Multidisciplinary Cancer Investigation Review Article

October 2021, Volume 5, Issue 4

Clinical Differences Among Volumetric Modulated Arc Therapy, Intensity Modulated Radiation Therapy, and 3D-Conformal Radiation Therapy in Prostate Cancer: A Brief Review Study

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DOI: 10.30699/mci.5.4.522-1

Submitted: 12 June 2021

Revised: 24 July 2021

Accepted: 30 August 2021

e-Published: 28 December 2021

Keywords:
Radiotherapy, Intensity-Modulated
Radiotherapy, Conformal
Prostatic Neoplasms
Clinical Protocols

The present study aimed at identifying monitor unit (MU), treatment time variations, volume coverage dissimilarity, and second tumor incidence among Volumetric Modulated Arc Therapy (VMAT), Intensity Modulated Radiation Therapy (IMRT), and 3D-Conformal Radiation Therapy (3D-CRT), and treatment plans for prostate cancer based on literature review. A literature search was conducted on Pubmed/MEDLINE, BioMed Central (BMC)-part of Springer Nature, Google Scholar, and Insight Medical Publishing (iMED-Pub LTD) using the following keywords for filtering: 3D-CRT, IMRT, VMAT, Prostate Cancer, Conformity, and Homogeneity Index. IMRT was consisted of several treatment fields with different directions, hundreds of beamlets with modulated intensity, and an advantage over 3D-CRT, whereas VMAT had the advantage over IMRT due to rotating-beam utilization. VMAT usually required a longer dose optimization time and a rapid treatment, allowing patient comfort, reduced intra-fraction motion, and increased throughput compared to IMRT and 3D-CRT. VMAT has slightly better conformity and homogeneity with lower doses to normal tissue and MUs and treatment times compared to IMRT and 3D-CRT. Lower MUs reduce the risk of secondary malignancies. If target coverage and normal tissue sparing are comparable among different techniques, the risk of secondary malignancy should then be an important factor to choose the treatment modality.

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INTRODUCTION

Prostate cancer (PC) is the 2nd most common malignancy in males worldwide, counting 1.4 million new cases and causing 375,000 deaths in 2020. It was the 5th leading cause of cancer death worldwide among males in 2020, as mentioned in Globocan 2020 [1, 2]. The incidence and mortality of PC steadily increased over the last decade, which is correlated with aging and the average age of 66 years. It is the most common male malignancy in the US, with a higher incidence in African-Americans compared to White-Americans due to social, environmental, and genetic differences [3, 4]. Radiation therapy (RT) plays a critical role in the management of PC. Most patients with PC are treated with photon-based radiation techniques, such as 3-D conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT). IMRT

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or VMAT (a form of IMRT utilizing rotating gantry and dynamic dose rate) is the advanced form of 3D-CRT that utilizes non-uniform radiation beam intensities determined by various computer-based optimization techniques. These techniques generate a steep dose fall-off to nearby uninvolved structures and deliver a highly conformal radiation dose to the tumor, while minimizing the dose to normal, healthy tissues [5, 6]. The accuracy and effectiveness of radiotherapy requires accurate tumor localization, considering internal organ motion, and setup error [7-10].

The present study aimed at comparing monitor unit (MU), treatment time variations, volume coverage dissimilarity, second tumor incidence, etc., among treatment plans of 3D-CRT, IMRT, and VMAT for prostate cancer based on literature review. The study also compared treatment plans as 3D-CRT with IMRT, IMRT with VMAT, and 3D-CRT with VMAT.

