Dosimetric and Radiobiological Comparison of Three-Dimensional Conformal Radiotherapy and Helical Tomotherapy in Whole Pelvic Radiotherapy of Prostate Cancer Patients

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ABSTRACT

Background: Modern radiotherapy techniques can destroy tumors with less harm to surrounding normal tissues. Normal Tissue Complication Probability (NTCP) models are useful to evaluate treatment plans.

Objective: This study aimed to use the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) program to evaluate dose-volume indicators and radiobiological parameters for complications of the rectum and bladder in prostate cancer patients undergoing pelvic radiotherapy.

Material and Methods: In this retrospective cross-sectional study, treatment planning information was gathered from 35 patients with pelvic lymph node involvement. Of these, 17 and 18 were treated using the three-dimensional Conformal Radiotherapy Technique (3D-CRT) and the Helical Tomotherapy (HT) technique, respectively. The Lyman-Kutcher-Burman and Relative Seriality models were used in conjunction with dose-volume histograms to calculate the NTCP values for the rectum and bladder.

Results: In the HT group compared to the 3D-CRT group, the values of D-Mean, V-40, V-50, V-60, and V-65 were lower for both the rectum and bladder. The NTCP values for grade 2 rectal bleeding, proctitis, and bladder toxicity were lower in the HT group. The dose-volume data of 67% of the HT patients satisfied all QUANTEC criteria, while only 30% of the 3D-CRT those met criteria.

Conclusion: The QUANTEC criteria were satisfied for the rectum and bladder in the HT and 3D-CRT groups, except for V-50, V-60, and V-65 of the rectum in 3D-CRT patients. The NTCP values for both organs were lower in the HT group than in the 3D-CRT group.

Keywords

Radiotherapy, Intensity-Modulated; Radiotherapy, Conformal; Prostate; Radiation Injuries; Rectum

Introduction

External Beam Radiation Therapy (EBRT) is widely recognized as an effective treatment for prostate cancer. Modern radiotherapy techniques are developed to increase the dose delivered to the Planning Target Volume (PTV) with less radiation exposure to the Organs

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at Risk (OAR) to improve treatment outcomes [1]. Intensity-Modulated Radiation Therapy (IMRT) is an example of such a technique enabling the increase of tumor dose while lowering the risk of side effects compared to the three-dimensional Conformal Radiotherapy Technique (3D-CRT) [2-6]. However, increasing the dose to the PTV can increase the probability of successful prostate treatment, doses above 70 Gy lead to increasing rectal and bladder complications using 3D-CRT [7]. Helical Tomotherapy (HT), a new type of IMRT technique, results in a highly conformal dose distribution and improves OARs sparing compared to the conventional IMRT techniques [7-9]. Both conventional IMRT [4, 10] and Helical HT [11] offer superior treatment outcomes compared to 3D-CRT, with improved target homogeneity, conformity, and OARs sparing, the same as studies comparing HT to conventional IMRT [7, 9]. However, some benefits of modern radiotherapy techniques are reported [2-6, 9, 11], their respective advantage for the risk of radiation-related complications remains unclear in prostate cancer treatment [12]. Radiation therapy aims to determine the response of critical organs to radiation and establish their maximum tolerated dose. The primary method for predicting possible side effects of radiation is through the calculation of the Dose-Volume Histogram (DVH), which provides information on the volume of tissue receiving a given dose of radiation. Accordingly, this leads to estimating radiation-induced side effects in critical organs [13]. Several studies have demonstrated the correlation between DVH criteria and gastrointestinal or genitourinary complications following radiation therapy for prostate cancer [14-19]. However, the DVH methodology has some limitations, including the lack of organ-specific spatial information [13, 20], the use of the Normal Tissue Complication Probability (NTCP) models can simplify complicated dosimetric and anatomic information to a single risk indicator [20, 21]. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) program provides recommendations for volume dose indicators to limit rectal and bladder complications based on observed complications and models of the probability of complications in normal tissues [22-24]. This study aimed to compare the dosimetric and radiobiological parameters for predicting the radiation complications of the rectum and bladder in Whole Pelvic Radiation Therapy (WPRT) for prostate cancer patients using 3D-CRT and HT techniques in two radiation therapy departments, Isfahan, Iran. Parameters, such as NTCP, mean dose (D_{mean}), and V_D (volume exposed to dose higher than D Gy), are recommended by the QUANTEC program for future studies.

