REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 20 (2015) 99–103

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Integral dose: Comparison between four techniques for prostate radiotherapy

Krzysztof Ślosarek[a], *Wojciech Osewski*[b], *Aleksandra Grządziel*[a], *Michał Radwan*[a], *Łukasz Dolla*[a], *Marta Szlag*[a,*], *Małgorzata Stąpór-Fudzińska*[a]

[a] *MSC Memorial Cancer Center and Institute of Oncology Gliwice Branch, Department of Radiotherapy and Brachytherapy Planning, ul. Wybrzeża Armii Krajowej 15, 44-101 Gliwice, Poland*

[b] *MSC Memorial Cancer Center and Institute of Oncology Gliwice Branch, Radiotherapy Department, ul. Wybrzeża Armii Krajowej 15, 44-101 Gliwice, Poland*

ARTICLE INFO

Article history:
Received 1 July 2013
Received in revised form
17 June 2014
Accepted 17 October 2014

Keywords:
Prostate cancer
Integral dose
CyberKnife
VMAT
TomoTherapy

ABSTRACT

Aim: Comparisons of integral dose delivered to the treatment planning volume and to the whole patient body during stereotactic, helical and intensity modulated radiotherapy of prostate.

Background: Multifield techniques produce large volumes of low dose inside the patient body. Delivered dose could be the result of the cytotoxic injuries of the cells even away from the treatment field. We calculated the total dose absorbed in the patient body for four radiotherapy techniques to investigate whether some methods have a potential to reduce the exposure to the patient.

Materials and methods: We analyzed CyberKnife plans for 10 patients with localized prostate cancer. Five alternative plans for each patient were calculated with the VMAT, IMRT and TomoTherapy techniques. Alternative dose distributions were calculated to achieve the same coverage for PTV. Integral Dose formula was used to calculate the total dose delivered to the PTV and whole patient body.

Results: Analysis showed that the same amount of dose was deposited to the treated volume despite different methods of treatment delivery. The mean values of total dose delivered to the whole patient body differed significantly for each treatment technique. The highest integral dose in the patient's body was at the TomoTherapy and CyberKnife treatment session. VMAT was characterized by the lowest integral dose deposited in the patient body.

Conclusions: The highest total dose absorbed in normal tissue was observed with the use of a robotic radiosurgery system and TomoTherapy. These results demonstrate that the exposure of healthy tissue is a dosimetric factor which differentiates the dose delivery methods.

* *Corresponding author*. Tel.: +48 32 278 92 53.
E-mail address: mszlag@io.gliwice.pl (M. Szlag).

http://dx.doi.org/10.1016/j.rpor.2014.10.010

1. Background

The past two decades have witnessed a huge progress in new radiation technologies used for treatment of prostate cancers.[1] A single four-field coplanar beam arrangement was used in the early 1980s of the last century. Nowadays, different radiation modalities exist to deliver a high dose to the prostate,[2] including static intensity modulated radiotherapy (IMRT) with multileaf collimators (MLC),[1] volumetric or helical treatment such as Volumetric Modulated Arc Therapy (VMAT) and TomoTherapy (HT Accuray, Sunnyvale, CA, USA) with gantry rotation around the patient body[3] or non-isocentric frameless advanced robotic system CyberKnife (CK Accuray, Sunnyvale, CA, USA).[4] Improvement in dose delivery techniques enables better sculpturing of a high dose region and safe delivery of high total doses to the Planning Treatment Volume (PTV) with simultaneous sparing of organs at risk and adjacent healthy tissue.[3] However, multifield techniques, used in modern radiotherapy produce large volumes of low dose inside the patient body. Delivered dose is related to the energy absorbed in the tissue and can be the result of cytotoxic injuries of cells even away from the treatment field.[5–7] Dose in normal tissue may also increase the risk of secondary malignancies.[8,9] Different delivery techniques are represented by different spatial dose distribution for the same localizations of target and for the same planned dose delivered to PTV. Methods of beam collimation, beam angles, conception of the dynamic treatment, etc. employed in the modern radiotherapy techniques influence the isodose shape. Can we therefore expect that for different treatment modalities the level of integral dose deposited to the patient body will also be different even if the same dose is delivered to the treated volume? To investigate whether some methods of dose delivery have a potential to reduce patient exposure to radiation, the integral dose in the patient body was calculated for four selected radiotherapy techniques.

