes a rubber membrane with given tension and it is demanded to have a minimal surface.[9] Smoothness could be a necessary condition of fluence profiles for applicability of treatment plans in the treatment of rectal cancer. At least smoother profiles can be applied faster and can be verified more easily in practice, especially when considering patient and organ movement.

RESULTS AND DISCUSSION

Two-dimensional intensity profiles calculated with both inverse planning methods show a general agreement. However, as expected, intensity profiles resulting from method 2 are smoother than intensity profiles resulting from method 1 that did not have scatter contributions and a smoothing function implemented in the optimisation searching. Figure 1 shows typical intensity profiles calculated with both inverse planning methods for a beam with 72-degree gantry angle.

The final IMRT plans created with method 1 fulfilled the given objectives well. The small bowel volume irradiated to a dose 95% of the isocentre dose was reduced by about 70% compared to 3D conformal treatment planning (Fig. 2a,b). However, parameter adjustment for the objectives and the DVH constraints was necessary and therefore several optimisations had to be run for each patient. The complete procedure of creating a treatment plan with the reference method, including optimisation, translation of calculated intensity profiles into step-and-shoot fields and recalculation of the dose distribution in Pinnacle took about 2 hours. The number of resulting MLC segments was above 120 (Table 1). No constraints for the smoothness of intensity profiles were specified during the optimisation process to decrease this number. Spikes at the edges of intensity profiles rather increased the number of MLC segments and lead to very small field segments with large offsets. One explanation for spikes in the intensity profiles could be, that with method 1 scattering was not taken into account when backprojecting dose to fluence values and changing fluence values. Another reason for spikes could be, that circular finite sized pencil beams were used to calculate the dose contributions of the quadratic matix elements of intensity profiles with this method. Because of this, the effect of an increased intensity can be small for voxels which are only hit by the corner of a matrix element. Consequently, fluence values of such matrix

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elements would be increased significantly during the optimisation searching.

After the recalculation of dose distributions in Pinnacle, an unacceptable increase of the dose inhomogeneity (hot and cold spots) was sometimes found for the PTV and the small bowel (Fig. 3a,b). There are several reasons for this. Firstly, intensity profiles almost never can be exactly delivered as calculated. Before the recalculation of IMRT plans in Pinnacle, intensity profiles were converted into MLC segments. In this study a maximum difference between calculated intensity profiles and profiles resulting from the translation into step-and-shoot segments of between 5 and 7% was tolerated.[10] Secondly, intensity values must be converted into monitor units (MU). The calculation of monitor units for small fields with large offsets is difficult and therefore can be inaccurate.[11] Thirdly, the dose calculation algorithms of the used inverse planning engines and Pinnacle are different. As a result of all this, high and low intensity values of beams irradiated from different directions sometimes do not average out in terms