Background and Technology

The first step in the radiotherapy treatment plan is to define the planning target volume (PTV), which is the clinical target volume with organ motion and setup margin. For PC treatment with 3D-CRT, multiple overlapping beams are usually used to treat PTV with high-dose distribution, resulting in irradiation of significant volumes of small bowel, rectum, and bladder, which may cause side effects, such as, bowel dysfunction, urethral stricture, etc. Advancements in diagnostic imaging, and RT planning and delivery modernized the photon-based PC treatments with IMRT and VMAT because studies show that it can reduce the grade 2 acute gastrointestinal (GI) toxicity [11], resulting in highly conformal dose distributions with reduced normal tissue toxicity, faster treatment, and less MU compared to 3D-CRT. VMAT provides somewhat improved efficiency compared to IMRT. Recent studies indicated potential clinical advantages for IMRT and VMAT compared to 3D-CRT, where VMAT planning was shown as the most effective modality to maintain or improve PTV coverage with the most reduction in rectal and bladder dose. IMRT and VMAT showed superiority with lower variation among themselves compared with 3D-CRT plans [12-20]. IMRT was first conceptualized in the 1960s. However, it was not implemented until the 1980–1990s when computing the capability required for complex inverse planning algorithms became available commercially. In 1994, the NOMOS Peacock system (NOMOS Corporation, Sewickley, Pennsylvania, USA) was introduced as the first commercial IMRT delivery unit [21, 22]. The unique feature of IMRT is that the leaves, known as multi leaf collimators (MLCs), help create the complex shape of the beam to conform radiation to the shape of the tumor while minimizing the exposure of surrounding critical structures. The first IMRT delivery for PC treatment was done when the prostate immobilization was achieved by an endo-rectal balloon inflated with 100 mL of air, pushing the prostate towards pubic symphysis and rectal wall away from the prostate [8, 10, 23, 24].

The current IMRT technology affords the ability to treat patients with different modes [19]. The static modes, step-and-shoot (SS) and sliding window (SW), deliver dose from a discrete number of beam angles. For SW, the beam is maintained while MLCs slide across the treatment aperture at various rates to paint a continuous fluence pattern. In contrast, SS steps MLCs to a set of discrete aperture shapes, and delivers the beam when the leaves are stationary at each position. It produces a fluence pattern at discrete levels equal to the number of steps. VMAT, a special type of IMRT, is the most modern and complex mode, which rotates the gantry of the linear accelerator at a constant or variable rate around the patient for a partial or full-arc. During the rotation, MLCs are in a constant motion while the dose rate is continuously varied to weigh the angular beam. Similar to SW, the fluence is continuous and painted by the moving MLCs, moving gantry, and variable dose rates across an optimized full- or partial-arc. VMAT reduces streaking and normal tissue dose by distributing the incoming beam over a larger volume. IMRT is usually oriented up to nine beam angles, and a low dose bath of radiation is created outside the PTV. This effect, which is not spread out widely, also occurs in 3D-CRT where only 2-4 beam angles are usually used. Complex shapes of radiation with IMRT sometimes result in unwanted hot- or cold-spots. Hotspots in organs at risk (OAR) put patients at a higher risk, and cold-spots within the PTV put patients with tumor under-dosing. IMRT is a technique where hundreds of small radiation beams with different intensities

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are delivered to provide a precise tumor dose while minimizing adjacent normal tissue doses and generating a conformal dose distribution with steep dose fall-off at the boundary between the tumor and normal structures. VMAT usually consists of 2-3 full or partial arcs, significantly reducing the time and MU required for delivering a treatment. IMRT or VMAT plans are based on the inverse planning system where a mathematical equation is solved to determine optimum beam intensities needed to provide planned-dose distributions.

The dose homogeneity index (HI) is usually measured as the standard deviation (SD) of the PTV dose. With homogeneous dose, the dose falloff is very steep, and SD is very small. The dose conformity is expressed by conformity index (CI), which is defined as the ratio between the PTV covered by reference isodose (for example, 95% of prescribed dose) to that of PTV. During radiation treatments, patients are required to stay comfortably immobilized since small movements may offset the conformity. VMAT is probably the best choice to treat a complex shape tumor with high conformity and lower treatment time [25]. A major source of concern with VMAT and IMRT is the increase in low-dose irradiation to surrounding normal tissue, which potentially increases the risk of secondary malignancy.

Data Comparison

A literature search was conducted using Pubmed/MEDLINE, BioMed Central (BMC)-part of Springer Nature, Google Scholar, and Insight Medical Publishing (iMED Pub LTD) with the following keywords for filtering: 3D-CRT, IMRT, VMAT, Prostate Cancer, Conformity, and Homogeneity Index. A total of 12 publications were finally selected to compare clinical differences among VMAT, IMRT, and 3D-CRT treatment techniques. A number of PT cases were studied using conformity, HI, and 10-year secondary tumor-free survival.

