

Comparison of Dose Distribution between Intensity Modulated Radiation Therapy and Dynamic Arc Therapy in and out-of-Field for Prostate Cancer Treatment

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ABSTRACT

AIM: The aim of this study is to compare intensity modulated radiation therapy (IMRT) and dynamic conformal arc therapy (DAT) for prostate cancer treatments.

METHODS: Doses received by in-field and out-of-field organs were estimated for both techniques. We have selected ten patients with prostate cancer and we simulated their treatment using IMRT and DAT. A 6-beams (6MV) ballistic was used for the IMRT treatment, whereas a 4-arc (6MV) ballistic was used for the DAT. Dose volume histograms (DVHs) were computed. For both techniques, Planning Target Volume (PTV), Planning Organ at Risk Volume (PRV) and Remaining Volume at Risk (RVR), as well as estimates of the dose out-of-field for thirteen anatomical sites were analyzed and compared. The out-of-field dose evaluation was performed using experimental data from previous work.

RESULTS: The mean absolute RVR volume, included between 2-45

Gy for IMRT, was about 1500 cm³ larger than with DAT. On the other hand, IMRT significantly increased the irradiated volume of the rectum wall in the dose range 2 to 60 Gy and also significantly increased the irradiated volume of the bladder wall. However, IMRT significantly reduced the dose to the femoral heads, as compared to the DAT. For both techniques, the dose to the PTV remained similar. For the thirteen out-of-fields anatomical sites evaluated, IMRT provided doses about 5% higher than DAT.

CONCLUSIONS: DAT improves the dosimetric parameters of the prostate cancer treatment by reducing the doses not only to the PRV's but also to the RVR while keeping the same PTV coverage.

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Key words: Intensity Modulated Radiation Therapy (IMRT); Dynamic Arc therapy (DAT); Remaining Volume at Risk (RVR); Dose out-of-field; Planning Organ at Risk Volume (PRV)

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INTRODUCTION

Report 83 from the International Commission on Radiation Units and Measurements (ICRU)^[1], introduced the concept of Remaining Volume at Risk (RVR), allowing a convenient global risk assessment of the dose delivered to a given patient. Today commercial treatment planning systems' (TPS) accuracy has been improved to calculate the dose to the Planning Target Volume (PTV) and its immediate vicinity, but do not allow to suitably calculate as well the peripheral dose outside the irradiated volume. To assess the risk of second cancers^[2], the whole patient volume must be considered: the PTV, the Planning Organs at Risk Volumes (PRV) and the RVR. Prostate cancer is a frequent tumor for which radiotherapy is a major treatment. The ballistic of external beam radiotherapy for prostate cancer has changed dramatically during the last decades from two-

dimensional (2D) to three-dimensional (3D) conformal techniques, and then to intensity modulated radiation therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) and dynamic conformal arc therapy (DAT).

Studies based on the results of the epidemiological survival suggested an increase in the development of a secondary cancer in the bladder and rectum after radiotherapy for prostate cancer^[3-5] and the role of hyper/hypo-fractionation is still discussed^[6,7]. Other recent studies^[8,9] have shown that stereotactic techniques for prostate cancer increase patient comfort and improve quality of life. IMRT has been shown to significantly increase the pelvic volume receiving doses under the 15 Gy isodose, but to reduce the irradiated volume of the rectum in the dose range of 5 to 40 Gy and also to significantly reduce the irradiated volume of bladder and femoral heads^[10]. The dose coverage in the PTV remains similar for all three RT techniques. The objective of the current study is to compare IMRT and DAT radiotherapy techniques for prostate cancer treatment performed at the Institut Gustave Roussy. We have evaluated the dose distribution in the PTV and PRV's in the immediate and distant vicinity of the PTV, as well as the delivered dose to the RVR for both techniques to assess risk factors for secondary cancers.

MATERIALS AND METHODS

Patients' selection

The study focused on data from ten patients treated by RT at the Institut Gustave Roussy (IGR) between 2012 and 2013. The patients' selection scheme was such as to include 10 individuals for whom the type of RT was IMRT or DAT. Anatomical characteristics of the patients were derived from clinical parameters, namely age, size and body mass index.

The BMI was calculated by using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \frac{W(\text{Kg})}{H^2(\text{m}^2)}$$

More details on anatomical characteristics of the population are presented in table 1.

Table 1 Anatomical characteristics of the series of selected patients treated with IMRT and DAT: mean values of anatomical data and related standard deviation (SD) are reported.

