Pulsed-dose rate brachytherapy in prostate cancer

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COMPARISON OF BIOLOGICALLY EQUIVALENT DOSE-VOLUME PARAMETERS FOR THE TREATMENT OF PROSTATE CANCER WITH CONCOMITANT BOOST IMRT VERSUS IMRT COMBINED WITH BRACHYTHERAPY

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With appendix for description of BED calculation and conformation number

ABSTRACT

Background and Purpose. The two main modalities to deliver high dose to the prostate and preventing high doses to neighboring organs are intensity modulated radiotherapy (IMRT) or external beam radiotherapy combined with brachytherapy. Because of the different biological effectiveness the physical dose distributions were converted to 3-dimensional linear quadratic dose at 2 Gy per fraction (EQD_2). From the latter, cumulative EQD_2-volume histograms were determined for comparison of the modalities.

Material and Methods. An IMRT plan was made on the contoured planning target volume (PTV1) and organs at risk (OAR) of 20 patients (IMRT-only). A dose of 70 Gy was prescribed on the PTV1 with a concomitant boost to a total of 76 Gy on a sub volume (PTV2). Also a 46 Gy IMRT plan was made combined with either a pulsed-dose rate (PDR) or a high-dose rate (HDR) brachytherapy boost. The EQD_2 on the PTV1 of the combined IMRT-PDR and IMRT-HDR plans were made equivalent to the EQD_2 of the 70 Gy IMRT-only plan. The α/β-ratio for prostate was set to 1.5 Gy and 10 Gy. For normal tissues an α/β-ratio of 3.0 Gy was taken. Several EQD_2-volume histogram parameters were calculated for comparison and analyzed by two-way-ANOVA.

Results. The mean EQD_2 to 95% of the prostate volume was slightly higher for the IMRT-only plan than for the brachytherapy modalities ($P<0.001$), in contrast to the mean EQD_2 to 50% of the prostate volume in which the opposite was the case ($P<0.001$). Rectum and bladder doses for IMRT-only are significantly higher ($P<0.001$). The urethra dose for IMRT-HDR was much higher than the other modalities only when the α/β-ratio for prostate was 10 Gy.

Conclusion. Because of the high doses within an implant, the dose in 50% of the prostate volume is much higher with the brachytherapy modalities than IMRT-only which may have clinical consequences. With brachytherapy the doses to the OAR are lower or similar to IMRT-only. Dose escalation for prostate tumors is more easily achieved with brachytherapy than with IMRT alone. Therefore brachytherapy might be the preferred modality to achieve further dose escalation.

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INTRODUCTION

Different radiation treatment modalities exist for the treatment of intermediate to high-risk prostate cancer. The most common treatment is external beam radiotherapy. With the introduction of Intensity Modulated Radiotherapy (IMRT), this modality is increasingly used with the aim to deliver high doses to the prostate and sparing neighboring organs adequately. The ability to increase the delivered dose while avoiding high doses in normal tissues is not only a matter of a new treatment delivery technique, but also a matter of better imaging of the prostate, better position verification on the treatment machines, thereby reducing planning target volume margins, and improvement in both treatment equipment and planning software. Zelefsky *et al.* reported on 561 patients treated to 81 Gy [33]. Compared to conventional 3-dimensional conformation radiotherapy no increase in late toxicity was observed and even a decrease in rectal bleeding was seen. IMRT has also been used with hypofractionated radiotherapy to increase the dose on the prostate because of the presumed low α/β-ratio of prostate cancer cells [17].

Another modality to increase the dose on the prostate while simultaneously preventing high doses on surrounding normal tissue is brachytherapy. To treat intermediate to high-risk prostate cancer, brachytherapy is usually combined with external beam radiotherapy [8, 11, 12, 23, 29]. Reported severe grade 3-4 toxicity is less than 7% while biochemical tumor control is high (80-90%). Both techniques aim to minimize the dose to rectum and bladder in order to have a high dose on the prostate.