Material and Methods

Patient characteristics and CT simulation

This retrospective cross-sectional study collected treatment planning information from 35 men with prostate cancer, who had lymph nodes and underwent definitive or postoperative radiation therapy using 3D CRT (17 patients) and HT (18 patients) between December 2020 and May 2022 at Omid and Milad hospitals, Isfahan, Iran. The planning CT images, with 3-5 mm slice thickness, were acquired with the patients in the supine position using a Siemens SOMATOM Scope CT scanner for the 3D-CRT patients and a Siemens SOMATOM Definition AS or Siemens SOMATOM Confidence CT scanner (Siemens Medical solutions PA, USA) for the HT patients, with the average age 69 years.

Treatment planning and prescribed doses

The Planning Target Volumes (PTVs) and OARs were delineated by the radiation oncologist. The following systems were used for treatment planning: Prowess Panther® TPS version 5.5 (Prowess Inc., Concord, CA) com-

missioned for the 15 MV beam of a Siemens Artiste linac unit, and an Accuray Precision® TPS commissioned for the 6 MV beam of an Accuray Radixact tomotherapy system (Accuray, USA, version 2.0.1.1). The treatment planning of the 3D-CRT patients involved two serial steps, as follows: 1) the pelvic nodes and PTV with a dose of 45 Gy (25 fractions, 1.8 Gy/fraction) and 2) the PTV with a dose of 22-28 Gy (11-14 fractions, 2 Gy/fraction). The total physical doses were 45 Gy and 67-73 Gy for the pelvic nodes and the PTV, respectively. The HT technique involved delivering a dose of 50-54 Gy to the whole pelvic region, while irradiation of the PTV was simultaneously integrated boost at 68-78 Gy.

Plan evaluation parameters

D_{Mean}, V_{40}, V_{50}, V_{60}, V_{65}, V_{70}, and V_{75} were calculated for both the rectum and bladder. NTCP values for the rectum and bladder were also determined using the BioSuite software [25] and two NTCP models: Lyman-Kutcher-Burman (LKB) [26] and Relative Seriality (RS) [27]. Table 1 presents the radiobiological parameters [24, 28-32] to calculate acute and late toxicity for the rectum and bladder in LKB and RS models.

Statistical analysis

For both the rectum and bladder, the volume exposed to a dose higher than D Gy (VD) for dose ranges of 40-75 Gy, as well as the D-mean and NTCP values, were compared between the two patient groups. Statistical analysis was conducted using the independent samples t-test for parametric data and the Mann-Whitney U test for nonparametric data, with IBM SPSS version 26 software.

Results

For the 3D-CRT patients, the average volumes of the rectum and bladder were 97.72±43.97 cm^3 and 194.12±123.77 cm^3, respectively, and for the HT patients, they were 90.26±35.96 cm^3 and 307.42±168.05 cm^3, respectively. Table 2 displays the DVH parameters for 3D-CRT and HT techniques. The D-mean values for the rectum and bladder in the 3D-CRT patients were remarkably higher than those in the HT patients (P-value=0.001). The mean values of V-40, V-50, V-60, and V-65 obtained for the rectum in the HT patients were significantly lower than those in the 3D-CRT

Table 1: Values of radiobiological parameters used to calculate rectal and bladder normal tissue complication probability values in Lyman-Kutcher-Burman and Relative Seriality models

Endpoint	LKB			RS		
	TD_{50} (Gy)	m	n	TD_{50} (Gy)	γ	s
Rectum						
G2 Bleeding	68.2	0.14	0.12	--	--	--
G2 Proctitis	67.0	0.20	0.15	--	--	--
Bleeding ≥G2	76.9	0.13	0.09	--	--	--
Bleeding G2/G3	--	--	--	83.1	1.69	0.49
Bladder						
Late Bleeding	85.3	0.30	0.36	--	--	--
Acute Urgency	64.2	0.50	1.00	68.5	0.51	10^{-4}

LKB: Lyman-Kutcher-Burman, RS: Relative Seriality, TD_{50} The effective dose that leads to a complication probability of 50%, m: is a parameter, which is inversely related to the steepness of the dose-response curve, n: is the volume exponent, γ: is a slope parameter which affects the steepness of the sigmoid shape dose-response curve, s: is a parameter that represents the 'relative seriality' of organ/tissue under consideration