	Mean value	SD
Patient weight in kg	83	4.6
Patient size in m	1.7	0.3
Patient age in years	70	0.3
BMI in kg/m ²	28.7	1.4

Computed tomography (CT) scan technique

Patient data for treatment planning were acquired using the same CT-scan (*Siemens sensation 40 open*). A CT-scan was performed in the treatment position exploring about 29 cm of the pelvic region. In total, 97 slices were recorded with a thickness of 3 mm.

Volume delineation

Target volumes were defined as the clinical target volume CTV-1 prostate and seminal vesicles, and CTV-2 prostate only. According to the current local policy for daily IGRT treatment using fiducial markers, PTVs are defined with a margin of 5 mm around the CTV in all directions. For prostate radiotherapy PRV's are usually rectum, rectal wall, bladder, bladder wall and femoral heads. These structures were delineated by the same physician to maintain consistency in the definition of volume.

The mean volume of PTV-1 was 150 cm³ (ranging from 90 cm³ to 245 cm³) and the mean volume of PTV-2 was 130 cm³ (ranging from

74 cm³ to 210 cm³). The mean volumes of the rectum, bladder and the femoral heads for the ten patients, as calculated by the TPS, were 70 cm³ (ranging from 43 cm³ to 114 cm³), 275 cm³ (ranging from 172 cm³ to 330 cm³), and 160 cm³ (ranging from 132 cm³ to 190 cm³), respectively.

Dose prescription

Ten patients with localized prostate cancer and different PTV-1 and PTV-2 volumes were included in this study. For each patient, a clinical IMRT and a clinical DAT have been planned, considering a total dose of 78 Gy to the prostate (2 Gy per fraction). Total delivered dose represents the cumulated dose to the prostate for the two PTVs irradiation. The first treatment phase aims at delivering a 46 Gy dose to the prostate and seminal vesicles. In the second phase, a 32 Gy dose is delivered to the prostate only.

TPS dose calculation

In the present study, dose distributions for the PTV, RVR and PRV's were calculated with the treatment planning system Konrad (4.1 version, Siemens) for IMRT (Step and Shoot) treatment, while arc therapy treatment plan calculations were performed using iPlan TPS (iPlan Cranial 3.0 software, BrainLab, Germany). Both TPS are based on the Pencil beam algorithm for dose calculation and have been compared on basic data. DAT ballistic is composed of four coplanar 6 MV dynamic arc beams: PTV-1 is treated by 2 arc beams from 20 to 150 degrees and from 210 to 340 degrees approximately (these angulations are adapted according to patient anatomy). The same angulations of the two previous arc beams are used to irradiate the PTV-2. IMRT ballistic is composed of six coplanar 6 MV beams with gantry angles of 25°, 70°, 135°, 225°, 290° and 335°.

According to ICRU report 83, the PTV dose was assessed with recommended parameters such as median dose (D_{50%}), which represents the prescribed dose, near maximum dose (D_{2%}) and near minimum dose (D_{98%}). Note that VD_{Gy} is the percentage of organ volume exceeding D Gy and D_{x%} is the minimum dose to x% of the organ's volume. In accordance with the ICRU 83 guidelines, the homogeneity index (HI) was calculated by using the following equation: $\text{HI} = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$. The analysis of RVR and PRV's was made according to ICRU 83 recommendation as well. The IMRT and DAT results of all analyses were based on the data of the mean dose volume histograms of the patients' selection.

Calculation limits of the TPS and estimated dose out-of-field

In order to verify the calculation limits of the TPS and dose estimates, dose measurements were performed on the Novalis Tx™ linear accelerator (*Varian Medical Systems, Palo Alto, CA, USA*). 6 MV photon beams were used for the tests. The doses were measured with thermoluminescent dosimeters type TLD-700 (Harshaw Chemical Company, Cleveland, OH). The dosimeters were read on a PCL-3 (*FIMEL, Velizy, France*) automated reader. A water tank of 100 cm × 50 cm × 30 cm dimensions was used for dose to water measurements. The tank was filled with water up to 20 cm. A special holder was designed for the TLD capsules, allowing their positioning at different depths, outside the irradiation field. This support facilitates a reproducible positioning of the capsules. The distance between the source and water surface (SSD) was set to 100 cm. Measurements were performed using four different field sizes: 5 cm × 5 cm, 10 cm × 10 cm, 15 cm × 15 cm and 20 cm × 20 cm. The measurement points were spaced with a constant step of 5 cm, up to 30 cm from the central axis of the beam. From this position,

the measurement points were separated with a 10 cm step, up to 70 cm from the central axis of the beam, at depth of 10 cm in the water tank. All TLDs were prepared and read by Equal-Estro Laboratory (Estro-Equal, Villejuif, France), which is a European reference in the use and analysis of TLDs^[11-13]. For each irradiation technique, dose estimated to the organs distant from PTV for the patients' selection was performed using experimental data from previous work^[2,10,14,15].

