IMRT of Prostate Cancer: a Comparison of Fluence Optimisation with Sequential Segmentation and Direct Step and Shoot Optimisation

IMRT des Prostatakarzinoms: ein Vergleich der Fluenz-Optimierung mit anschließender Segmentierung und der Direct-Step-and-Shoot-Optimierung

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Background and Purpose: Intensity-modulated radiation therapy (IMRT) has shown its superiority to 3D conformal radiotherapy in the treatment of prostate cancer. Different optimisation algorithms are available: algorithms which first optimise the fluence followed by a sequencing (IM) and algorithms which involve the machine parameters directly in the optimisation process (DSS). The aim of this treatment planning study is to compare both of them regarding dose distribution and treatment time.
Patients, Material and Methods: Ten consecutive patients with localized prostate cancer were enrolled for this planning study. The planning target volume (PTV) and the rectum volume, urinary bladder and femoral heads as organs at risk (OAR) were delineated. Average doses, the target dose homogeneity H, D_5, D_{95}, monitor units per fraction and the number of segments were evaluated.
Results: While there is only a small difference in the mean doses at rectum and bladder, there is a significant advantage for the target dose homogeneity in the DSS-optimised plans compared to the IM-optimised ones. Differences in the monitor units (nearly 10% less for DSS) and the number of segments are also statistically significant and reduce the treatment time.
Conclusion: Particularly with regard to the tumor control probability the better homogeneity of the DSS-optimised plans is more profitable. The shorter treatment time is an improvement regarding intrafractional organ motion. The DSS-optimiser results in a higher target dose homogeneity and, simultaneously, in a lower number of monitor units. Therefore it should be preferred for IMRT of prostate cancer.

Key Words: Direct step and shoot, direct machine parameter optimisation, intensity-modulated radiation therapy, IMRT, prostate cancer

Hintergrund und Ziel: Die intensitätsmodulierte Strahlentherapie (IMRT) hat ihre Überlegenheit gegenüber der 3D-konformalen Strahlentherapie in der Behandlung des Prostatakarzinoms gezeigt. Verschiedene Optimierungsalgorithmen stehen zur Verfügung: Algorithmen, die erst die Fluenz optimieren und anschließend eine Segmentierung durchführen und Algorithmen, die die Maschinenparameter direkt in den Optimierungsprozess integrieren. Das Ziel dieser Planungsstudie ist es, beide hinsichtlich Dosisverteilung und Bestrahlungszeit zu vergleichen.
Patienten, Material und Methode: In die Planungsstudie wurden zehn aufeinanderfolgende Patienten mit lokalisiertem Prostatakarzinom eingeschlossen. Das Planungszielvolumen und als Risikostrukturen das Rektumvolumen, Harnblase und beide Femurköpfe wurden markiert. Die durchschnittliche Dosis in den Risikoorganen, die Homogenität im Zielvolumen, D_5, D_{95}, die Monitoreinheiten pro Fraktion und die mittlere Segmentzahl wurden ermittelt.
Ergebnisse: Während nur ein kleiner Unterschied in der mittleren Dosis in Rektum und Blase besteht, findet sich ein signifikanter Vorteil bezüglich der Homogenität im Zielvolumen für die mit „Direct step and shoot“ optimierten Pläne gegenüber denjenigen mit Fluenzoptimierung (Tabelle2). Die Unterschiede bei den Monitoreinheiten (fast 10% weniger für den DSS-optimierten Plan) und der Segmentzahl sind ebenfalls statistisch signifikant .
Schlussfolgerung: Insbesondere im Hinblick auf die Tumorkontrollwahrscheinlichkeit ist die größere Homogenität der DSS-optimierten Pläne vorteilhafter. Die kürzere Behandlungszeit stellt eine Verbesserung in Bezug auf intrafraktionelle Organbewegung dar. Der DSS-Optimierer führt zu einer

besseren Homogenität im Zielvolumen bei einer reduzierten Anzahl von Monitoreinheiten. Deshalb sollte er für die IMRT des Prostatakarzinoms bevorzugt werden.

Schlüsselwörter: Direct step and shoot, direct machine parameter optimisation, intensitätsmodulierte Strahlentherapie, IMRT, Prostata

Background and Purpose

Recently it has been pointed out, that over the past decade intensity-modulated radiation therapy (IMRT) has shown its superiority to three-dimensional conformal radiotherapy (3DCRT) in the treatment of prostate cancer, producing more conformal dose distributions for the target volume with minimal long-term toxicities in the organs at risk (OAR) [7, 12, 15]. Thereby image guidance is recommended to reduce errors of patient setup and internal motion of the prostate [12, 19, 24,25].Different algorithms for the optimisation have been described. Two systematically different procedures are applied generally: the first begins with searching for the ideal fluence and then subsequentely creates segments for the multileaf collimator (MLC). The second approach involves the machine parameters in the optimisation process like the direct machine parameter optimisation (DMPO) or direct step and shoot (DSS) [5, 14]. The aim of this treatment planning study is to compare the techniques of fluence optimisation with sequential segmentation and direct step and shoot optimisation to determine the achievable advantages for prostate cancer patients.