2. Aim

The aim of this study was to compare the integral dose delivered to the treatment planning volume and to the whole patient body during radiotherapy of prostate cancer with CK, VMAT, IMRT and HT techniques.

3. Materials and methods

In this study CyberKnife plans were analyzed as calculated for 10 patients with localized prostate cancer. Plans were not allowed to exceed the volumetric and dosimetric criteria included in the institutional treatment protocol established for stereotactic radiotherapy. In CyberKnife, the total dose of 36.25 Gy was delivered in 5 fractions, once every two days, fraction dose was 7.25 Gy to PTV. PTV was a 5 mm margin around the Clinical Target Volume (CTV). CTV encompassed prostate gland with 1 cm of proximal part of seminal vesicles. At the posterior wall of CTV, PTV was reduced to 3 mm. Prescribed dose was specified to isodose that covered PTV at an acceptable level (95% of PTV covered with at least the prescribed dose). Depending on the dose distribution, the isodose selected as a reference one ranged from 75% to 85% to ensure proper coverage of the PTV with the prescribed dose. Dose–volume constraints for the rectum were: $V_{18Gy} = 50\%$, $V_{29Gy} = 20\%$, $V_{32.6Gy} = 10\%$ and $V_{36.2Gy} = 5\%$ and for the bladder: $V_{18Gy} = 55\%$, $V_{29Gy} = 25\%$, $V_{32.6Gy} = 15\%$ and $V_{36.2Gy} = 10\%$. 45% of the femur head should not exceed 25 Gy.[10]

3.1. *Treatment planning*

For the purpose of this study, a set of five alternative plans for each patient were calculated in VMAT, IMRT, HT and CK techniques. VMAT and IMRT plans were calculated for X-6MV and X-20MV photon beams separately. Single plans were calculated for CK and HT because these treatment modalities deliver only X-6MV photon beams. Alternatively, hypothetical plans were calculated with the same stereotactic fractionation scheme as for the CK plans. Moreover, plans were prepared according to the protocol accepted for CK plans. Method used to normalize CK dose distributions was based on a reference isodose selected for the individual plan. Total dose of 36.25 Gy was prescribed to IMRT, VMAT and HT plans. For these treatment modalities plans were normalized with a "non-standard" method based on the mean dose in PTV. It was for experimental purpose only. The aim was to achieve comparable dose distribution inside PTV regardless of the therapeutic technique used for the calculation. At the same time, we investigated differences between integral dose inside the patient body for different therapeutic techniques. The aim of this study was to compare total dose absorbed in the patient's body, whereas the same integral dose was delivered to the PTV. Comparison of the optimal dose distribution obtained with different calculation methods and optimization algorithms was not the object of these study. All treatment plans were computed based on the same series of CT scans and structure set. Contouring of the targets and organs at risk were performed in the Multiplan v. 4.6 (Accuray, Sunnyvale, CA, USA) planning system and then transferred, with CT scans, to Eclipse v. 10.0 (Varian Medical System, Palo Alto, CA, USA) and TomoTherapy Planning Systems v. 1.2.1 to create alternative IMRT, VMAT and HT treatment plans, respectively.

VMAT and IMRT plans were calculated in Eclipse with AAA algorithm (Anisotropic Analytical Algorithm, Varian Medical Systems). Calculation grid was 2.5 mm. HT treatments delivered by TomoTherapy unit were computed with a convolution-superposition algorithm (C/S) based on a collapsed cone (CCC) approach (TomoTherapy Planning System, Accuray). Calculation grid was 2.34 mm. For CyberKnife, dose calculation was performed with Ray-Tracing algorithm in a high resolution mode. Number of non-coplanar, therapeutic beams used in IMRT plans ranged from 7 to 9. VMAT plans were realized with 4 non-coplanar complete arcs with intensity modulation of radiation (at 0° and 90° angles). Parameters of HT plans were as follows: modulation factor MF = 2.4, field width FW = 1.5 cm and pitch 0.215.

3.2. *Comparison and analysis*

All dose distribution comparisons were performed in the Eclipse planning system. To transfer dose distribution from CK

Table 1 – Mean integral dose ID (with standard deviations) delivered to PTV calculated for the group of 10 plans computed with the IMRT, VMAT, CK and HT irradiation techniques. Differences between ID in this group were not statistically significant (ANOVA test, $p < 0.05$).