To date only one full paper has been published on a prospective randomized trial comparing external beam radiotherapy to a combined modality of external beam radiotherapy and high-dose rate (HDR) brachytherapy [13]. In this study a better biochemical control outcome is observed for the combination treatment at a limited follow-up time of only median 30 months. This outcome is not surprising because the prescribed dose in the combined modality treatment was much higher than the other.

In this study we computed three different 3 dimensional linear quadratic equivalent dose at 2 Gy per fraction (EQD_2) dose distributions for 20 consecutive patients, treated at the Academic Medical Center [10]. Comparable dose schedules were chosen for comparison: (a) 46 Gy IMRT on the prostate plus 24 pulses pulsed-dose rate (PDR) brachytherapy boost; (b) 46 Gy IMRT on the prostate plus 3 fractions (HDR) brachytherapy boost; and (c) 70 Gy IMRT with a concomitant boost of 6 Gy to the prostate. The aim was to look for the magnitude of the differences in the biological equivalent doses on prostate cancer and normal tissues that are undoubtedly caused by differences in dose distribution patterns, even when a comparable dose is prescribed on the same target volume.

METHODS AND MATERIALS

Patient data

Data from 20 consecutive treated patients with combined 46 Gy conformal external beam therapy and PDR brachytherapy for prostate cancer was used. Details of this treatment are given in a previous publication [23].

The prostate was implanted with 12 needles on average (range 8-13) under transrectal ultrasound guidance. Before the brachytherapy treatment a continuous 2 mm thick CT dataset was acquired with the needles *in situ*. The clinical target volume (CTV) was considered to be the prostate with base of the seminal vesicles. Besides the CTV also the rectum, bladder neck and urethra were delineated. The rectum and urethra were delineated from 4 mm cranially to 4 mm caudally of the CTV. The bladder was delineated as the 1 cm part adjacent to the CTV, being the part receiving the highest dose from brachytherapy.

Brachytherapy treatment plan

For generation of planning target volume (PTV) margins dose delivery uncertainties must be taken into account. Source size and source positioning uncertainties are considered to be negligible [2]. With proper fixation of catheters movement of the implant has no marked influence on the dose distribution [23]. So no further expansion from CTV was utilized to generate the PTV. Constraints for dose planning were that 95% of the PTV was covered by the reference dose, a maximum of 10% of the rectum volume receiving 80% of the reference dose, and a maximum of 10% of the urethra receiving 120% of the reference dose. Brachytherapy planning was performed with the BPS 14.2 software (Nucletron B.V., The Netherlands). This plan was used to simulate both the PDR and HDR treatments, with different reference doses.

46 Gy IMRT treatment plan

For the 46 Gy IMRT-plan (23 fractions) the PTV1 was defined as the CTV with an isotropic margin of 8 mm. This PTV1 was planned to receive at least 95% of 46 Gy. A five-beam step-and-shoot IMRT technique with 10 MV photons was used and treatment planning was done with PLATO-ITP (Nucletron B.V., The Netherlands) [21].

70-76 Gy IMRT treatment plan

For this plan a similar approach as for the 46 Gy IMRT-plan was taken. Additionally an extra PTV was defined (PTV2), consisting of the CTV with an 8 mm margin, except at the rectum and bladder interface where no margin was taken. The dose prescription to the PTV1 was at least 95% of 70 Gy and at least 95% of 76 Gy to PTV2, so that the isocenter received 70 Gy and 6 Gy, respectively. Constraints to the rectum and bladder were a maximum of 50 Gy to 50% of the rectum volume and a maximum of 72 Gy to 5% of the bladder volume, respectively. Again, a five-beam 10 MV technique was used and treatment planning was performed using PLATO-ITP. The patients were planned for 35 fractions [21].