Patients, Material and Methods

Between March 2006 and December 2007, ten consecutive patients with a mean age of 71 years were enrolled for primary EBRT for localised prostate cancer. All ten patients were immobilised in a vacuum mattress (BlueBAG™ BodyFIX®, Medical Intelligence) and had three-dimensional treatment planning with a CT slice thickness of 5 mm.
In the treatment planning system (Oncentra® MasterPlan, V3.0 (Nucletron BV, Veenendal, Netherlands) the Gross-Target-Volume (GTV: prostate gland and seminal vesicules), Clinical-Target-Volume (CTV, 5mm 3D-margin added to the GTV excluding the rectal volume), Planning-Target-Volume (PTV, 10mm 3D-margin added to the GTV without respect to the rektum) and normal tissues were delineated in each slice. The delineation of the volumes of interest follows the description of Bos et al. [6]. The rectal volume (according Guckenberger et al. [12]) and urinary bladder as well as the femoral heads were delineated as organs at risk (OAR).
The planning is accomplished using the data of a Siemens Primus® linear accelerator. This machine is equipped with a multileaf collimator of 29 leaf pairs. The inner 27 leaf pairs have a nominal width of 10mm at the isocentre; the outer pairs with a nominal width of 65mm at isocentre are not used for intensity modulation. The beam quality is 6 MV.
For the optimisation of the IMRT, different algorithms are used. Nucletron offers as a part of the optimising module both their IM (intensity modulation) optimisation software and their new module DSS (direct step and shoot).

The earlier IM-optimisation software searches first for the ideal fluence for each beam, followed by the segmentation. Due to approximations in calculations and limitations in MLC the resulting, deliverable fluence will no longer be optimal [4]. The new DSS module integrates the segmentation into the optimisation process, using the first iterations to find a set of control points (described by the leaf positions and the weights of the segments) that meets the machine specific requirements. During the remaining iterations the leaf positions and segment weights are optimised directly [14]. No post processing is necessary.

In this planning study the average dose to PTV was close to 60 Gy in 30 fractions, representing the first treatment sequence before the treatment volume is shrinked to the CTV. This was done by setting the minimum and maximum dose volume objectives to 59 and 64 Gy respectively. Seven equispaced beams were chosen, starting at a gantry angle of 0°, followed by 51°, 103°, 154°, 206°, 257° and 309°.

To find ideal weighting schemes for the dose-volume objectives, we started in a pre-study of four patients with a fixed weight for the PTV of 3000, as used by Dobler et al. [10] and varied the weight for the bladder and rectum from 100 to 1000 and 3000. The medium value of 1000 proved to be the best for both algorithms. Actually there exists no clear consensus on precise constraints [20] neither unique in dose nor in volume fraction [2, 6, 8, 11, 12, 20, 22]. Our relatively narrow constraints, especially for the rectum, should pose a challenge for the optimising algorithms. The dose-volume objectives were defined by the scheme in table 1.

For the optimisation the basic conditions were : minimum field size of 4 cm², at least two open leaf pairs, maximum number of 60 segments and minimum 4 monitor units per segment. The tumor overlap option was activated. That means, that regions, which are part of the PTV as well as of an OAR are handled as PTV and there is no penalty in the objective function for these parts of the OAR. All calculations were done by pencil beam algorithm with a calculation grid spacing of 5mm.

The number of segments and the number of monitor units (MU) per fraction, that is per 2.0 Gy single dose were taken into account as further parameters of plan quality. Additionally the resulting overall treatment times were measured, including gantry and MLC movements.

The mean doses in the OARs and the homogeneity H and D_5 and D_{95} in the PTV were calculated. H is defined as $H = (D_5-D_{95})/ D_{Average}$ [11, 21]. D_5 and D_{95} are defined as the dose where the cumulative DVH of the PTV intersects with 5% respectively 95% of the PTV.

The student's test (t-test) for paired samples was used to analyse whether differences between the results of both algorithms are significant. The zero hypothesis was, that there is no difference for the mean values. As level of significance $\alpha = 5\%$ was taken.