The dose rate and gantry speed are constant for 3D-CRT and IMRT and variable for VMAT. For beam intensity, IMRT and VMAT are modulated and 3D-CRT is uniform. Twenty-four patients treated on an Elekta InfinityTM linear accelerator were selected to generate and compare IMRT and single arc VMAT plans [16]. Treatment plans were hatched using the Philips Pinnacle Version 9.0. The SmartArc component of the system was used for single arc 360-degree VMAT Plans. MUs were 485 (374-693) for IMRT versus 484 (376-633) for VMAT. Treatment delivery times were 1.5-2 minutes for VMAT versus 7-9 minutes for the fixed-field IMRT. VMAT plans offered the potential for reduced doses to adjacent organs, especially at the low-dose level. VMAT plans were delivered significantly faster than IMRT ones, allowing operational efficiency and improved patient comfort. Data from 10 patients with PC were used to generate 3D-CRT, five-field IMRT, constant dose rate VMAT (Cdr-VMAT), and variable dose rate VMAT (Vdr-VMAT) treatment plans [5]. Organs at high-risk doses, HI, CI, and MUs were evaluated for all plans. IMRT, Cdr-VMAT, and Vdr-VMAT plans resulted in lower doses to OAR than 3D-CRT ones. The Vdr-VMAT resulted in more favorable dose distributions than IMRT or Cdr-VMAT. The Cdr-VMAT and Vdr-VMAT plans required fewer MUs than IMRT but more MUs than 3D-CRT. The improved dose distribution with Vdr-VMAT resulted in decreased toxicity. A long-term follow-up is required to determine the VMAT's potential to decrease the rate of secondary malignancy compared with that of IMRT.

Treatment plans were generated in the present study using 3D-CRT, IMRT, and VMAT techniques [17]. CI, HI, V5%, V2%, V1% (receiving 5, 2, and 1 Gy, of PTV, respectively), and MUs were compared among plans. The study confirmed that VMAT had slightly better CI while the volume of lower doses was higher. VMAT had lower MUs than IMRT, while 3D-CRT had the lowest MU, CI, and HI. Treatment delivery times were shorter for VMAT with a single-gantry rotation time of approximately one minute, versus 3-4 minutes for IMRT. Lower MUs with VMAT reduced the risk of secondary malignancy. If PTV coverage and OAR sparing were comparable among different techniques, the risk of secondary malignancy should be an important factor in choosing the treatment technique. Data of nine patients with PC were used to generate SS IMRT, serial Tomo Therapy (MIMic), 3D-CRT, and VMAT plans for comparison [18]. HI, CI, OAR doses, isodose encompassing 95% of PTV, treatment time, and MUs were considered. VMAT and MIMic provided a better target coverage compared to SS IMRT that was superior to CI. HI was similar for all techniques. The 3D-CRT provided good

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target coverage but resulted in the highest dose to the rectum. VMAT plans had fewer MUs (371) compared to 544 (IMRT) and MIMic (2714). IMRT yielded treatment plans of significantly improved quality compared to 3D-CRT with MIMic providing the best OAR sparing, and VMAT was the most efficient treatment delivery option with 1.8 minutes, compared to six (IMRT), and 12 minutes (MIMic).

Twenty-six patients with PC were enrolled in the study [20]. The study aimed at evaluating the dose differences received by major OARs for both 3D-CRT and VMAT. In the 3D-CRT, two distinct techniques were utilized: four-field box and 6-8 field conformal plans. VMAT (RapidArc®) was performed with two arcs. VMAT plans had significantly better femoral heads, rectum, and bladder sparing. Eleven patients with PC and prescription dose of 86.4 Gy were enrolled in the present study to compare a single arc VMAT with a standard five-field IMRT [6]. PTV, OAR doses, tumor control probability (TCP), normal tissue complication probability (NTCP), MUs, and delivery times were examined to assess the delivery efficiency. The PTV mean dose and TCP were 88.5 Gy and 92% for VAMT versus 88.9 Gy and 92.9% for IMRT, respectively. All OAR dose requirements were met. MUs for VMAT were 290 against 642 for IMRT. VMAT technique reduced the beam-on time by up to 55% while maintaining dosimetric quality compared with IMRT. The VMAT plans presented better rectal wall sparing, with a reduction of 1.5% in NTCP.