Equivalent dose calculations

To enable comparison between treatment modalities the prescription dose for the brachytherapy treatment was redefined. The IMRT dose prescription of 70 Gy on PTV1 was used as the reference dose. EQD_2 were computed to design equivalent schedules for the brachytherapy modalities on the PTV1. First the Biologically Effective Dose (BED) was calculated with the relevant α/β-ratio of the tissue of interest. Subsequently the EQD_2 can be calculated by dividing the BED by the relative effectiveness for 2 Gy fractions (see appendix) [10].

Nowadays much debate is going on about the α/β-ratio for prostate cancer. Modeling studies suggest that the α/β-ratio for prostate could be as low as 1.5 Gy, while other studies show higher α/β-ratios [4, 5, 9, 14, 20, 26, 30, 32]. Prospective studies are being carried out to find the real α/β-ratio for prostate cancer [18, 24]. Because valid data is still not known and because probably a range of α/β-ratios could be found depending on tumor characteristics, we have decided to do our investigation with two extremes rather than choosing only one α/β-ratio for prostate cancer. An α/β-ratio for prostate cancer of 1.5 Gy (α/β-p_1.5) and 10 Gy (α/β-p_10) was chosen. Also the same uncertainties can be found for the assumed half time of sublethal repair (T1/2) values (0-2.9 hours) [9, 14, 30]. We have chosen to use in this report a fixed intermediate value of 1 hour.

Calculations of the BED for the 70 Gy IMRT schedule was according to the linear-quadratic model assuming complete repair between fractions [1].

For the combined IMRT-brachytherapy model the 46 Gy IMRT was converted to BED as described above. Next a schedule was calculated for 24 pulses PDR and 3 fractions HDR brachytherapy treatment, such that the summed BED of the 46 Gy IMRT part and the PDR or HDR part yielded an EQD_2 of 70 Gy.

For the PDR brachytherapy part the model of Thames and Dale was used for dose calculations assuming incomplete monoexponential repair between pulses [6, 25]. The schedule was designed with 2.2 hours period time between the pulses. In the same way as for PDR brachytherapy also an HDR brachytherapy schedule was designed. Since the time between HDR brachytherapy fractions of more than 6 hours apart was much longer than the presumed T1/2, complete repair was assumed between HDR fractions. Treatment schedules are given in Table 1. The resulting isodose distribution of the different treatment modalities is illustrated in Fig. 1.

For all patients cumulative dose-volume histograms of the prostate (CTV), rectum, urethra, and bladder were calculated corresponding to the different treatment modalities. The dose was expressed as EQD_2 to account for differences in fraction dose and dose-rate. The EQD_2 was calculated for each voxel separately. The EQD_2 values for each fraction (including the brachytherapy fractions) were summed up to a total EQD_2 dose. From this

Table 1. Fractionation dose schedules for different α/β-ratio for prostate used in the models

	PTV1 IMRT	PTV1 Brachytherapy	PTV2	EQD_2 to PTV1
α/β-ratio for prostate is 1.5 Gy.				
IMRT-only	35 x 2.0 Gy	-	35 x 0.17 Gy	70 Gy
IMRT-PDR	23 x 2.0 Gy	24 x 1.10 Gy		70 Gy
IMRT-HDR	23 x 2.0 Gy	3 x 4.60 Gy		70 Gy
α/β-ratio for prostate is 10 Gy.				
IMRT-only	35 x 2.0 Gy	-	35 x 0.17 Gy	70 Gy
IMRT-PDR	23 x 2.0 Gy	24 x 1.04 Gy		70 Gy
IMRT-HDR	23 x 2.0 Gy	3 x 6.10 Gy		70 Gy

In the last column the equivalent dose of 2 Gy per fraction to PTV1 is given.

3-dimensional EQD_2 distribution cumulative dose-volume histograms were calculated. An α/β-ratio of 3 Gy was taken for the rectum, urethra, and bladder [28]. T1/2 was 1 hour for all tissues. From the different cumulative EQD_2-volume histograms parameters were derived for comparison. When calculating EQD_2 for the IMRT plans random geometrical deviations were taken into account. Systematic deviations were corrected assuming application of a position verification protocol. The physical dose distribution matrix of a patient was convolved with a Gaussian distribution to simulate random positioning variations. The standard deviations were 2.2 mm in the lateral direction, 3.8 mm in the anterior-posterior direction, and 2.4 mm in the longitudinal direction [7]. Calculation of EQD_2 was done for 95%, 90%, 50%, and 5% of the CTV volume. Also the EQD_2 for the most exposed 2ml of the rectum and bladder were calculated and 10% of the urethra.