Statistics

Friedman test was used to compare DVHs of the two techniques at each dose level. Statistical analyses were performed using SPSS 17.0 for Windows^[16].

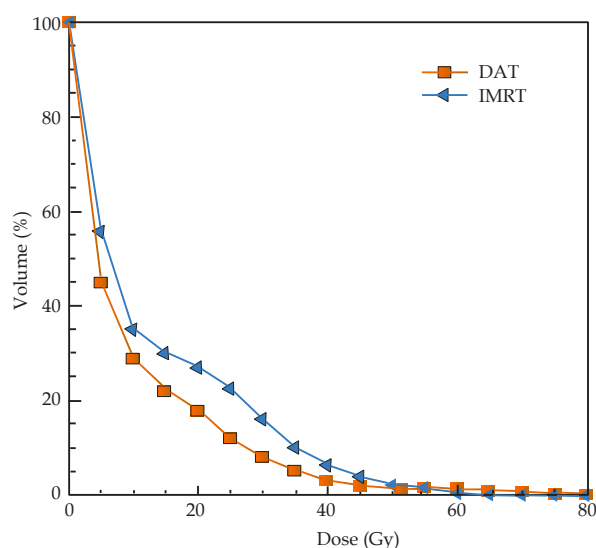
RESULTS

Dose volume calculations by the TPS for RVR

Figure 1 presents the results of the dose distribution in RVR. This distribution shows that DAT reduces the dose in the RVR volume as compared to the IMRT. On average, the indicator V_{10Gy} is 35% for IMRT and 29% for DAT. The volume covered by isodose 15 Gy reaches 30% and 22% for IMRT and DAT respectively. The volume covered by various isodose surfaces below 30 Gy with the IMRT and DAT is 16% and 8% respectively. Similarly, the comparison between the two radiotherapy techniques shows that the 5 Gy isodose covers more volume of the RVR with the IMRT than with the DAT, since the percent of volume covered by this isodose is 53% for IMRT versus 43% for DAT. Figure 2 shows that IMRT irradiates a larger volume of the RVR with lower doses than DAT. The mean absolute RVR volume included between 2-45 Gy for the IMRT is about 1500 cm³ larger than when using DAT. In this dose range, the mean relative volume increase with IMRT, as compared with DAT, is 32%. The difference between the two techniques is statistically significant, as shown by the Friedman statistical test.

Dose volume calculations with the TPS for PRV's

Figure 3 presents the mean dose volume histogram results for PRV's of the patients' selection and shows that, for rectum wall, DAT significantly reduces the volume of irradiated rectum wall receiving



RVR Dose (Gy) 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 78
 Friedman test 0.02 0.02 0.02 0.02 0.02 0.03 0.03 0.02 0.62 0.32 0.21 0.42 0.53 0.63 0.54 0.36

Figure 1 Mean Dose-Volume Histograms comparison between IMRT and DAT techniques for the selected patients, corresponding to the absorbed-dose distributions for the RVR. The volume axis is relative to the total volume of region of interest and reported in percent.

2 to 60 Gy compared with the IMRT (p -values 0.02). DVH of the rectal wall shows that the volume receiving at least 60 Gy increases with IMRT as compared with DAT by 27%. For the bladder wall DAT significantly reduces the volume of irradiated bladder wall, as compared to the IMRT (p -values 0.02): the mean relative volume increases with IMRT, as compared with DAT, by 55%. However, the IMRT significantly reduces the irradiated volume of femoral heads, compared to the DAT (p -values 0.02). For PTVs, no significant difference was observed in the doses delivered to the 98%, 50% and 2% of the PTVs volume between the two techniques of irradiation. For PTV-1 the homogeneity indexes for IMRT and DAT were 0.30 and 0.34 respectively. For PTV-2 the homogeneity indexes for IMRT and DAT were 0.07 and 0.05 respectively.