Fifteen patients with PC treated with 10 MV photon beams were enrolled in the study [19]. SS IMRT, SW IMRT and VMAT plans were generated and compared. PTV and OAR doses, TCP, NTCP, CI, and MUs were considered. TCP differences were insignificant among modalities (P>0.99); NTCP was the lowest for VMAT in all structures, except the bladder. MUs were at least 40% less for VMAT plans compared to SS and SW IMRT plans. No clear dosimetric superiority in PTV and OAR doses was found for any of the delivery modes. Treatment planning and delivery time should be of greatest consideration when choosing a treatment method.

Ten patients with PC using an endo-rectal balloon for prostate immobilization were enrolled in the study [10]. IMRT and 3D-CRT treatment plans were generated to compare prostate and normal tissue dosimetry. Insignificant differences were found for prostate and seminal vesicles in TCP between IMRT and 3D-CRT. Compared to 3D-CRT, IMRT resulted in a significantly reduction in NTCP for the upper rectum and femurs. IMRT achieved superior normal tissue avoidance, especially for the rectum and femurs, compared to 3D-CRT with a comparable target dose escalation. A total of 485 treated male patients with localized prostate cancer were enrolled in the study to compare the treatment outcomes in a cohort of patients with PC treated with conventional fractionation using IMRT or 3D-CRT technique [26]. Late GI and genitourinary (GU) toxicities were retrospectively evaluated according to modified RTOG criteria. The comparison included biochemical recurrence-free survival (bRFS), overall survival (OS), and late toxicity. IMRT significantly reduced the risk of late GI complications compared with 3D-CRT without any differences for bRFS and OS. No significant differences were observed for late GU toxicity between IMRT and 3D-CRT techniques.

A retrospective study of 2526 patients with PC patients treated with 3D-CRT (21.3%), IMRT (68.1%), and VMAT (10.6%) was reviewed in the present study [27]. The impact of 3D-CRT versus IMRT/VMAT on the incidence of second tumors (ST) in patients with PC was studied. The correlation of ST incidence with radiotherapy technique was analyzed using the log-rank test and Cox proportional hazard method. ST free survival (STFS) was studied. Ten-year STFS of patients with 3D-CRT and IMRT/VMAT was 85.8% and 84.5%, respectively. A significantly higher 10-year ST incidence in the pelvis was found in patients using IMRT and VMAT compared with 3D-CRT (10.7% versus 6%).

Fifteen high-risk patients with PC treated with 6 MV photon beams were enrolled in the study to compare IMRT and VMAT in terms of plan quality and efficacy [28]. For IMRT, seven fixed beam angles were used, and the dose was optimized using the SW method. In case of VMAT, one or two full-arcs were used for dose optimization, keeping all dose constraints and other planning parameters, same as those used in IMRT planning. VMAT took lesser dose delivery time and number of MUs and was more efficient in terms of plan quality and dose delivery than IMRT. Twenty-three patients with localized PC