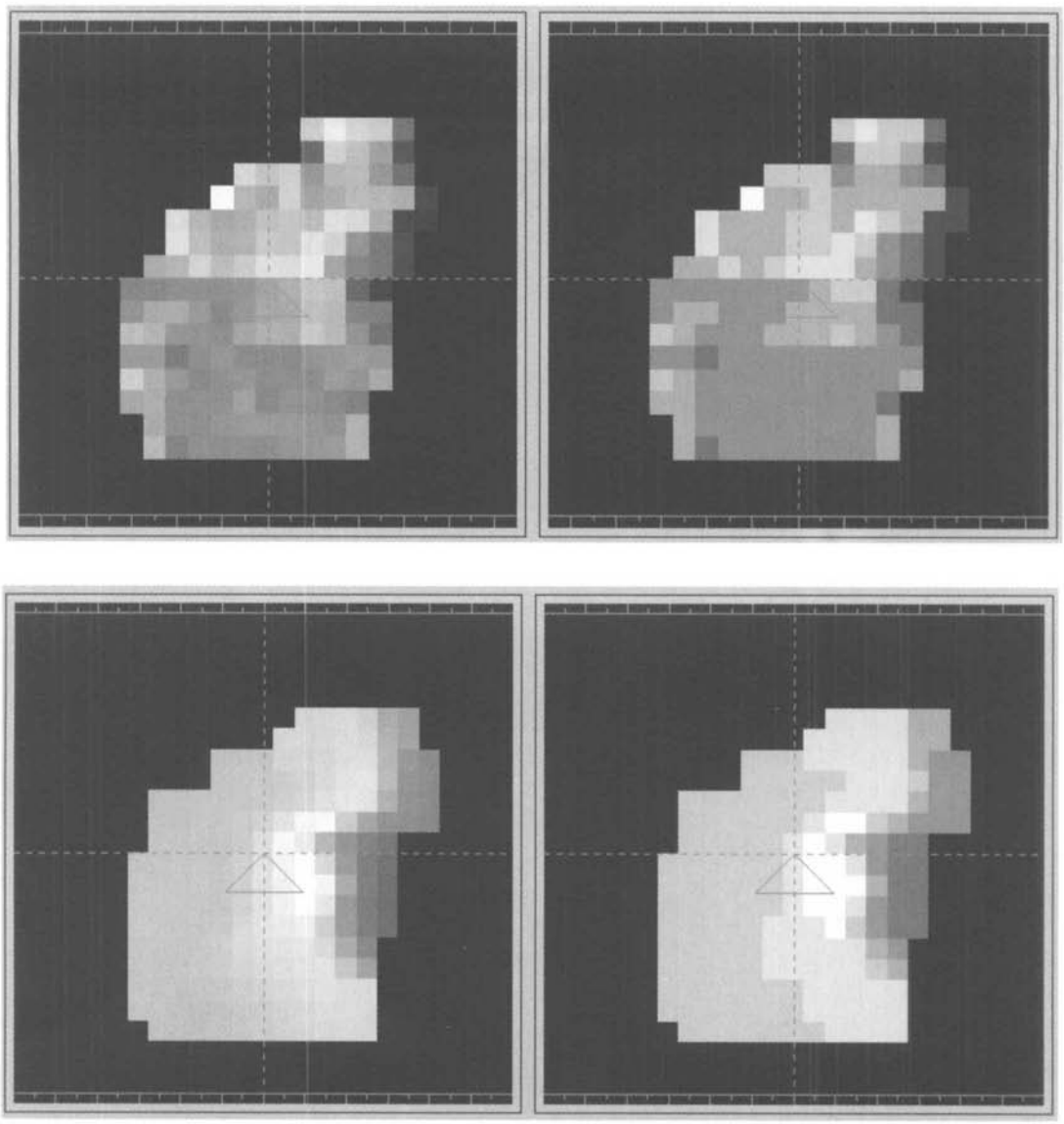

Figure 1. Intensity profiles of beams with a gantry angles of 72° as calculated i. without and ii. with a smoothing constraint during the optimisation procedure(from top to bottom). On the left side the intensity profiles are displayed as calculated in the inverse planning systems, on the right side the intensity profiles are displayed as they result from the translation into step-and-shoot fields.

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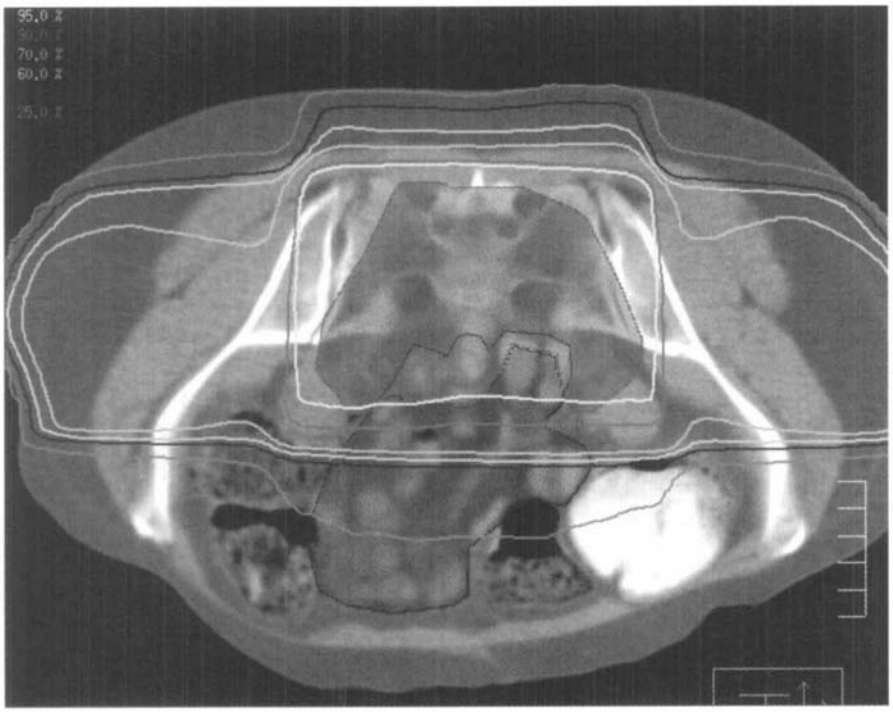

