The comparison of radiotherapy techniques for treatment of the prostate cancer: the three-field vs. the four-field

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Our purpose was to compare the three-field and the four-field planning techniques in patients with localized prostate cancer.

Twenty patients with localized prostate cancer stage (T1-T2N0M0) were chosen for the analysis of treatment plans. Simulation and CT planning were performed in all cases in the supine position with a "comfortably" full bladder. The planning treatment volume (PTV) was defined as the prostate gland with a 10 mm margins around the clinical target volume (CTV), except for the posterior margin (prostate gland – the anterior part of rectum wall), where a 5 mm margin was applied. The clinical target volume (CTV) was defined as prostate gland. For each patient the following organs at risk (OAR) were outlined: rectum, bladder, and right femoral head. The following three-field and four-field plans were made: 3 field techniques with beam angles orientations 0˚, 120˚, 240˚ and 0˚, 90˚, 270˚, and 4 field technique (0˚, 90˚, 180˚, 270˚). Two versions of treatment plans were also made including different range of applied energy of photons (6 MV or 20 MV) for the therapeutic machine – Clinac 2300 CD. Beam portals were conformal by shaped by a multileaf collimator (MLC). The daily fractionation dose 1.8 Gy and the total dose 73.8 Gy were applied in each case. One hundred and twenty treatment plans were made and compared according to the following parameters: the mean total dose (MTD) in the target, the tumor control probability (TCP), the mean total dose (MTD) in the OAR (rectum, bladder, and right femoral head), the normal tissue complication probabilities (NTCP), and the volume of OARs which received arbitrary chosen fraction (%) of the total prescribed dose (73.8 Gy=100%). ANOVA statistical methods to verify the significance of differences between the treatment plans were used.

There were no significant differences in the distribution of MTD and TCP in the PTV for the evaluated treatment plans. There were no significant differences in the MTD, NTCP, V80, and V90 distribution in bladder. The distribution of MTD, NTCP, and V80 for rectum indicated that lower parameters were achieved in the case of the three-field technique with the orientation of beams 0˚, 90˚, 270˚. The distribution of MTD, NTCP, and V70 in right femoral head for each treatment plan was below the tolerance dose.

The study has shown that the three-field technique (an anterior and two opposing lateral fields with the portals orientation 0˚, 90˚, 270˚) and applied energy photons 20 MV, provides the best rectal protection. All evaluated plans according to the dose distribution in the target (PTV) have not indicated any significant differences. None of the techniques has shown any significant advantages in sparing bladder. The risk of morbidity in the femoral heads for all the applied techniques, in a dose up to 73.8 Gy was not a therapeutic problem. However, the three-field technique with beams orientation 0˚, 120˚, 240˚ gave the best sparing effect for femoral heads.

Key words: prostate cancer, conformal radiotherapy, planning techniques

High dose conformal radiotherapy has become one of the most important method of treatment in patients with localized prostate cancer [7, 8]. Several oncological centers have reported improved outcomes measured as biochemical disease free survival (bDFS), when the tumor target dose increased [9, 14, 17, 28, 29]. Technological advances in the treatment planning have provided a great number of options in treatment plans. The optimal number of beams, their orientation, the width of margins around the clinical target volume, and the most efficient way of patient's immobilization during irradiation are still under debate [1, 2, 11, 12, 15, 21, 26, 27]. Many radiotherapy techniques have existed in clinical practice. The simplest of them involve three- or four-fields, while more complicated techniques use five to even eight-fields. For example, the most popular techniques used in the USA are those from five to eight, rarely more fields, while in the European countries simplier techniques using three- or four-fields beam are more popular. An evaluation of these techniques according to the risk of injury of organs at risk (OAR) may lead to answer the following question: which of these techniques seems to be the best in clinical routine? The outline of literature on the treatment of prostate cancer provides no significant indication which of these techniques is better. Moreover, even the simplier techniques such as 3- or 4-fields may provide a similar therapeutic index as more sophisticated techniques.

In 1999 in the Greatpoland Cancer Center, the treatment of prostate cancer patients with the implementation of three-dimensional conformal radiotherapy (3D CRT) using the techniques 3- and 4-fields, was started. The main aim of the study was to compare the above mentioned techniques, which have been used in our center.