Table 2: Mean Dose values and percentage of volumes exposed to dose higher than D (Gy) value of rectum and bladder for Three-Dimensional Conformal Radiotherapy and Helical Tomotherapy patient groups

Variables	3D-CRT	HT	*P*-Value		QUANTEC Recommendation
	Mean (±SD)	Mean (±SD)	t test	Mann-Whitney U	(%)
Rectum					
D_{Mean}(Gy)	51.61 (±5.05)	44.23 (±6.64)	0.001	--	--
V_{40}%	80.73 (±13.64)	60.77 (±19.15)	0.001	--	--
V_{50}%	51.81 (±14.52)	37.17 (±16.74)	0.009	--	<50
V_{60}%	36.19 (±12.99)	18.40 (±10.43)	0.001	--	<35
V_{65}%	26.33 (±12.46)	12.35 (±8.53)	0.001	--	<25
V_{70}%	6.42 (±10.34)	6.77 (±6.91)	0.907	0.067	<20
V_{75}%	0.00 (±0.00)	1.83 (±3.67)	0.049	0.001	<15
Bladder					
D_{Mean}(Gy)	53.42 (±5.77)	41.14 (±8.16)	0.001	--	--
V_{40}%	82.08 (±11.58)	48.06 (±17.41)	0.001	--	--
V_{50}%	56.12 (±20.82)	31.02 (±15.51)	0.001	--	--
V_{60}%	39.55 (±20.35)	19.55 (±14.27)	0.002	0.002	--
V_{65}%	28.00 (±17.74)	15.52 (±13.49)	0.025	0.006	<50
V_{70}%	7.35 (±9.43)	9.81 (±12.31)	0.514	0.265	<35
V_{75}%	0.45 (±1.56)	2.11 (±3.69)	0.093	0.022	<25

3D-CRT: Three-Dimensional Conformal Radiotherapy, HT: Helical Tomotherapy, SD: Standard Deviation, QUANTEC: Quantitative Analysis of Normal Tissue Effects in the Clinic

patients (*P*-value<0.05). Also, these values were significantly smaller in the HT patients (*P*-value<0.05) for the bladder. There was no statistically significant difference between the mean values of V-70 and V-75 for the rectum and bladder between the 3D-CRT and HT groups. In 67% of the HT patients compared to 30% of the 3D-CRT patients, all QUANTEC criteria for the rectum were satisfied. However, for the bladder, 94% of patients in 3D-CRT and HT groups met all of the QUANTEC criteria. As shown in Table 3, the mean NTCP values for grade 2 rectal bleeding and proctitis toxicity were significantly lower in the HT patients than in the 3D-CRT patients (*P*-value<0.05), using LKB and RS models. The NTCP values obtained for the bladder in the HT patients were also significantly lower than those in the 3D-CRT patients (*P*-value<0.05).

Discussion

Clinical trial studies have demonstrated that modern radiotherapy techniques, including IMRT, VMAT, and HT, yield superior treatment outcomes for prostate cancer patients in terms of reduced rectal and bladder toxicities compared to the traditional 3D-CRT [33-35]. Techniques, such as HT, can produce a conformal dose distribution to the PTV, significantly reducing the irradiated volume of adjacent normal tissues. Differences in the characteristics of the HT technique, as compared to the 3D-CRT technique, may lead to better target volume dose coverage, OARs sparing, and improved treatment outcomes [4, 7, 9, 33]. However, radiation-induced side effects in the rectum and bladder, particularly in patients with pelvic lymph node complications, continue to be a significant dose-limiting issue.