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Table 1: Plan Comparison

	Year	Type of Comparisons	Results/ Summary
Rosenthal, et al., [16]	2010	IMRT and single-arc VMAT plans were compared.	VMAT plans were faster than IMRT with better patient comfort.
Palma et al., [5]	2008	VMAT plans required fewer MUs than IMRT but more MUs than 3D-CRT.	IMRT and VMAT resulted in lower toxicity than 3D-CRT.
Cakir et al., [17]	2015	3D-CRT, IMRT and VMAT techniques were used for treatment plan comparison where treatment delivery times were shorter for VMAT plans.	VMAT plans had better CI and; lower MUs than IMRT, while 3D-CRT had the lowest MUs, CI, and HI.
Wolf et al., [18]	2009	SS IMRT, serial TomoTherapy (MIMic), 3D-CRT, and VMAT plans were compared.	VMAT and MIMic had superior target coverage than SS IMRT, which had a superior CI.
Barreiros et al., [20]	2011	3D-CRT and VMAT (Rapid-Arc®) plans were compared in the study.	VMAT plans had a significantly better bladder, rectum, and femoral head sparing.
Zhang et al., [6]	2010	VMAT plans were compared with 5- field IMRT plans.	VMAT plans had better rectal wall sparing and NTCP against IMRT.
Herman et al., [19]	2013	Step and Shoot IMRT, sliding window IMRT, and VMAT (Rapid-Arc®) plans were compared.	No clear dosimetric superiority was found for any of the delivery modes.
Vlachaki et al., [10]	2005	IMRT and 3D-CRT plans were compared in the study.	With a comparable tumor dose, normal tissue avoidance was generally superior for IMRT to 3D-CRT.
Viani et al., [26]	2019	IMRT and 3D-CRT plans were compared in the study.	GI toxicity reduced in IMRT, but no significant differences were observed in GU toxicity.
Buwenge et al., [27]	2020	3D-CRT plans were compared against IMRT/ VMAT to study ST-free survival.	No significant differences were found in ST-free survival among all techniques.
Mukhtar et al., [28]	2020	IMRT and VMAT plans were compared to find better plan quality and efficacy.	VMAT was more efficient and had lesser dose delivery time and MU than IMRT.
Abu-Hijlih et al., [29]	2020	IMRT and VMAT plans were compared for patients treated with hypo-fractionation.	VMAT plans had better PTV coverage, reduced normal tissue toxicity, better CI and HI, lower MUs, and shorter treatment times than IMRT.

receiving moderate hypo-fractionated radiotherapy were enrolled in the dosimetric comparison study to compare IMRT against VMAT [29]. The IMRT plans were performed with 7 to 9 field 6 MV photon beams using the direct machine parameter optimization technique, and the VMAT plans were made with a single-arc technique. Dose-volume histograms, MUs, treatment delivery times, CI, and HI were compared between the two techniques. VMAT resulted in better PTV coverage, reduced mean bladder and rectal doses, improved CI, and HI, and lowered MUs, and shortened treatment time compared to IMRT.

Plan comparisons for 3D-CRT, IMRT and VMAT are summarized in Table 1.

CONCLUSION

Following the review of the literature, it was difficult to definitely indicate the best treatment plan and delivery technique in all PC cases. VMAT and IMRT treatment plans, in general, provide a superior delivery technique with tumor dose escalation, better PTV conformity, and OAR sparing compared to 3D-CRT. Presently, VMAT and IMRT are increasingly utilized to treat PC though the complexity requires additional time and effort in treatment planning optimization, safety check, and quality assurance procedures. IMRT and VMAT achieve an accurate and similar PTV dose coverage. VMAT provides a more homogeneous dose distribution with slightly improved HI, though the differences are statistically insignificant. VMAT also provides better CI than IMRT, when 3D-CRT provides the worst. IMRT and VMAT uses more radiation fields during treatment, exposing a larger volume of normal tissue to lower doses. VMAT, however, has the most volume of low doses. The risk of secondary malignancies thus increases with IMRT and VMAT compared to 3D-CRT with a smaller low-dose region. VMAT is superior to IMRT because of fewer MUs, and faster and efficient delivery time. Shorter treatment time with VMAT may reduce the risk of significant intra-fraction prostate motion. VMAT, with lower MUs, may also reduce the risk of secondary malignancy. Even if the same planning objectives and calculation algorithms

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are used, it is extremely difficult to completely eliminate planner bias if multiple planners are involved in the process. Direct comparison among various studies is impossible because of differences in the target volume definition, dose prescription, and fractionation schedules. Future studies are required to clarify the impact of reduced delivery time with cost-utility on clinical outcomes and possible improvement on small OAR sparing.

ACKNOWLEDGMENTS

None declared.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICS APPROVAL

This is a review article and doesn't not require ethical approval.

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