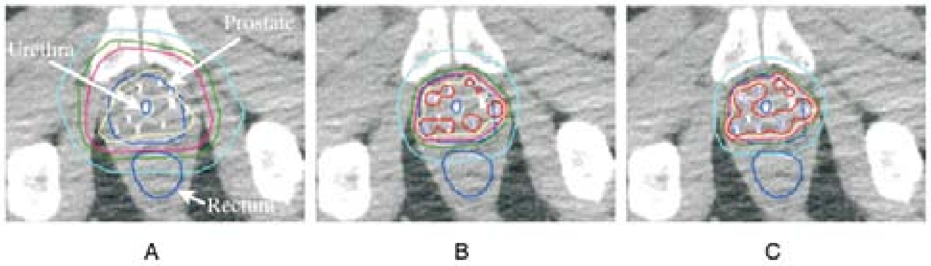

Figure 1. Physical isodose distribution of an IMRT-only plan (A), an external beam radiotherapy with HDR boost plan (B), and an external beam radiotherapy with PDR boost plan (C). These dose distributions are valid for the fractionation schedule belonging to an α/β-ratio of 1.5 Gy for prostate cancer. This means for (A) 100% equals 70 Gy; for (B) 100% equals 59.8 Gy; and for (C) 100% equals 72.4 Gy. The illustrated isodoselines are from the outside to the center the 80%, 95%, 100%, 107%, 120%, and 150% of the prescribed physical dose.

To calculate and to compare the degree of conformity the conformation number according to van 't Riet was used [27]. The conformation number was calculated on physical dose-volume parameters.

Statistical analysis

The relationship between treatment modality (IMRT-only, IMRT-PDR, and IMRT-HDR) and EQD_2-volume parameters or conformation number was analyzed by two-way-analysis of variance. Assumption to use the model was checked by exploring the distribution of the residuals. P-values < 0.05 were considered statistically significant. Where significant associations were found, pairwise comparisons with the Bonferroni method were taken to identify the differences. Differences were expressed as mean differences with the 95% confidence intervals (95% CI). Statistical analysis was performed with Statistical Package for the Social Sciences, version 11.0 for Mac OS X (SPSS, Chicago, IL, USA).

RESULTS

In Table 2 a frequency table is illustrated with a summary of the results. Details of the relationship between treatment modality and the dependent variables are given in Table 3.

α/β-Ratio for prostate is 1.5 Gy.

A significant association was found between treatment modality and Prostate_EQD_2(95%) (P<0.001). The IMRT-only mean Prostate_EQD_2(95%) was 2.1 Gy more than the brachytherapy modalities. No statistically significant associations were observed for Prostate_EQD_2(90%) (P=0.51). Again statistically significant associations were observed for Prostate_EQD_2(50%) and Prostate_EQD_2(5%), where higher mean EQD_2 values were observed for both brachytherapy modalities. When looking at the calculations for the organs at risk all associations were statistically significant. For both rectum and bladder the IMRT-HDR treatment yields lower dose compared to the IMRT-PDR treatment, which in its turn yields much lower values compared to the IMRT-only treatment. For the mean Rectum_EQD_2(2ml) and mean Bladder_EQD_2(2ml) the differences were 13.3 Gy and 13.4 Gy, respectively (IMRT-only minus IMRT-HDR) and 9.2 Gy and 8.9 Gy, respectively (IMRT-only minus IMRT-PDR). Comparing IMRT-PDR to IMRT-HDR shows 4.1 Gy and 4.5 Gy more for the mean Rectum_EQD_2(2ml) and the mean Bladder_EQD_2(2ml) in case of IMRT-PDR. When analyzing Urethra_EQD_2(10%) there is no statistically significant difference between IMRT-HDR and IMRT-only (P=0.11), although the Urethra_EQD_2(2ml) for IMRT-PDR was 6.9 Gy higher than IMRT-only (P<0.001). No difference in conformation number exists between the two brachytherapy modalities (P=0.35). However, the conformation numbers of the brachytherapy modalities are much better than IMRT-only (both P values <0.001).