Calculation limits of the TPS and estimated dose out-of-field

Figure 4 compares the dose profiles obtained experimentally by TLD measurements and those from TPS calculations, for a 10 cm×10 cm field size at a depth of 10 cm in water. The TLD measurements were performed up to 70 cm from the central axis of the beam. For the 10 cm×10 cm field size, for distances between 5 cm and 10 cm from the central axis, we observed that the calculations of both of the TPS overestimate the dose outside the field with an average of 1.5%. This overestimation increases with distance and reaches 2% at 13 cm from the central axis. Table 2 shows the magnitudes of the estimated doses to a selection of thirteen anatomical sites near and distant to the field edge, processing with IMRT and DAT for the patients' selection. The analysis of these results shows that the estimated doses with IMRT are slightly higher than with DAT. In a region distant from the fields' edge, the ratio between the estimated mean doses for both techniques ($\frac{D_{IMRT}}{D_{DAT}}$) varies between 1.01 and 1.10. The maximum ratio was estimated for the right eye located at a distance of approximately 68 cm from the PTV. The minimum ratio was estimated for the spleen located at a distance of approximately 33 cm from the PTV. The mean of estimated doses ratio ($\frac{D_{IMRT}}{D_{DAT}}$) between IMRT and DAT is almost equal to 1.05 for all PRV's at a distance from the PTV.

DISCUSSION

The present work compares IMRT and DAT for prostate cancer treatments. Doses received by in-field and out-of-field organs were assessed for both techniques. Regarding the ten selected patients, DVHs were computed for PRV's and RVR for both techniques, and the dose delivered to thirteen selected out-of-field anatomical sites were analyzed and compared.

Our study shows that for the same coverage of PTV, and for satisfactory dose constraints conformance to the PRV's, the IMRT technique increases the dose to the rectum and bladder as well as for RVR and out-of-field organs. In the dose range from 2 to 45 Gy, the mean relative volume is increased with the IMRT by 35%, compared to the DAT technique and for the thirteen out-of-fields anatomical sites evaluated, the ratio between the estimated doses for both techniques varied between 1.01 to 1.10, DAT providing lower doses. These results are consistent with data of previous publications comparing dose distribution between IMRT and DAT for prostate cancer^[17]. Indeed Metwaly *et al*^[17] have shown that DAT significantly reduces the irradiated volume of the rectum and bladder, compared to IMRT for the same coverage of PTV and a recent work^[18] has shown that DAT provided dose distributions at almost the same level of conformity and homogeneity as IMRT, with treatment times shorter by about 45%.