Irradiation technique	Mean ID [Gy L]	Std. Dev.
CK	2.89	1.12
VMAT (X-6MV)	2.88	1.11
VMAT (X-20MV)	2.88	1.13
IMRT (X-6MV)	2.84	1.07
IMRT (X-20MV)	2.86	1.09
HT	2.83	1.07

Table 2 – Mean integral dose ID (with standard deviations) delivered to body structure calculated for the group of 10 plans computed with four different irradiation techniques: IMRT, VMAT, CK and HT. ANOVA test showed that differences were statistically significant ($p < 0.05$).

Irradiation technique	Mean ID [Gy L]	Std. Dev.
CK	81.59	24.71
VMAT (X-6MV)	54.01	12.31
VMAT (X-20MV)	49.81	10.35
IMRT (X-6MV)	69.38	16.63
IMRT (X-20MV)	61.07	15.07
HT	116.08	38.50

planning system to Eclipse, an in-house software DDcom was used.[11] Evaluation of statistical significance was performed by nonparametric dependent samples tests: Friedman ANOVA and Wilcoxon for matched pair analysis (Statistica v.10, StatSoft, Inc., Tulsa, OK, USA). Level of statistical significance was set at $\alpha = 0.05$. Integral dose values calculated for: IMRT (X-6MV), IMRT (X-20MV), VMAT (X-6MV), VMAT (X-20MV), CK and HT plans delivered to PTV and whole body where compared with ANOVA. Wilcoxon test was then used for detailed analysis of difference between each pair of treatment technique.

The integral dose (ID) of radiation delivered to the PTV and whole patient body was defined as a $\mathrm{ID}\,[\mathrm{Gy}\cdot\mathrm{L}] = \bar{D}\,[\mathrm{Gy}]\cdot V\,[\mathrm{L}]$, where $\bar{D}\,[\mathrm{Gy}]$ is the mean dose delivered to volume V [L] (where L – liter). ID formula, which was used by the Aoyama et al.[12] to calculate the integral dose in normal tissue was employed to calculate and compare the absorbed dose in PTV and the whole patient body, for various irradiation techniques.

4. Results

CK plans for 10 patients with prostate cancer were generated according to the clinical acceptable criteria to cover PTV sufficiently. For comparison purpose, for each patient, alternative VMAT, IMRT and HT plans were calculated. Additionally, VMAT and IMRT plans were calculated for beams energy of X-20MV and X-6MV. Integral dose in PTV volume was calculated for all techniques and beam energies with the ID formula. Table 1 presents mean integral dose in PTV for different treatment delivery methods and beam energies. Non-parametric statistical analysis for the dependent samples showed that differences are statistically insignificant ($p > 0.5$). The same integrated dose was deposited to the treated volume despite different methods of treatment delivery and beam energy. The results are obvious because different treatment modalities provide similar dose distributions inside PTV but, at the same time, completely different dose distribution is observed in the surrounding healthy tissue. Advanced technological solutions, such as collimation systems, available beam directions and beam modulations influenced the distribution of dose for the whole patient body.

ANOVA test showed that the mean values of integral dose delivered to patient body differed significantly for each analyzed treatment technique (Table 2). The highest ID (mean value was equal to 116.0 Gy L) was absorbed in the patient body during HT treatment session. The lowest ID was absorbed in the patient body when VMAT technique with beams of X-20MV was applied (mean dose was below 49.8 Gy L). Differences were statistically significant with p-value less than the significance level $\alpha = 0.05$ ($p = 0.00$). Wilcoxon test showed that integral dose delivered to the patient body was significantly higher for CK and HT than for the rest of the analyzed techniques. Treatment plans for VMAT and IMRT techniques were calculated regarding two beam energies (X-6MV and X-20MV). Friedman ANOVA followed by Wilcoxon test showed statistically significant ($p < 0.05$) difference between whole body ID values for plans calculated for X-6MV and X-20MV beam energies. ID is lower for higher energy beams, regardless of the technique (VMAT, IMRT). The results are consistent with the literature,[13] indicating a comparable dose distribution in the dynamic techniques (IMRT and VMAT) in radiotherapy of prostate cancer. Simultaneously Wilcoxon test showed that there is no difference between ID delivered to PTV for VMAT (X-6MV vs. X-20MV; $p = 0.53$) and for IMRT (6 MV vs. 20 MV; $p = 0.2$).