Table 2a. Mean EQD$_2$ values (Gy) and mean CN for different organs if α/β-ratio for prostate is 1.5 Gy. P-value found by 2-way ANOVA and F-test.

	IMRT-only	IMRT-PDR	IMRT-HDR	P
Prostate_EQD$_2$(95%)	75.0	72.9	72.9	<0.001
Prostate_EQD$_2$(90%)	75.9	75.9	76.3	0.510
Prostate_EQD$_2$(50%)	79.5	89.8	92.3	<0.001
Prostate_EQD$_2$(5%)	83.0	207.2	228.2	<0.001
Rectum_EQD$_2$(2ml)	67.0	57.8	53.7	<0.001
Bladder_EQD$_2$(2ml)	71.2	62.2	57.8	<0.001
Urethra_EQD$_2$(10%)	80.7	87.6	79.1	0.010
CN	0.30	0.59	0.58	<0.001

Table 2b. Mean EQD2 values (Gy) and mean CN for different organs if α/β-ratio for prostate is 10 Gy. P-value found by 2-way ANOVA and F-test.

	IMRT-only	IMRT-PDR	IMRT-HDR	P
Prostate_EQD$_2$(95%)	73.7	72.1	72.3	<0.001
Prostate_EQD$_2$(90%)	74.3	74.3	74.8	0.180
Prostate_EQD$_2$(50%)	76.9	83.5	86.5	<0.001
Prostate_EQD$_2$(5%)	79.4	144.3	171.7	<0.001
Rectum_EQD$_2$(2ml)	67.0	56.8	58.4	<0.001
Bladder_EQD$_2$(2ml)	71.2	61.1	63.2	<0.001
Urethra_EQD$_2$(10%)	80.7	84.1	96.5	<0.001
CN	0.30	0.57	0.59	<0.001

α/β-Ratio for prostate is 10 Gy.

Comparable statistical significant differences were observed for the prostate EQD$_2$-volume parameters, as α/β-p_1.5. In contrast to the α/β-p_1.5 situation, the IMRT-PDR mean EQD$_2$ values for rectum and bladder were less than IMRT-HDR (1.6 Gy; P=0.33 and 2.2 Gy; P=0.002, respectively). The mean Urethra_EQD$_2$(10%) doses for IMRT-PDR and IMRT-HDR are significantly higher than for IMRT-only (3.4 Gy; P=0.05 and 15.8 Gy; P<0.001, respectively). As in the situation of α/β-p_1.5 the conformation number for the brachytherapy modalities are much better than for IMRT (both P values <0.001).

DISCUSSION

This modeling study is based on patients who were actually treated with brachytherapy using a temporary implant. As a consequence, the position of the catheters and the resulting isodose distribution is not from a perfect implantation but exactly as it happens in practice. An IMRT plan was made on the same CT dataset to allow a reliable comparison.

Table 3. Mean differences between modalities with 95% confidence intervals for different α/β-ratio's for prostate.