Material and methods

Twenty randomly chosen patients with localized prostate cancer (T1-T2N0M0), who were irradiated in the Greatpoland Cancer Center in Poland, were investigated retrospectively. The median age of patients was 65 years (range: 56–72 years). Median pretreatment PSA level was 10 ng/ml (range: 5–16 ng/ml). The simulation and CT scanning in the supine position with "comfortably" full bladder were performed. The CT images were obtained at 5 mm increments through the planning treatment volume (PTV), and then automatically transferred to the CadPlan ver 3.1.2 planning workstation. The PTV was defined as the prostate gland with 10 mm margins around the clinical target volume (CTV) except for the posterior margin (the prostate gland – the anterior wall of rectum), where a 5 mm margin was applied. In each case the CTV was defined as prostate. Such margins around CTV were performed because the following factors were considered: the patient set-up error, penumbra, and internal organs movements. For each patient the following organs at risk were outlined: rectum, bladder and right femoral head. The following treatment plans were made: the three-field (3F) technique with beam angles orientation 0˚, 120˚, 240˚ and with the arrangement of beam angles 0˚, 90˚, 270˚, and the four-field technique (4F) with angles orientation 0˚, 90˚, 180˚, 270˚. We also made two versions of plans including different ranges of the applied energy of photons: 6MV and 20 MV for the therapeutic machine Clinac 2300 CD. Each portal beam was conformally shaped by the application of a multileaf collimator (MLC). The daily prescribed dose to the isocenter point was 1.8 Gy and the total dose was 73.8 Gy. The following beam weights were applied: the 3-field technique (angles 0˚ – 40%, lateral angles – 30%), the 4-field technique for each angle 25%. All 3-field techniques were wedged for two lateral beams with the orientation of the wedges with the thin end of the wedge positioned posteriorly. In this way one hundred and twenty treatment plans were made and then compared. For rectum we have chosen two parameters for evaluation of an optimal treatment plan:

a) mean total dose (MTD),

b) volume which received a greater dose than 80 % (V80) of total prescribed dose (73.8 Gy),

c) NTCP.

Lyman's NTCP radiobiological model to estimate a risk associated with particular treatment plans was used. Parameters (n=0.12, m=0.15) used in the Lyman's model of NTCP [16] were obtained from the data published by Kutcher and Burman [4].

The evaluation of treatment plans considering bladder was based on comparisons of:

a) mean total dose (MTD),

b) volume of bladder which received a dose higher than 50% (V50) and 80% (V80) of prescribed total dose (73.8 Gy),

c) NTCP.

For right femoral head the following parameters were compared: mean total dose (MTD), the fraction of volume, which received a higher, dose than 70% (V70) of total prescribed dose, and NTCP.

All above mentioned parameters have been compared in the plans using ANOVA statistic methods. In each case the tumor control probability (TCP) for all evaluated treatment plans was calculated. This calculation was based on the model described by Webb and Nahum [30]. This model allows to calculate TCP from the dose volume histograms (DVHs) in PTV. Basic parameters for this calculation are radiosensivity (=0.35 Gy^{-1}), mean density of clonogenic cells (10^4 mm^{-3}), and inter-patient standard deviation (=0.08 Gy^{-1}). These parameters were presented by Nahum and Tait [19] and then confirmed by Sanchez-Nietero and Nahum [22], and correleated with results of seven-years follow-up conducted by Hanks et al [10].

Calculation of NTCP was based on the radiobiological model estimating the risk of the radiotherapy injury and was proposed by Lyman [16]. This model was based on data published by Burman et al [4]. The basic radiobiological parameters used in this model for the NTCP calculation have the following variables: m – parameter described the slope of curve which describe correlation between NTCP and dose and n – describes the correlation between risk of injury and percentage volume of irradiated organs at risk. For analyzed organs the following parameters were incorporated: rectum (n=0.12; m=0.15), bladder (n=0.5; m=0.11), and femoral head (n=0.25; m=0.12).