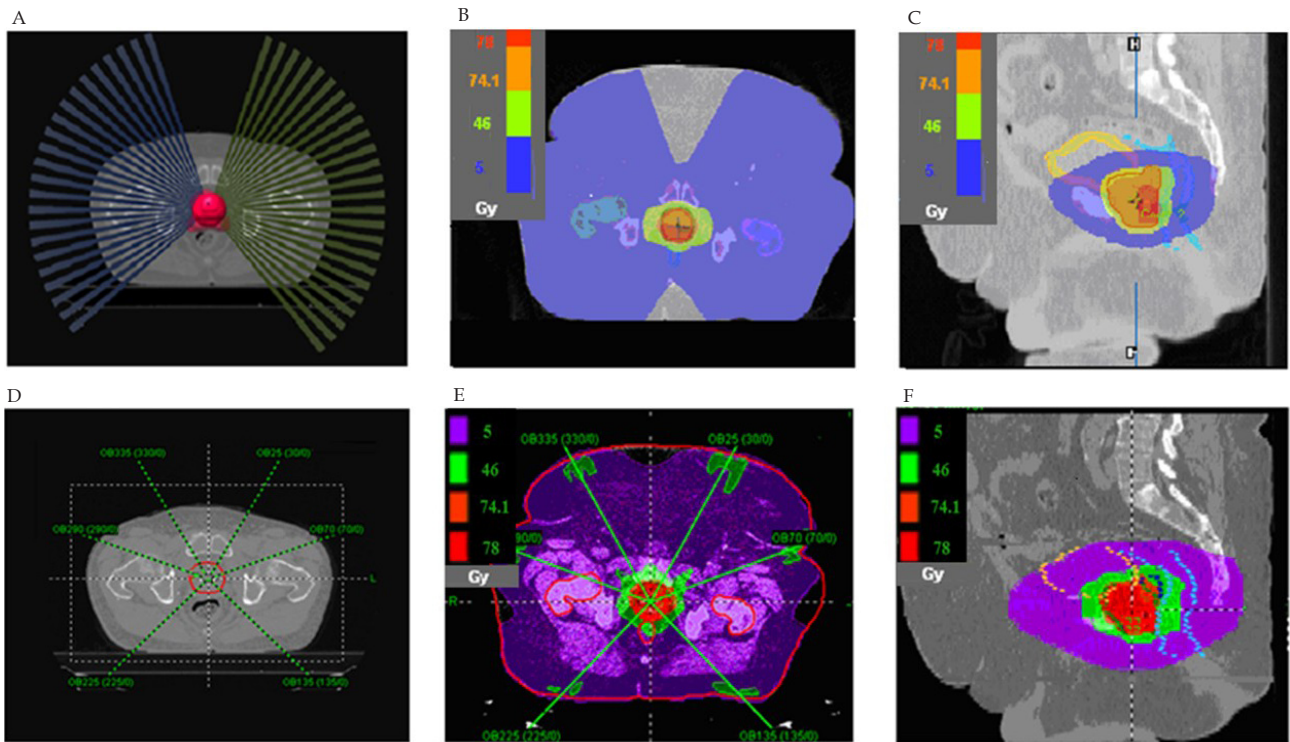


Figure 2 Example of a typical prostate case optimization using: A DAT ballistic is composed of four 6 MV coplanar dynamic arc beams; B IMRT technique ballistic is composed of six 6 MV coplanar beams; C and E show the dose distribution of the DAT treatment techniques in a central transverse and sagittal section respectively; D and F show the dose distribution of the IMRT treatment techniques in a central transverse and sagittal section respectively.