	α/β-ratio for prostate = 1.5 Gy			α/β-ratio for prostate = 10 Gy		
		95% CI	P		95% CI	P
P_EQD$_2$(95)	-2.1	-3.4 to –0.9	<0.001	-1.6	-2.5 to –0.7	<0.001
P_EQD$_2$(50)	10.3	8.6 to 12.0	<0.001	6.7	5.4 to 7.8	<0.001
P_EQD$_2$(5)	124.2	110.4 to 138.0	<0.001	64.8	57.3 to 72.4	<0.001
R_EQD$_2$(2ml)	-9.2	-10.5 to -7.9	<0.001	-10.3	-11.7 to –8.8	<0.001
B_EQD$_2$(2ml)	-8.9	-10.1 to –7.7	<0.001	-10.1	-11.6 to –8.7	<0.001
U_EQD$_2$(10)	6.9	5.0 to 8.9	<0.001	3.4	0.9 to 5.9	0.050
CN	0.30	0.27 to 0.32	<0.001	0.29	0.27 to 0.32	<0.001

PDR minus IMRT-only.

	α/β-ratio for prostate = 1.5 Gy			α/β-ratio for prostate = 10 Gy		
		95% CI	P		95% CI	P
P_EQD$_2$(95)	-2.1	-3.3 to –0.9	<0.001	-1.5	-2.4 to –0.5	0.001
P_EQD$_2$(50)	12.9	11.1 t 14.6	<0.001	9.6	8.4 to 10.8	<0.001
P_EQD$_2$(5)	145.2	131.4 to 159.0	<0.001	92.3	84.7 to 99.8	<0.001
R_EQD$_2$(2ml)	-13.3	-14.6 to –12.2	<0.001	-8.6	-10.1 to –7.1	<0.001
B_EQD$_2$(2ml)	-13.4	-14.6 to –12.2	<0.001	-8.0	-9.4 to –6.5	<0.001
U_EQD$_2$(10)	-2.8	-6.1 to 0.4	0.110	15.8	13.3 to 18.3	0.050
CN	0.28	0.25 to 0.31	<0.001	0.29	0.26 to 0.31	<0.001

HDR minus IMRT-only

	α/β-ratio for prostate = 1.5 Gy			α/β-ratio for prostate = 10 Gy		
		95% CI	P		95% CI	P
P_EQD$_2$(95)	-0.1	-1.3 to 1.2	1.000	-0.2	-1.1 to 0.8	1.000
P_EQD$_2$(50)	-2.5	-4.3 to –0.8	0.002	-2.9	-4.2 to –1.8	<0.001
P_EQD$_2$(5)	-21.4	-34.8 to –7.2	0.002	-27.4	-35.0 to –19.8	<0.001
R_EQD$_2$(2ml)	4.1	2.8 to 5.4	<0.001	-1.6	-3.1 to 0.1	0.330
B_EQD$_2$(2ml)	4.5	3.3 to 5.7	<0.001	-2.2	-3.6 to –0.7	0.002
U_EQD$_2$(10)	8.6	6.7 to 10.6	<0.001	-12.4	-14.9 to –9.8	<0.001
CN	0.02	-0.01 to 0.04	0.350	0.01	-0.02 to 0.03	1.000

PDR minus HDR.
The prefix P is for prostate, R is for rectum, B is for bladder, and U is for urethra.

A model with radioactive seed implantation as a boost was not performed, because obviously no comparison of a seed implant and a temporary implant could be made for the same patient. In a similar modeling study of King *et al.* external beam radiotherapy

(45 Gy) with a seed implantation was compared to dose-escalated IMRT. In this study tumor control probabilities (TCP) were calculated. They predicted a superior outcome for the external beam radiotherapy with seed implantation for high-risk prostate tumors [15].

Dose distribution in target volume

In this study we found that for both α/β-prostate_1.5 and α/β-prostate_10 the mean Prostate_EQD_2(90%)is similar for IMRT-only compared to the brachytherapy modalities. This means that at least 90% of the prostate should receive the same minimal dose whatever modality is chosen. Because of better coverage of the target volume with IMRT-only the Prostate_EQD_2(95%) values are higher. It is debatable these small differences (1.5 to 2.1 Gy) would have any significant clinical impact. By looking at the dose distribution for brachytherapy the under dosage is particularly at the base of the prostate and has been recognized by others before [22]. Larger differences are found for Prostate_EQD_2(50%) values. Fifty percent of the prostate receives at least 7-13 Gy more dose with brachytherapy. This extra dose in the central parts of the prostate, where it is assumed that the tumor load is greatest, is more likely to have clinical consequences for tumor control. The same observation was also found by Wang *et al.* who calculated equivalent uniform dose (EUD) to compare different radiotherapy modalities [31]. In their study the combination of external beam radiotherapy with both permanent and non-permanent brachytherapy yields a higher EUD than dose-escalated external beam radiotherapy, particularly if low α/β-ratio for prostate cancer is assumed. Based on the higher EUD, TCP-values were also higher.