Table 1. Comparison of the MTD in CTV and probability of TCP for all analyzed treatment plans. ANOVA, α=0.05

Variable	Technique and rate of photons energy						ANOVA statistical significance
	3F 6MV	3F 20MV	T 6MV	T 20MV	4F 6MV	4F 20MV	
MTD±SD (Gy)	74.4±0.5	73.7±0.9	74.3±0.6	73.8±0.6	74.4±1.0	74.0±1.0	No
TCP±SD (%)	73.3±3.1	73.1±2.9	72.8±3.4	73.7±3.4	74.1±2.7	73.8±3.2	No

3F – 3-field technique with angles 0˚, 90˚, 270˚; T – 3-field technique with angles 0˚, 120˚, 240˚; 4F – 4-field technique; MTD(Gy) – the mean total dose which received the whole volume of structure; TCP – tumor control probability; SD – standard deviation.

ANOVA statistic analysis was used to compare analyzed techniques. H_0 hypothesis was established as lack of any differences between analyzed techniques of treatment planning. In the case of rejection of statistical importance many post hoc tests were performed to analyze accured differences between analyzed groups. The main statistical tests which have been performed were the Turkey test and the Newman-Keules test. The third of them was the Scheffy test. For all tests the level of statistical significance was established as 0.05.

Results

The analysis of the mean total dose distribution (MTD) and the TCP in the PTV did not indicate any statistical differences in the analyzed treatment plans.

The best distribution of MTD, NTCP and arbitrary chosen volumes in rectum were achieved by using the 3-field technique with the following beams orientation 0˚, 90˚, 270˚. No statistical differences concerning bladder for the analyzed treatment plans were shown. Right femoral head was spared in the best way by using the 3-field technique with the fields orientation 0˚, 120˚, 240˚. The analysis of all treatment plans is shown in Table 1 and statistical analysis of the treatment plans including MTD, NTCP and arbitrary chosen volumes of irradiated organs are shown in Table 2.

Discussion

The implementation of three-dimensional conformal radiotherapy gives opportunity to improve results of the localized prostate cancer treatment [7, 8, 9, 14, 17, 28, 29]. An important goal of 3D CRT is to enhance local control by increasing the radiation dose to the target, without significant increase of treatment toxicity or even in some cases its reducing. The standard treatment beam arrangement is still being searched because in particular clinical situation such a standard could ascertain that a proposed treatment plan is one of the best options. In addition, such solution may be convenient in clinical practice, especially for radiation department with great burden of work. The last factor is extremely important, since the possibility of preparing numerous plans triggers problems with choosing the optimal treatment factors such as number and fields orientation, and might spare a time.

In our study, for evaluation of radiotherapy techniques we have chosen two versions of the three-field technique (3F) and a typical four-field technique (box-technique). The results from our analysis indicated that a technique which spared rectum the best was the 3F technique involving angles 0˚, 90˚, 270˚. Our data have also demonstrated that the sparing effect was better when a higher energy of photons i.e. 20 MV was used. On the other hand, the technique with the worst sparing effect of rectum, was the 4F technique (box technique). Another OAR which was evaluated, was bladder. Generally none of the analyzed techniques indicated the advantage or disadvantage in a sparing effect of bladder, and these techniques were comparable. The last analyzed OAR was right femoral head. The comparison of analyzed parameters indicated that the 3 fields techniques with the fields orientation 0˚, 120˚, 240˚ provided the best sparing effect.

In our study we compared only simple techniques of radiotherapy treatment in the prostate cancer such as the 3 F and 4 F technique, because the available data from literature did not indicate that more complicated plans using more fields might significantly increase the therapeutic index [1, 6, 13, 15]. Another reason for choosing only the 3- and the 4-field techniques for the evaluation was the fact that in more complicated techniques, the risk of introducing any errors is generally higher. Moreover such techniques are more time consuming.