Figure 2a. Transversal view of a dose distribution of a 3D conformal three field plan. From the inner to the outer: 95%, 90%, 70%, 60%, 25% and 10% isodose lines. PTV and small bowel are shown in colorwash.

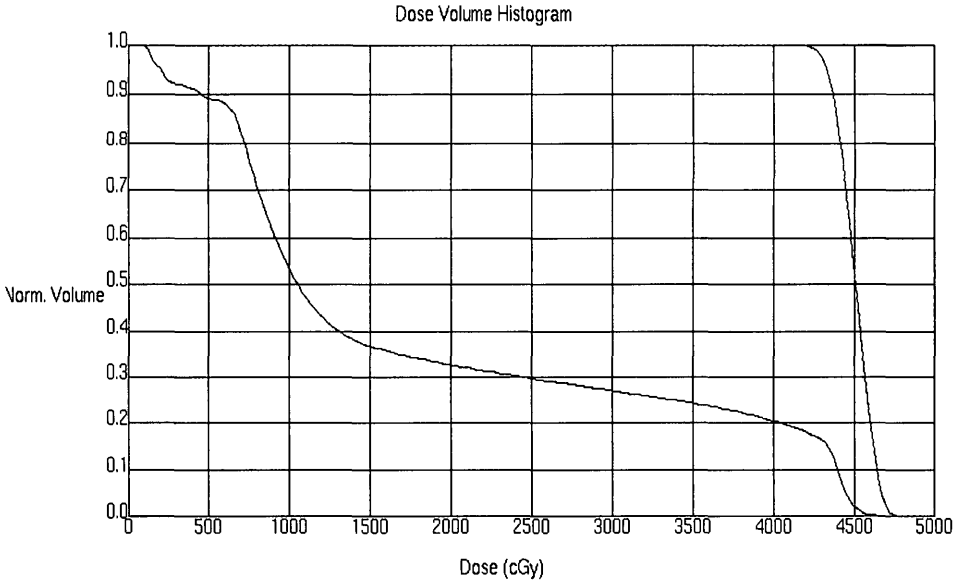

Figure 2b. DVH of a 3D conformal three field plan.

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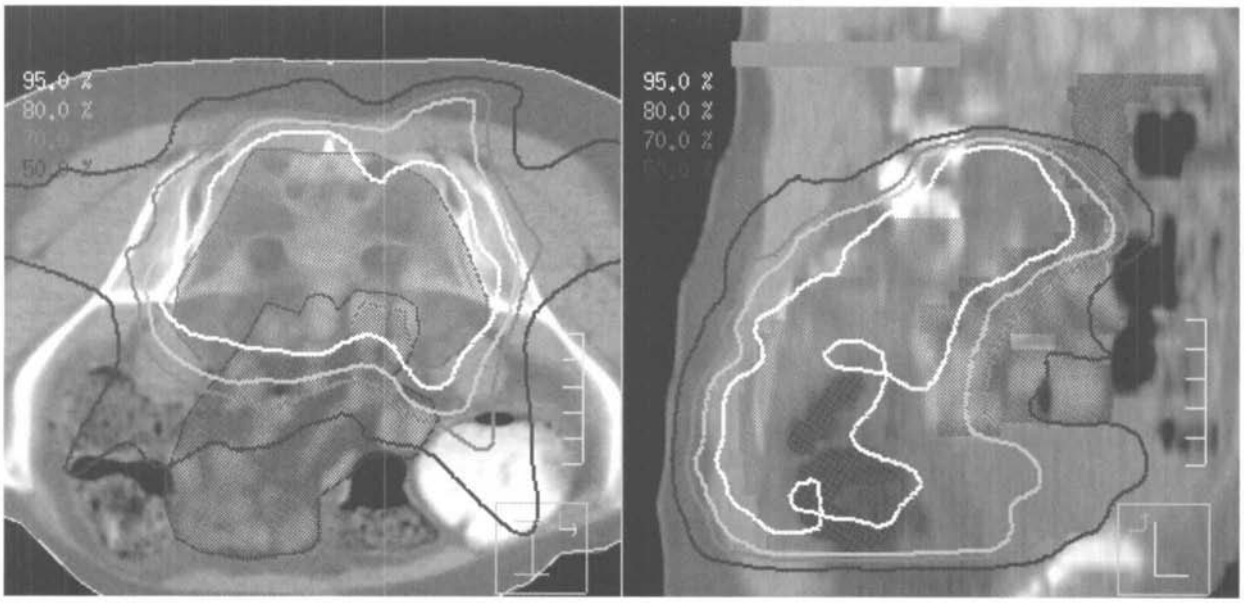