Results

After the DSS- optimisation the average of the mean dose in the PTV was 60.5 Gy, for the IM-optimisation it was 60.1 Gy. The PTV maximum dose objective was respected in seven cases for the DSS- optimiser, only in two for the IM- optimiser. The PTV minimum dose could not be achieved. There was a clear advantage for the target dose homogeneity H in the DSS- optimised plans (10.0±2) compared to the IM- optimised ones (19.2±4), due to a significantly lower D95 for the IM-plan (52.5Gy versus 56.7 Gy). This can also be seen in figure 1, showing the dose distribution for one specific

patient in two orthogonal slices. Table 2a lists the homogeneity in the PTV and the mean doses in the different regions of interest.
In all regions the DSS-optimiser respected the dose volume objectives better or equal than the IM-optimiser: the lower dose volume objective for the urinary bladder (15Gy / 70%) for seven plans (DSS) versus three plans (IM), the upper (40 Gy / 20%) for one plan each. The lower dose volume objective for the rectum (15Gy / 70%) is achieved in three (DSS) versus two (IM) cases, the upper one is missed in every single plan. The average dose at rectum and bladder shows only a small difference. The femoral heads are combined taking the average of the left and the right side. The average value for the femoral heads is higher for the DSS- algorithm. But the set dose volume constraint is never exceeded and reached only in two cases of the DSS- optimiser.
The doses, the MU per fraction, the number of segments and the treatment times are averaged in table 2b. The saving in time is less than a minute of more than 13 minutes treatment time.
For all parameters of table 2, except the mean value of the rectum, the better values for the DSS-optimiser are significant with a value of $p<0.05$.

Discussion

Both algorithms produce feasible plans, which are comparable in the average dose at the OARs. There is always the risk, that the set of the chosen constraints favours one of the algorithms. Also the inverse planning is an iterative process and there are several ways of user interaction [4]. Having conflicting goals, we kept the doses fixed and increased the weights for the OARs until the DVH for the PTV became worse in a pre-study as written above.
The mean dose for the rectum and bladder is equal or smaller for the DSS-optimised plans but with a larger volume in the high dose region in most cases. Generally this refers to the parts of the organs which are included in the PTV and such improves the homogeneity there. The higher dose at the femoral heads for the DSS-optimised plans is a sign of the more effective mode of operation for the DSS-optimiser, although the set dose volume constraint is only reached twice and so there is no penalty for most of the plans. But the IM-optimiser does not exhaust the dose objective at the femoral heads or the other way round the violations of the other dose objectives are not sufficiently punished. As it has been shown earlier in the case of IMRT of the hypopharyngeal carcinoma, the resulting dose distribution complies better with the dose volume objective of the PTV for the DSS- optimised plan than for the IM- optimised one and produces a significant better homogeneity [10].
From the clinical point of view there is no doubt, that the better homogeneity in the PTV has the potential to increase the tumor control probability, while the better fulfilment of dose volume objectives for the OARs reduces the probability of complications.
The number of segments stays for both algorithms plainly below the allowed maximum number what reduces the time for MLC movements and is a sign for effective segmentation in both algorithms. The reduction of treatment time is greater for the DSS-optimised plans especially due to the reduced number of MU – which was also found for the hypopharyngeal carcinoma by Dobler et al. [10] - and that is advantageous with regard to intrafractional movements of the prostate [3, 9, 16- 19, 25, 28]. But otherwise it is obvious, that the reduction of treatment time is not large enough to reduce the problems

connected to intrafractional organ motion sufficiently. This is a special problem of IMRT, because the treatment times in 3DCRT are clearly shorter and the intrafractional organ variability is therefore not so pronounced as it is in IMRT. Furthermore it is essential while in the case of the 3DCRT at a correct setup of the patient always the whole PTV is inside of the field, in the case of IMRT between segments, which should complement one another there might result an overlap or gap due to intrafractional movements. Interfractional movements are no particular problem of IMRT and the treatment accuracy can be improved by image guidance [1, 19, 23, 24, 27].
Another aspect to be regarded is the induction of a second cancer by radiotherapy [26]. The risk of getting a colon cancer after radiotherapy of the prostate might be reduced by decreasing the number of monitor units.

Conclusion

Due to the higher target dose homogeneity of the DSS- optimised plan, the lower number of monitor units and segments and the lower dose to the organs at risk the algorithm with direct machine parameter optimisation should be preferred. The reduction of the treatment time might only be regarded as a first step reducing problems with intrafractional organ motion. Further reduction of the treatment time at equivalent or better dose distribution is an aim, which might be achieved by improving the basic optimisation conditions like minimum field size, minimum number of open leaf pairs, maximum number of segments and minimum number of monitor units per segment and upcoming improvements of the algorithms. Other improvements are necessary, which might be achieved by investigations of IMRT-techniques with reduced uncertainties with respect to PTV- and OAR-movement.