Rectum. Generally it is agreed that the most dose-limiting organ at risk (OAR) in the prostate cancer radiotherapy is rectum [3, 24, 25]. Mainly, rectal side effects limit the dose escalation in radiotherapy of the prostate cancer. Therefore, each plan should be precisely evaluated according to the received dose and the probability of radiation injury risk in this organ. There is still a lack of sufficient clinical data, which allow to estimate the tolerance dose in the case of

Table 2. Comparison of the MTD and NTCP for OAR for all evaluated treatment plans. ANOVA, testes post-hoc (Turkey and Newman-Keuls), α=0.05

Parameter	Technique and applied energy of photons						ANOVA
	3F 6MV	3F 20MV	T 6MV	T 20MV	4F 6MV	4F 20MV	statistical significance
Rectum							
MTD ± SD (Gy)	48.4 ± 11.1	48.1 ± 10.1	34.4 ± 8.1	35.6 ± 7.7	47.3 ± 5.7	46.6 ± 5.6	Yes
V80 ± SD (%)	33.3 ± 11.2	31.2 ± 10.6	22.8 ± 8.2	21.1 ± 7.5	27.8 ± 8.2	26.4 ± 7.6	No
NTCP ± SD (%)	13.3 ± 4.7	12.6 ± 2.8	4.8 ± 3.1	3.6 ± 2.4	10.9 ± 4.1	8.7 ± 4.4	Yes
Bladder							
MTD ± SD (Gy)	50.0 ± 11.1	48.4 ± 10.8	45.4 ± 8.7	43.9 ± 8.5	47.7 ± 8.8	46.9 ± 8.7	No
V_{80} ± SD (%)	33.2 ± 10.2	31.4 ± 8.2	25.7 ± 9.5	25.9 ± 7.4	29.3 ± 6.9	29.1 ± 8.7	No
V_{90} ± SD (%)	29.8 ± 9.4	27.7 ± 8.2	22.8 ± 10.9	23.3 ± 8.3	26.4 ± 10.1	25.6 ± 9.7	No
NTCP ± SD (%)	6.2 ± 3.1	5.8 ± 2.9	4.3 ± 3.3	4.5 ± 2.7	5.1 ± 2.8	4.8 ± 2.5	No
Femoral head							
MTD ± SD (Gy)	12.4 ± 5.4	11.4 ± 5.1	40.3 ± 13.4	37.0 ± 12.1	35.5 ± 10.5	32.5 ± 9.7	Yes
V_{70} ± SD (%)	1.7 ± 2.2	1.0 ± 1.3	9.6 ± 8.7	2.8 ± 3.2	2.4 ± 1.7	1.3 ± 1.8	No
NTCP ± SD (%)	0.2 ± 0.2	0.0 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.8 ± 1.1	0.3 ± 0.2	No

3F – 3-field technique with angles 0°, 90°, 270°; T – 3-field technique with angles 0°, 120°, 240°; 4F – 4-field technique; NTCP – normal tissue complication probability; TCP – tumor control probability; 3F-angles (weight): 0 degree (40%), 120 degrees (30%) and 240 degrees (30%); T-angles (weight): 0 degree (40%), 90 degrees (30%), and 270 degrees (30%); 4F-angles (weight): 0 degree (25%), 180 degrees (25%), 90 degrees (25%), and 270 degrees (25%); MTD(Gy) – the mean total dose which received the whole volume of structure; Vx (%) – percentage of volume of OAR which received x (%) of total prescribed dose (73.8 Gy=100%); NTCP (%) – normal tissue complication probability for total prescribed dose 73.8 Gy.

a partial organ irradiation, and many of the interpretations have been speculative. Probably few factors influence this situation, first is the change in the day-to-day volume of irradiated rectum caused by the difference in contents of this organ, which leads to impossibilities of an accurate in vivo dosimetry for part of the irradiated volume. Such situation may correspond to an improper analysis of the reported intensity and quantity of late toxicities. It is obvious that the incidence of rectal complications is not only associated with radiation total dose but also with the amount of irradiated volume of the organ [5, 23]. EMAMI et al [5] estimated that the dose which was considered to give 5% complications during 5 years follow-up (TD5/5) was 60 Gy for the whole organ irradiation. According to the study of EMAMI et al [5] dose of 80 Gy for the whole rectum giving 50% (TD50/5) of patients severe proctitis/necrosis/fistula/stenosis. In our study calculations of NTCP were based on the dose-volume histograms (DVHs), which included the whole cavities and walls of rectum. This solution was chosen since it is very complicated to outline only the wall of this organ, and in addition such a procedure is time consuming.