Table 3: Mean values and standard deviation for normal tissue complication probability for rectum and bladder, Three-Dimensional Conformal Radiotherapy and Helical Tomotherapy modalities

Variables	3D-CRT	HT	*P*-Value	
	Mean (±SD)	Mean (±SD)	t test	Mann-Whitney U
Rectum (LKB) (%)				
G2 Bleeding	20.65 (±9.40)	13.64 (±10.28)	0.043	0.019
G2 Proctitis	27.61 (±8.57)	19.33 (±9.77)	0.012	--
Bleeding ≥G2	6.86 (±3.87)	5.07 (±4.76)	0.234	0.086
(RS) (%)				
G2&3 Bleeding	5.45 (±2.85)	2.68 (±2.21)	0.003	0.001
Bladder (LKB) (%)				
Bleeding	12.94 (±4.22)	7.32 (±4.13)	0.001	0.001
Urgency	37.03 (±6.74)	24.15 (±7.98)	0.001	--
(RS) (%)				
Urgency	39.02 (±4.26)	29.95 (±5.91)	0.001	--

3D-CRT: Three-Dimensional Conformal Radiotherapy, HT: Helical Tomotherapy, SD: Standard Deviation, LKB: Lyman-Kutcher-Burman, RS: Relative Seriality

This study aimed to compare the dosimetric and radiobiological parameters of patients with pelvic lymph node complications who received treatment using either 3D-CRT or HT techniques. As shown in Table 2, the mean rectum and bladder dose values for the rectum and bladder were lower in the HT patients. Additionally, the percentage of the irradiated volume of the rectum and bladder with doses of 40, 50, 60, and 65 Gy was lower in the HT group, as compared to the 3D-CRT patients. The current study's results are consistent with those reported by Malone et al. [11], who demonstrated that the tomotherapy plans resulted in significant sparing of OARs compared to 3D-CRT plans for prostate cancer. Nadia Di Muzio et al. [33] reported similar findings for the rectal volume receiving doses greater than 65 Gy. Cesare Cozzarini et al. [8] also reported a significant reduction in the irradiated rectal and bladder volume for prostate cancer patients treated with HT. The HT group had lower NTCP values for the rectum and bladder, as calculated using the LKB and RS models. The analysis revealed significant differences between the NTCP values for the two patient groups, with the most significant disparities in the LKB model calculations, in which a difference of 34% and 43% was recorded for rectal and bladder bleeding, respectively. The RS model also showed a significant difference in the NTCP for rectal bleeding, with a difference of 50% between the two groups.

The parameters utilized in DVH-based NTCP models have limitations, as follows: 1) possible sources of patient-related data variability, such as differences in pre- and post-treatment patient characteristics, 2) follow-up times, and 3) patient-reported symptoms for toxicity scoring [13]. Differences are reported in imaging data for treatment planning, resulting in varying methods of OAR contouring and calculation of volume-related data [36]. The current study also revealed inconsistencies, with a maximum of 58% relative difference between the contoured bladder volumes. One of the significant drawbacks of using DVH-based NTCP modeling is the lack of spatial information in the DVH [13, 20, 37]. There have also been reports of uncertainty in

the applicability of the NTCP model parameters derived from the 3D-CRT-treated patient to fit the IMRT patient data [29].

Conclusion

HT method can deliver higher prescribed doses to the target in prostate cancer patients with pelvic lymph involvement while minimizing the dose to the surrounding healthy organs, compared to 3D-CRT methods. Also, HT resulted in better preservation of healthy tissue, reducing radiation damage to the rectum and bladder. However, the complexity of the HT technique requires a longer treatment time and more effort in planning, safety checks, and quality control before starting the patient's treatment. Despite these challenges, the use of HT leads to increasing the tumor dose to an acceptable level while preserving healthy organs. Therefore, helical tomotherapy is a more effective method for treating prostate cancer patients with lymph node involvement.

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Authors' Contribution

P. Shokrani and M. Mirzaeiyan conceived the idea. The introduction of the paper was written by M. Mirzaeiyan and P. Shokrani. M. Mirzaeiyan gather the images and the related literature and also help write the related works. The method implementation was carried out by M. Mirzaeiyan. Results and analysis were carried out by M. Mirzaeiyan. The research work was proofread and supervised by P. Shokrani, Ali. Akhavan, A. Amouheidari, M. Etehadtavakol, S. Hemati, A. Adibi and H. Khanahmad. All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

The study was performed following the Helsinki Declaration on ethical principles for medical research involving human subjects and also approved by the Institutional Committee for Ethics in Biomedical Research of the Isfahan University of Medical Sciences (approval ID: IR.MUI.MED.REC.1399.862).

Informed Consent

Written informed consent was obtained from all individual participants in the study.

Conflict of Interest

None

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