4.1. *Research limitations*

Different algorithms used for plans calculation may have had an impact on ID values presented in this study. However, comparative planning studies showed that significant differences between dose distribution calculated with different algorithms are mainly for lung tissue and for volumes of different electron densities. The tissue type involved and location of anatomical region treated with radiation may influence ID values for different algorithms. However for prostate cancer, target is surrounded mainly by the soft tissue. Type of calculation algorithms have little impact on the doses calculated for this anatomical region. Mean absolute percentage error (MAPE) presented by Wu et al.[14] was 3.5% for points located inside the prostate gland (taking MC as the gold standard for comparison AAA algorithm and multigrid superposition (MGS)). MAPE values calculated for selected points located inside the soft tissue were $1.8 \pm 1.2\%$ and $1.8 \pm 1.9\%$ for AAA and MGS, respectively. The most significant differences between measured and planed dose were found for lung cancer radiotherapy and for points located on the edge of the field.[15,16] The discrepancies strongly depended on the lung tissue density and beam energy, especially for pencil beam algorithms. Most studies compare calculation algorithms based on the dosimetric or volumetric parameters of DVH or points.[17] However, It is difficult to estimate this effect when estimating an integral dose in the patient body.

5. Discussion

In the presented study the integral dose delivered to the whole patient body and to PTV during radiotherapy of the prostate was calculated with respect to different methods of treatment delivery and different beam energies. Four different delivery methods, including IMRT, VMAT, CK and HT, were used to calculate alternative treatment plans for each patient. The CK dose distribution was the reference one. For the CyberKnife technique dose to be delivered was defined on selected isodose; therefore, for other techniques it was defined so that their mean values were comparable. Regardless of the irradiation technique (VMAT, IMRT, CK and HT), statistical analysis demonstrated no significant difference between ID delivered to the PTV region. In opposite, ID in the whole patient body strongly depended on the technique used for treatment delivery. Unexpectedly, HT and CK were found to be the techniques where the integral dose delivered to the patient was significantly higher than in VMAT and IMRT. In CK, "irradiation source" is positioned in the nodes located on the sphere around patient's body. Active nodes do not cover the whole sphere. Nodes located under the patient's body are inactive for the robotic arm. Number of beams are then reduced to those passing through the patient body from above. Additionally, beam reduction is performed to remove beams with a very low number of monitor units and to reduce the duration of a single fraction. Beams that are left (usually from 150 to 250), produce a characteristic dose distribution with areas of a relatively high dose level located outside the PTV. Moreover, CK system is a non-isocentric radiotherapy technique where the central axis of each beam is adjacent to the PTV surface. This technique provides a highly conformal dose distribution with a steep dose gradient. CK is therefore suitable to treat small tumors located close to the organs at risk and tumors of irregular shapes, whereas prostate with a therapeutic margin is a relatively large volume of regular contour. Calculations showed that the lowest integral energy was delivered with the VMAT technique. In terms of radiation protection, rotational modulated therapy seemed to be a good choice for prostate therapy. Radiotherapy of prostate can be delivered efficiently and safely thanks to modern tools for radiation delivery. Radiotherapy with IMRT, VMAT, robotic CyberKnife and, finally, TomoTherapy are all techniques of choice for therapy of low risk prostate tumors. Comparison and evaluation of dose distributions computed regarding different delivery methods has been widely exploited in the literature.[18–21] Target coverage with simultaneous organs sparing was the main point of interest in most papers. Difference between integral dose for different treatment modalities used for localized prostate cancer was investigated by Aoyama et al.[12] and Hermant et al.[22] Aoyama et al. showed that integral dose in normal tissue (NTID) in HT was similar to the X-6MV conventional IMRT and higher than NTID for X-20MV IMRT. The advantage of HT over conventional IMRT and conventional three-dimensional conformal radiotherapy (3DCRT) was demonstrated in respect to dose sparing of organs at risk without increase in NTID. Our experiment showed larger differences between ID for the IMRT and HT techniques when non-coplanar fields for IMRT calculations were used.