Figure 3a. Transversal and sagittal view of a dose distribution of an IMRT plan as calculated with method 1 as prescribed in this paper after recalculation of the dose distribution in Pinnacle. The 95%, 80%, 70% and 50% isodose lines are displayed.

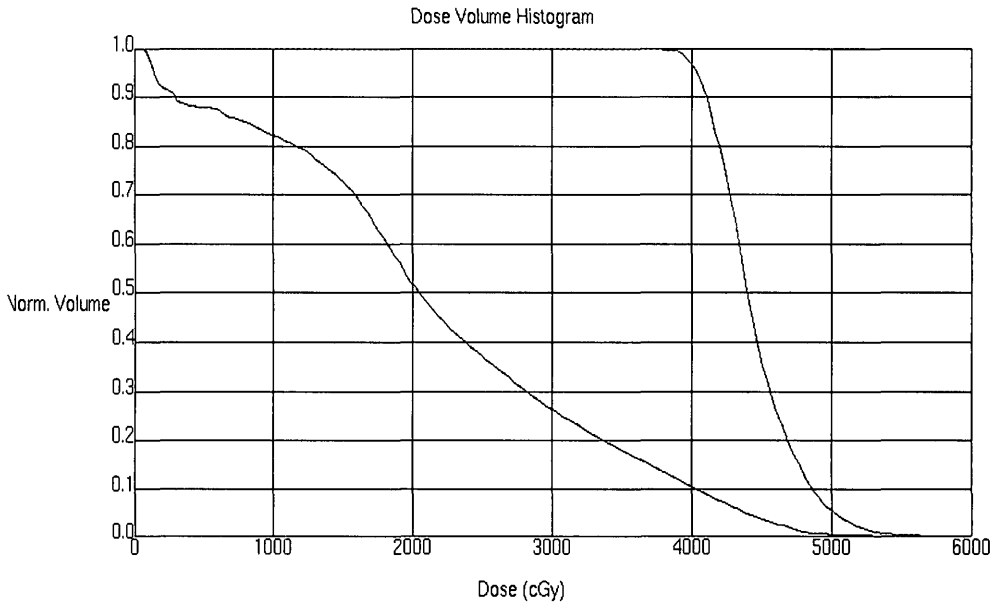

Figure 3b. DVH of an IMRT plan as calculated with the reference method (dotted line) and after (full line) recalculation of the dose distribution in Pinnacle.