Dose distribution in organs at risk

As expected, the EQD_2 values for rectum and bladder in our study are much lower for the brachytherapy modalities compared to IMRT-only, illustrating the better sparing of surrounding organs at risk for brachytherapy. Because of this sparing, dose escalation for prostate cancer is easier achieved with brachytherapy compared to IMRT-only. If for IMRT-planning a reduced margin for PTV2 is used towards the rectum instead of no margin, the prostate coverage will be improved. However, we expect that the dose in rectum will increase further, enlarging the differences we found on rectal dose between IMRT and the brachytherapy modalities.

The results in this study illustrate a different effect of treatment modality on urethra dose. Despite high doses within the brachytherapy implant it was possible to limit the dose to the urethra by optimization of dwell-times. However, because of hypofractionation, especially in case of α/β-p_10, the urethra dose for IMRT-HDR was the highest. The required physical dose for HDR was much less in case of α/β-p_1.5, reducing the urethra dose dramatically. Another way to reduce urethra dose is by placing more needles into the prostate to achieve a more homogeneous dose distribution [19].

When IMRT-PDR is compared to IMRT-HDR for α/β-p_1.5 it is obvious that because of the physical dose reduction for HDR therapy the EQD_2 to rectum and bladder is less than PDR; about 4 Gy for an organ volume of 2 ml. Notwithstanding that a higher rectal dose is given with IMRT-PDR compared to IMRT-HDR the probability of late rectal toxicity is minimal because the EQD_2 remains below 60 Gy [3]. For α/β-p_10 the differences are much smaller.

Alternative α/β-values for prostate cancer

One may wonder what the results would be if an α/β-ratio for prostate cancer of 3-5 Gy was chosen as proposed by several authors [14, 20, 26]. By looking at Table 2 it is clear that for the range of α/β-ratios for prostate cancer between 1.5 Gy and 10 Gy the EQD_2 for 90% for the prostate volume will be similar for both the IMRT only treatment as for the brachytherapy treatments. For this whole range of α/β-ratio the Prostate_EQD_2(50%) is the highest for the HDR treatment and the lowest for the IMRT only treatment. These results will also be valid for an α/β-ratio of 3-5 Gy. When the rectum and bladder dose are considered, the dose is lower for the brachytherapy treatments in the whole range of α/β-ratios. For low α/β-ratio for prostate cancer the EQD_2 on these organs is lower for HDR than for PDR treatments, but for high α/β ratio the opposite is the case. Equivalence in EQD_2 for both brachytherapy modalities is expected when the α/β-ratio for prostate cancer is the same as the organs at risk, i.e: 3 Gy.

Conformity of treatment

One of the main advantages of brachytherapy is the ability to have a very conformal treatment. In our study no differences were noticed between the brachytherapy modalities whichever α/β-ratio for prostate was chosen. The conformity of treatment expressed as conformation number was 27%-29% better than for IMRT-only. The explanation for this difference is the larger volume outside the CTV that is treated to a dose equal to the reference dose with IMRT-only. When applying IMRT certain margins must be taken from the CTV to account for geometrical uncertainties, such as inter-fraction and intra-fraction internal organ motion, but also delineation uncertainties [16]. With brachytherapy no extra margin are taken because the implant stays in and moves together with the target volume. Improvement of conformation number when only IMRT is given can be obtained by reducing the PTV volume with closer margins around the CTV. Closer margins can be accepted with for example improved position verification and higher delineation accuracy by means of Image Guided Radiotherapy [16]. Improving conformation number corresponds to less dose on the surrounding organs of the prostate and probably with lower incidence of late toxicity.