6. Conclusion

Our study investigated the integral dose absorbed in the healthy tissue in the whole patient body during radiotherapy of prostate. Surprisingly, the comparison revealed the highest integral dose in normal tissue for HT and CK plans. The lowest energy delivered to the patient body was related to the VMAT technique with energy of beams of X-20MV. At the same time, there was no significant differences, between energy absorbed in PTV for the four analyzed techniques. These results demonstrate that the exposure of healthy tissue is a dosimetric factor which differentiates the dose delivery methods, apart from PTV coverage and safety of organs at risk.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Khoo VS. Radiotherapeutic techniques for prostate cancer dose escalation and brachytherapy. *Clin Oncol* 2005;**17**:560–71.
2. Hermesse J, Biver S, Jansen N, et al. Dosimetric comparison of high-dose-rate brachytherapy and intensity-modulated radiation therapy as a boost to the prostate. *Int J Radiat Oncol Biol Phys* 2010;**76**:269–76.
3. Skórska M, Piotrowski T. Empirical estimation of beam-on time for prostate cancer patients treated on tomotherapy. *Rep Pract Oncol Radiother* 2013;**18**:201–8.
4. Morgia G, De Renzis C. CyberKnife in the treatment of prostate cancer: a revolutionary system. *Eur Urol* 2009;**56**:40–2.
5. Nguyen TVF. Risk of second malignant neoplasm after cancer in childhood treated by radiotherapy: correlation with the integral dose. *Int J Radiat Oncol Biol Phys* 2006;**66**:S566.
6. Zwahlen DR. Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2009;**74**:539–45.
7. Ruben JD. The effect of intensity-modulated radiotherapy on radiation-induced second malignancies. *Int J Radiat Oncol Biol Phys* 2008;**70**:1530–6.
8. Tyagi A, Supe S, Kaushik S, et al. A dosimetric analysis of 6 MV versus 15 MV photon energy plans for intensity modulated radiation therapy (IMRT) of carcinoma of cervix. *Rep Pract Oncol Radiother* 2010;**15**:125–31.
9. Ruben JD. A comparison of out-of-field dose and its constituent components for intensity-modulated radiation therapy versus conformal radiation therapy: implications for carcinogenesis. *Int J Radiat Oncol Biol Phys* 2011;**81**:1458–64.
10. Miszczyk L. *Recommendations of the Radiotherapy Department*. Gliwice: Centrum Onkologii – Instytut MSC; 2012.
11. Osewski W, Ślosarek K, Karaszewska B. Dose distribution transfer from CyberKnife to Varian treatment planning system. *J Phys: Conf Ser* 2014;**489**:012056.
12. Aoyama H, Westerly D, Mackie T, et al. Integral radiation dose to normal structures with conformal external beam radiation. *Int J Radiat Oncol Biol Phys* 2006;**64**:962–7.

13. Leszczyński W, Ślosarek K, Szlag M. Comparison of dose distribution in IMRT and RapidArc technique in prostate radiotherapy. *Rep Pract Oncol Radiother* 2012;**17**:347–51.
14. Wu V, Tse T, Ho C, et al. A comparison between anisotropic analytical and multigrid superposition dose calculation algorithms in radiotherapy treatment planning. *Med Dosim* 2013;**38**:209–14.
15. Bragg Ch, Conway J. Dosimetric verification of the anisotropic analytical algorithm for radiotherapy treatment planning. *Radiother Oncol* 2006;**81**:315–23.
16. Aarup L, Nahum A, Zacharatou Ch, et al. The effect of different lung densities on the accuracy of various radiotherapy dose calculation methods: implications for tumor coverage. *Radiother Oncol* 2009;**91**:405–14.
17. Yoo S, Wu Q, O'Daniel J, et al. Comparison of 3D conformal breast radiation treatment plans using the anisotropic analytical algorithm and pencil beam convolution algorithm. *Radiother Oncol* 2012;**103**:172–7.
18. Lin Y-W, Lin K-H, Ho H-W, et al. Treatment plan comparison between stereotactic body radiation therapy techniques for prostate cancer: non-isocentric CyberKnife versus isocentric RapidArc. *Phys Med* 2014, http://dx.doi.org/10.1016/j.ejmp.2014.03.008 (in press).
19. Sze H, Lee M, Hung W-M, et al. RapidArc radiotherapy planning for prostate cancer: single-arc and double-arc techniques vs. intensity-modulated radiotherapy. *Med Dosim* 2012;**37**:87–91.
20. Vargas C, Fryer A, Mahajan Ch. Dose–volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**: 744–51.
21. Hermesse J, Biver S, Jansen SN. Dosimetric comparison of high-dose-rate brachytherapy and intensity-modulated radiation therapy as a boost to the prostate. *Int J Radiat Oncol Biol Phys* 2010;**76**:269–76.
22. Hermanto U, Frija E, Lii M. Intensity-modulated radiotherapy (IMRT) and conventional three-dimensional conformal radiotherapy for high-grade gliomas: does IMRT increase the integral dose to normal brain? *Int J Radiat Oncol Biol Phys* 2007;**67**:1135–44.