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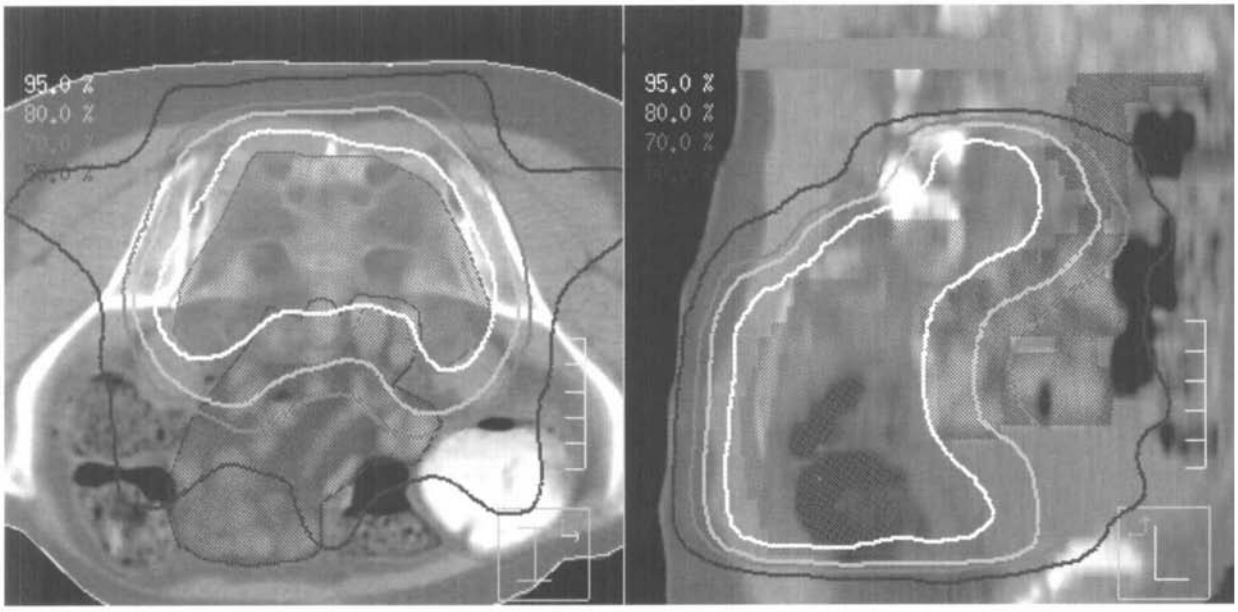

Figure 4a. Transversal and sagittal view of a dose distribution of an IMRT plan as calculated with method 2 as prescribed in this paper after recalculation of the dose distribution in Pinnacle. PTV and small bowel are shown in colorwash. Overlap between PTV and small bowel can be noticed. The 95%, 80%, 70% and 50% isodose lines are displayed.

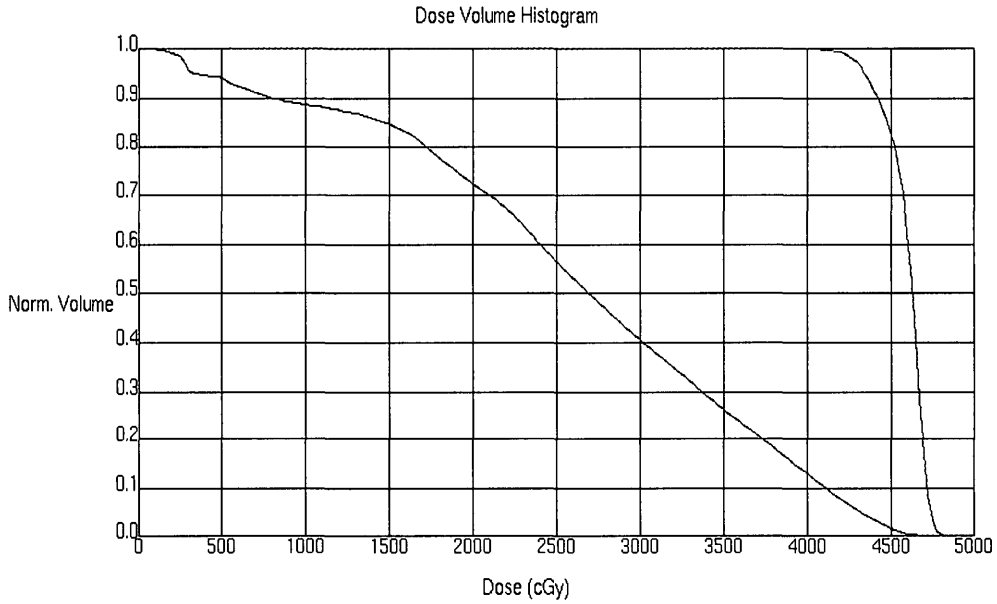

Figure 4b. DVH of an IMRT plan as calculated i. with method 2 as prescribed in this paper and ii. after recalculation of the dose distribution in Pinnacle (from top to bottom).