Results of our analysis indicated that the technique, which spared rectum the best, was the 3-field technique with fields orientation 0°, 90°, 270° and energy of photons 20 MV. In the case, when the same technique but with different energy photons of 6 MV was applied, the sparing effect was minor. All analyses of NTCP, MTD, and V80, and V60 of indicated the same outcome. However, the differences in NTCP for this technique with application energy of photons of 6 MV and 20 MV were small. On the other hand, the worse technique was the 4-field technique (box) with photons energy of 6 MV. FIORINO et al [6] obtained the same results. Also KHOO et al [13] indicated that the 3-fields plan (angles 0, 90, 270) allows to achieve the greatest rectal sparing with acceptable bladder and femoral heads doses. In contrast NEAL et al [20] concluded that the 4 F-box technique provided the best rectal sparing compared to 3 F techniques. We must underline that the 3F technique evaluated by NEAL et al [20] applied the beam angles 04°, 110°, 250° which according to KHOO et al [13] were inferior to 3F technique with angles orientation 0°, 90°, 270°.

It should be noted, that calculation of the NTCP based on the applied biological model may not accurately estimate the real risk of the organ damage. Therefore, the differences are not representative for the real clinical estimation but may be suitable for the comparison of treatment plans.

Bladder. Another important OAR in radiotherapy of the prostate cancer is bladder. Comparison of received dose in bladder did not show any significant differences between analyzed plans. We underline that in our example (T1-2) target encompassed only the prostate gland. It was probably one of the most important reasons, which has caused that the tolerance dose for the whole bladder was not exceeded. Probably, the different situation could have happened if the whole bladder had been irradiated. Bladder is an example of an organ in which late complications were correlated with the dose and the irradiated volume. According to MARKS et al [18] we can expect the complication rate in range from 5% to 10% at doses 50–65 Gy delivered to about 30% of the bladder volume, but the same rate of complications can be expected at the doses 65–75 Gy applicated to <20% of the bladder. On the other hand, EMAMI et al [5] estimated that the TD5 is for the whole bladder irradiated to the dose 65 Gy or 60% of the whole bladder irradiated to the dose 80 Gy.

Femoral heads. The last OAR, which was evaluated, was right femoral head. We chose only one bone because the dose distribution in the left was the same in each case. All evaluated plans for the right femoral head using NTCP did not indicate any significant differences in the quality of dose distribution. The same results were obtained by FIORINO et al [6]. However, even in this case there was no significant clinical impact on the toxicity because the received dose was below the tolerance dose. The data from literature have indicated that more sophisticated technique using of 6- or even more fields may lead to improvement of the femoral head protection, but on the other hand, the applied dose 73.8 Gy is not a limiting factor for escalating dose in 3D CRT. However, the accumulated dose in femoral head should be taken into account due to old age of treated patients and usually administered antiandrogen therapy. In our opinion no evaluated treatment technique gave advantage for sparing the femoral head, when the total dose was below 74 Gy. In this case, there was no significant clinical impact on the toxicity since the received dose was below the tolerance dose for femoral heads.

In summary, we have to emphasize that at present the NTCP model used for evaluation of the radiation plans was only an additional tool for evaluation of differences between plans. Even the application of these models had a lot of imprecisely established parameters. Probably one of the best biological models for their testing are rectum and bladder in 3D CRT of the prostate cancer due to a wide range of applied doses, 3 D-treatment planning, long-term follow-up, conventional fractionation without chemotherapy. The analyzed material was uniform because in each case the PTV encompasses prostate gland. In other clinical stages of prostate cancer, for example in the T3 stage the presented arrangement of beams which were evaluated may not indicate similar results, and other technique may be more suitable for treatment of such cases.

The best sparing effect for rectum was observed when the three-fields technique with angles 0°, 90°, 270° was used. The worst dose distribution in rectum was obtained with the 4 field technique. Generally, none of the evaluated techniques gave significant advantage in sparing the bladder. The risk of morbidity in femoral heads for the applied techniques with dose up to 73.8 Gy was not a therapeutic problem, but the 3 field technique with beams orientation 0°, 90°, 270° gave the best sparing effect. The higher applied energy of photons caused the lower risk of toxicity, especially in rectum.

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