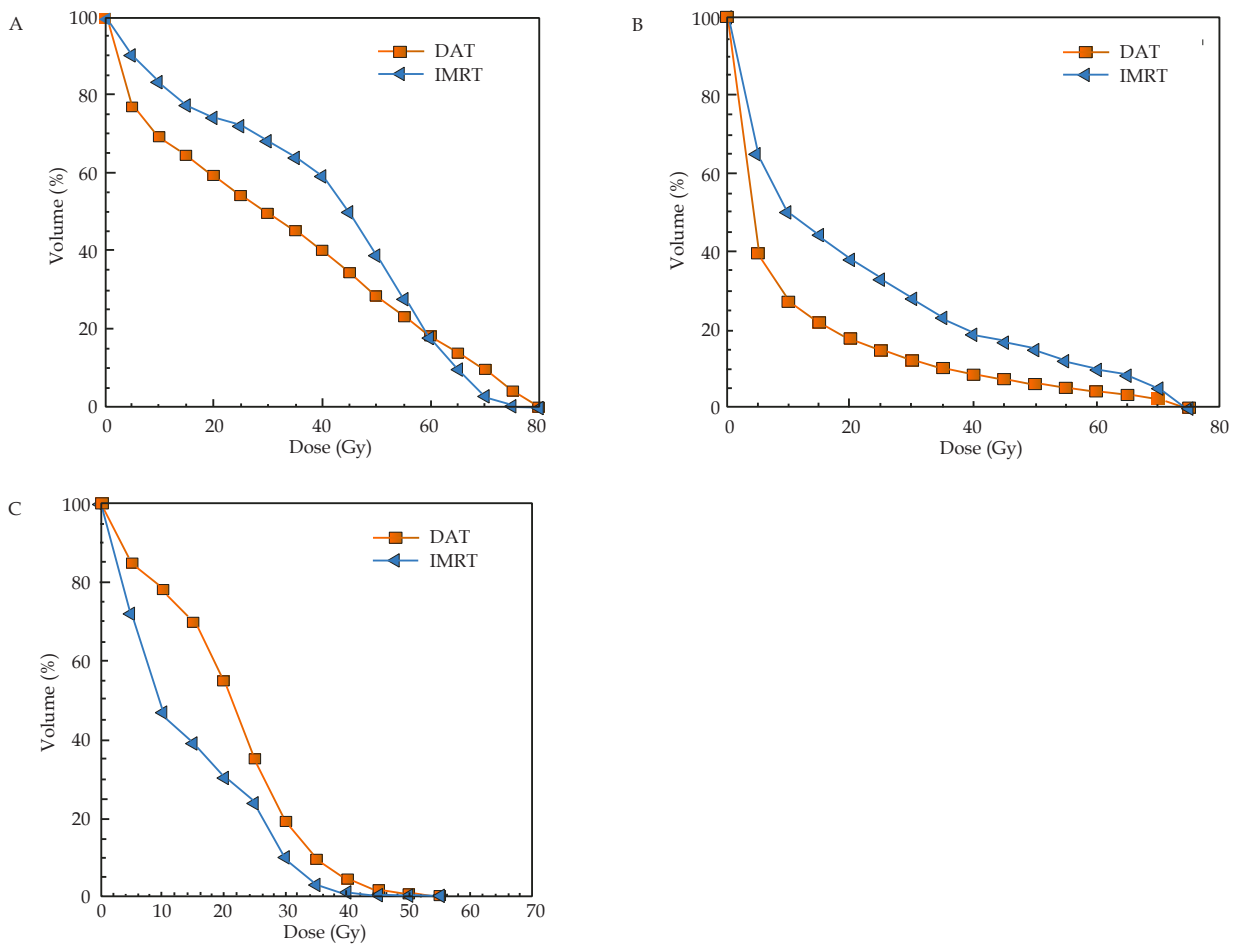


Figure 3 Mean Dose-Volume Histograms comparison between IMRT and DAT techniques for the selected patients, corresponding to the absorbed-dose distributions for the rectal wall A, for bladder wall B and for femoral heads C. The volume axis is relative to the total volume of region of interest and reported in percent.

Table 2 Estimation of doses at the center of PTV-distant organs for IMRT and DAT (means for the ten patients) and comparison between IMRT and DAT techniques.

	Technique						
	IMRT			DAT			$\frac{D_{IMRT}}{D_{DAT}}$
	Min(cGy)	Mean(cGy)	Max(cGy)	Min(cGy)	Mean(cGy)	Max(cGy)	
Right kidney	13.1	13.4	13.7	11.9	12.2	12.7	1.10
Left kidney	13.1	13.3	13.6	12.1	12.3	12.6	1.08
Pancreas	12.9	13.1	13.5	11.7	12.3	12.5	1.07
Spleen	10.4	10.5	10.7	10.1	10.4	10.5	1.01
Liver	9.9	10.2	10.3	9.8	10	10.2	1.02
Heart	8.8	9.1	9.3	8.3	8.6	8.8	1.06
Right lung	8.6	8.8	9.1	8.2	8.5	8.8	1.04
Left lung	8.8	9	9.2	8.2	8.3	8.5	1.08
Thyroid	6.4	6.7	6.9	6.2	6.5	6.8	1.03
Right parotid	4.4	4.7	4.8	4.3	4.5	4.7	1.04
Left parotid	4.4	4.6	4.8	4.4	4.5	4.7	1.02
Right eye	1.9	2.1	2.3	1.6	1.9	2.1	1.11
Left eye	2.0	2.1	2.4	1.9	2.0	2.2	1.05

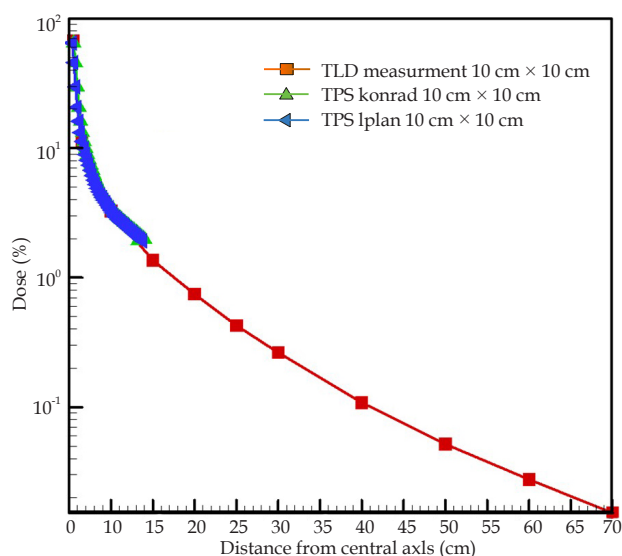


Figure 4 Percent dose as a function of distance from the central axis, which indicates the accordance between the TLD measurements, the TPS Konrad and Iplan calculation for 10 cm×10cm 6 MV beam at 10 cm depth using Novalis Tx™ linear accelerator.