Conclusion

For all α/β-ratio values between 1.5 and 10 Gy the dose with brachytherapy to a large part of the prostate is much higher than for IMRT-only and could be more favorable for tumor control. As expected, combined external beam radiotherapy plus brachytherapy modalities showed better conformation values than IMRT-only. This observation was in agreement with the lower dose to the rectum and bladder for the brachytherapy modalities. The dose to the urethra for IMRT-only and IMRT-PDR did not change much with the choice of the α/β-ratio for prostate. However, the influence was very pronounced in case of IMRT-HDR. This means that when applying HDR brachytherapy treatment careful attention should be paid to the urethra dose particularly when high fraction doses are used.

APPENDIX

BED modeling

The biologically effective dose (BED) can be calculated by multiplying the given physical dose (D) by the relative effectiveness (RE):

$$BED = RE \bullet D \ \text{[Gy]} \qquad \text{(Eq. 1)}$$

For fractionated external beam therapy and HDR brachytherapy assuming complete repair between fractions, RE is:

$$RE = 1 + \frac{d}{\alpha/\beta} \qquad \text{(Eq. 2)}$$

where d is the fraction dose and α/β is the α/β-ratio of the organ concerned.

For PDR brachytherapy RE is:

$$RE_{PB} = 1 + 2 \bullet \frac{1}{\alpha/\beta} \bullet \frac{T_{1/2}}{\ln(2)} \bullet \frac{D_P}{T_{pulse}} \bullet F_P(T_{1/2}, OTT, N) \qquad \text{(Eq. 3)}$$

where

$T_{1/2}$ is the half time of repair for sublethal damage,

D_p is the dose per pulse,

T_{pulse} is the time during which the dose of one pulse is delivered,

F_p is a modifying factor expressing the influence of repair kinetics.

$$F_P = 1 - \frac{1}{N \bullet \mu \bullet T_{Pulse}} \bullet (N \bullet Y - S \bullet Y^2) \qquad \text{(Eq. 4)}$$

where

$$\mu = \frac{\ln(2)}{T_{1/2}} [h^{-1}] \qquad \text{(Eq. 5)}$$

N is total number of pulses delivered

$$Y = 1 - e^{-\mu \bullet T_{Pulse}} \qquad \text{(Eq. 6)}$$

$$S = \frac{K}{(1 - K \bullet Z)^2} \bullet (N \bullet (1 - K \bullet Z) - 1 + K^N \bullet Z^N) \qquad \text{(Eq. 7)}$$

$$K = e^{-\mu \bullet (T_{Period} - T_{Pulse})} \qquad \text{(Eq. 8)}$$

$$Z = e^{-\mu \bullet T_{Pulse}} \qquad \text{(Eq. 9)}$$

To calculate EQD_2 the BED is divided by the RE of 2 Gy.

$$EQD_2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}} \qquad \text{(Eq.10)}$$

Conformation number

The degree of conformity can be quantitatively calculated by the conformation number (CN):

$$CN = \frac{TV_{ref}}{CTV} \bullet \frac{TV_{ref}}{V_{100}} \qquad \text{(Eq.11)}$$

where TV_{ref} is the volume within the CTV receiving a dose equal to or greater than the reference dose and V_{100} is the total volume receiving a dose equal to or greater than the reference dose.

The first ratio in the equation is the proportion of the CTV receiving a dose equal to or greater than the reference dose. The second ratio in the equation is the proportion of the treated volume (V_{100}) that covers the CTV and is in addition a measure of how much 'normal' tissue outside the CTV is covered by the reference dose. The CN has a value between 0 and 1. A CN of 1 means that the CTV is completely covered by the reference dose and that 'normal' tissue outside the CTV receives less dose than the reference dose. In case of a geographical miss or if the V_{100} is much larger than the TV_{ref}, the CN reaches a value of 0.

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