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Table 1. Number of Step-and-shoot fields necessary to deliver colo-rectal IMRT treatment plans with different tolerance levels between the calculated intensity profiles and the intensity profiles that resulted from the translation into step-and-shoot fields.

Patient	Method 1	Method 2
A	7% – 123	7% – 45
	6% – 133	6% – 47
	5% – 157	5% – 60
B	7% – 135	7% – 34
	6% – 153	6% – 36
	5% – 185	5% – 49
C	7% – 127	7% – 36
	6% – 147	6% – 41
	5% – 174	5% – 51
D	7% – 131	7% – 37
	6% – 150	6% – 43
	5% – 179	5% – 54

of dose in Pinnacle anymore, but obviously did in the inverse planning engine. This causes the observed increase of the inhomogeneity in the PTV.

IMRT plans created with method 2 also fullfilled the given objective parameters very well. The objectives did not have to be changed for each patient and the complete procedure of making an IMRT plan, translation of calculated intensity profiles into step-and-shoot fields and recalculation of the dose distribution in Pinnacle took only about 1.5 hours. Because the smoothness is part of the objective and because scatter contribution when backprojecting dose values to fluence values is incorporated in the optimisation searching, the number of resulting step-and-shoot fields was reduced to less than 50 (Table 1). Consequently, the time needed to recalculate the dose distribution in Pinnacle was shorter. More importantly, the resulting IMRT plans were more clinically practical with respect to the total time needed for delivery. Because of the smoothness of profiles, no significant increase of the dose inhomogeneity was found after the recalculation of dose distributions in Pinnacle (Fig. 4a,b). The small changes which can be noticed in the DVHs, are mainly caused by the step-and-shoot translation. These slight changes probably could be reduced by changing the resolution of the step-and-shoot fields in leaf direction. The number of necessary step-and-shoot fields is not expected to increase significantly, if doing so for smooth profiles. Unfortunately, the used version of the translator did not allow creating step-and-shoot segments with any other resolution than 10 × 10 mm^2. It should be noticed, that the 95% isodose line shown in Figure 4a does not completely encompass the PTV because of an overlap between PTV and small bowel that was accounted for during the optimisation process. Therefore, the underdosage region of the PTV is almost exactly positioned in this region to limit small bowel dose. Moreover, the same dose per fraction can be achieved for IMRT plans with about 50% less monitor units (MUs). This reduction is a consequence of the fact that step-and-shoot segments that resulted from the smoother fluence profiles in average were larger than segments that resulted from the profiles calculated with method 1. The reduction of MUs per fraction of course is also important for clinical practice. A reduction of MUs leads to less scattering and leakage dose from the linacs and field segments can be applied faster. Larger field segments also can be verified more easily in practice and make the IMRT delivery safer, especially when considering organ motion, patient movement and setup errors.

CONCLUSION

This study shows that IMRT can substantially reduce small bowel irradiation for patients with rectal cancer. However, IMRT treatment by means of step-and-shoot delivery is only clinically practical if the number of step-and-shoot fields does not lead to unacceptable long treatment times. To limit the number of step-and-shoot fields, intensity profiles must be as smooth as possible. Therefore, including scatter contribution when backprojecting dose values to fluence values in the iterative optimisation searching and an intensity profile smoothing function in the objective is necessary. Deliverable IMRT plans for patients with rectal cancer were calculated, using the following procedure: optimise, translate calculated intensity profiles into step-and-shoot fields and recalculate dose distribution and DVH in Pinnacle. The number of field segments was reduced to be less than 50, the number of MUs per fraction was reduced to about one half with respect to treatment plans with unsmoothed intensity profiles. Accordingly, uncertainties resulting from the deviation of MLC segmentation and the

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conversion of intensity values into monitor units were also reduced. It was also found that it is important, that inverse planning engines can account for overlap of organs to be able to avoid hot spots in severe regions and to get the full DVHs of all organs at the same time.

Future versions of inverse planning systems should incorporate the MLC segmentation, final dose computation and the monitor unit determination into the optimisation procedure. For further improvement of rectal cancer treatment, further study will be needed to incorporate the mobility of the small bowel during the treatment course into the intensity optimisation.

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