We focused on the analysis of the dose received by PRV's, as well as low-dose irradiated volume because of the long-term risk of secondary cancers. Regarding clinical consequences for second malignant neoplasms after radiotherapy for prostate cancer, some clinical data suggest that irradiated prostate cancer patients have an increased risk of radiation induced malignancy. Brenner *et al*^[19] showed that the risk of a secondary malignancy of any type was significantly greater after radiotherapy than after surgery, by about 6%, although the majority of clinical evidence is based on older RT techniques^[20,21]. For recent techniques, such as IMRT and DAT, clinical studies examining second primary cancers often have relatively low patient numbers and short durations of follow up^[4,5,22,23].

In the present work, concerning PRV's, compared to the DAT, the mean dose in the bladder and the rectum increases with IMRT by about 10 % and 7 % respectively. Currently, the literature regarding the risk of second cancer after DAT technique is dramatically rare due to the novelty of the technique, the short experience in clinics and the short follow-up of the patients treated by DAT. However, many long-term studies can be found, discussing effects of IMRT. For example, according to Patil *et al*, the incidence of radiation-induced malignancies after IMRT was 0.10 and 3.42 per 10,000 person-years for the bladder and rectum respectively^[24]. Furthermore, Brenner *et al*^[19] showed in their study that the risk of a second solid

tumor dramatically increased especially to the bladder and rectum at 10 years or more after diagnosis.

Regarding femoral heads, the mean dose increases with DAT by about 15 %, compared to the IMRT. A study showed that the femoral heads fractures are very rare event (<0.5%) and stated on the difficulty of establishing a dose-response relationship and define recommendations^[25]. Emami *et al*^[26] showed a risk of complications lower than 5% concerning femoral heads. Bedford *et al*^[27] recommended V_{52Gy} lower than 5%. In our study the two techniques respected these recommendations.

In our study, for the thirteen out-of-fields anatomical sites evaluated, the IMRT provided doses of about 5% higher than DAT. However, at present, there are limited data in the literature regarding out-of-field dose, especially for modern radiation therapy. In the case of prostate cancer, in this context, Tao *et al*^[10] estimated the out-of-field doses for thyroid organ with the IMRT using photon energies around 20 MV. Our results were similar, with a mean deviation of 7%. In the same way Kry *et al* showed that use of lower photon energies could minimize the out-of-field doses obtained by the IMRT (step-and-shoot)^[28]. Our dose estimation method matches the results of the previous out of field dosimetry studies within a difference of 3% to 7% in accordance to the distance from the field edge^[29].

It is important to estimate dose distribution out-of-field to evaluate the effect of low doses on normal tissues, especially for long-term effects such as second primary cancers. For example, to assess the likelihood of risk of second cancer in out-of-field organs, Bednarz *et al* calculated the lifetime attributable risk (LAR), which is defined as the probability that an irradiated individual will develop a cancer during their lifetime^[30]. These results showed for the class of age of patients included in this study that the IMRT technique LAR values as a function of exposure organ and age were 1.6×10^{-9} for thyroid, 1.89×10^{-6} for lung, 2.45×10^{-6} for spleen, 3.92×10^{-7} for liver, 2.39×10^{-6} for pancreas and 3.31×10^{-6} for kidneys, which is reassuring.

In out-of-field regions, according to Murray *et al*^[31] the increased volume of normal tissue receiving low doses with IMRT has also been thought to contribute to increase radiation induced second primary cancers risk in normal tissues. Therefore in the long-term, patients who are treated with DAT are likely to develop less secondary cancers than those treated with the IMRT technique. That is why the DAT technique for prostate cancer may increase the benefit risk ratio compared to IMRT.

CONCLUSION

DAT improves dosimetric parameters for treatment of the prostate cancer although PTV coverage is kept the same compared to the

IMRT. This is done by reducing the dose not only to the organs at risk but also to the RVR, especially between 2 and 45 Gy. Furthermore, through this technique, the organs out of the field receive lower doses. However, the DAT increases the dose to the femoral heads and high doses (>60 Gy) to the rectum. Indeed, modern techniques are well suited for the radiotherapy treatment of the prostate cancer; nonetheless, regarding to the low dose distributions, the assessment of the dose received at distance from the treated volume and the volume of RVR should be evaluated to investigate the possible correlation with second cancers. Moreover, more long-term follow-up, with higher number of patients, will be needed to assess the effects of DAT technique.

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