ROI	*Usage*	*Type*	*Dose level (Gy)*	*Volume (%)*	*Weight*
PTV	Target	Max. Dose	64	0	3000
PTV	Target	Min. Dose	59	100	3000
Rectum	OAR	Max. Dose	40	20	1000
		Volume	15	70	1000
Bladder	OAR	Max. Dose	40	20	1000
		Volume	15	70	1000
Femoral Heads	OAR	Max. Dose	50	0	300
		Volume			

Table 1

	PTV			*Rectum*	*Bladder*	*Femoral Heads*
	Homogeneity H in %	*D_5 in Gy*	*D_{95} in Gy*	*D_{Av} in Gy*	*D_{Av} in Gy*	*D_{Av} in Gy*
DSS	10.0	62.8	56.7	29.8	29.6	25.6
	2	0.54	1.3	2.9	4.8	5.3
IM	19.2	64.0	52.5	30.1	30.9	22.0
	4	1.1	2.2	3.3	4.9	4.2

Table 2a

	Monitor units per fraction	*Number of segments*	*Treatment time in min*
DSS	663	51	13,11
	73	2	0,63
IM	725	53	13,89
	117	3	0,95

Table 2b

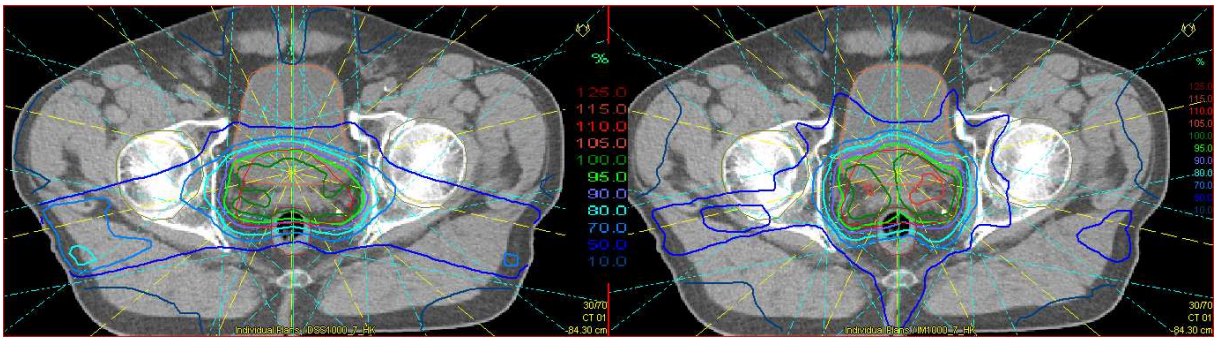

Figure 1 a, 1b

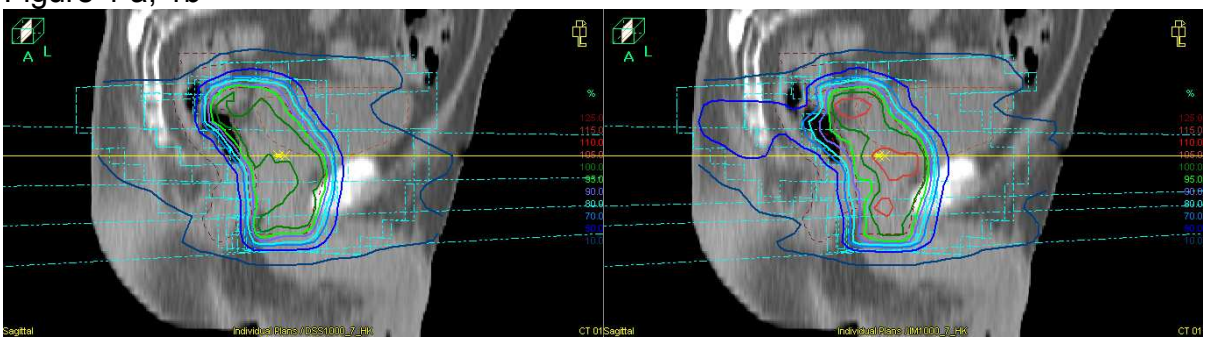

Figure 1c, 1d

Table 1 Dose volume objectives used for both optimisation algorithms. OAR: organ at risk; PTV: planning target volume; ROI: region of interest
Tabelle 1 Dosis-Volumen-Objectives, die für beide Optimierungsalgorithmen verwendet werden. OAR: Risikoorgan; PTV: Planungszielvolumen; ROI: „region of interest“

Table 2 Mittelwerte und Standardabweichung über alle zehn Patienten für Dosisparameter (a) und technische Parameter (b).
Tabelle 2 Average values and standard deviation over all ten patients for dose parameters (a) and technical parameters (b).

Figure 1a and 1b Dose distribution in one axial slice, left DSS-, right IM- optimised.
Figure 1c and 1d Dose distribution in the central sagittal plane
Abbildung 1a und 1b Dosisverteilung in einer Schicht, links DSS- rechts IM- optimiert.
Abbildung 1c und 1d Dosisverteilung in der zentralen Sagittalebene

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