RESEARCH ARTICLE

Comparison of Three Dimensional Conformal Radiation Therapy, Intensity Modulated Radiation Therapy and Volumetric Modulated Arc Therapy for Low Radiation Exposure of Normal Tissue in Patients with Prostate Cancer

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Abstract

Radiotherapy has an important role in the treatment of prostate cancer. Three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques are all applied for this purpose. However, the risk of secondary radiation-induced bladder cancer is significantly elevated in irradiated patients compared surgery-only or watchful waiting groups. There are also reports of risk of secondary cancer with low doses to normal tissues. This study was designed to compare received volumes of low doses among 3D-CRT, IMRT and VMAT techniques for prostate patients. Ten prostate cancer patients were selected retrospectively for this planning study. Treatment plans were generated using 3D-CRT, IMRT and VMAT techniques. Conformity index (CI), homogenity index (HI), receiving 5 Gy of the volume (V5%), receiving 2 Gy of the volume (V2%), receiving 1 Gy of the volume (V1%) and monitor units (MUs) were compared. This study confirms that VMAT has slightly better CI while thev olume of low doses was higher. VMAT had lower MUs than IMRT. 3D-CRT had the lowest MU, CI and HI. If target coverage and normal tissue sparing are comparable between different treatment techniques, the risk of second malignancy should be a important factor in the selection of treatment.

Keywords: Low dose volumes - secondary cancer - volumetric modulated arc therapy - prostate cancer

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Introduction

About 50% of all cancer patients in the world receive radiotherapy during their treatment. The aim of radiotherapy is to keep local tumour control and tolerable normal tissue complications for early and late effects (Cahlon et al., 2008; Zelefsky et al., 2008). Secondary malignancies are late complication arising after radiotherapy and chemotherapy. In all studies, atom bomb survivors, Chernobyl accident, irradiated patients, animal experiments show that ionizing radiation is a carcinogenic factor (Hall et al., 2003; Preston et al., 2003). Several studies have shown that the risk increases with dose. Hall and Cheng-Shie have expressed by increasing the volume of normal tissue receiving low doses, may increase the incidence of secondary cancer. A linear relation exists between cancer and dose from about 0,1 Sv up to about 2,5 Sv (Hall et al., 2006; NRCP report, 1993). These data represent the gold standard for our knowledge concerning radiation-induced cancer. In most cases, assessment of risk of second cancers in radiotherapy patients is difficult. Because there is almost not control group treated without radiation expect for cancer of prostate and cancer of the cervix, in which surgery is a viable alternative to radiotherapy (Ashman et al., 2005, Luxton et al., 2004).

Prostate cancer becoming one of the most frequent malignant cancer for men in the world (Zelefksy et al., 2000). Radiotherapy has an important role in the treatment of prostate cancer radiotherapy. In the last two decades, two-dimensional and three-dimensional conformal radiation therapy (3D-CRT) techniques were applied (Palma et al., 2008; Cao et al., 2007; Cozzi et al., 2008). In recent years, intensity modulated radiation therapy (IMRT) and intensity modulated arc therapy (VMAT) have been increasingly utilized to treat prostate cancer to give more conformal dose distribution. The basic principle of IMRT involves irradiation from a number of different direction with beams of nonuniform energy fluences, which have been optimized to deliver a high dose to the target volume and acceptably low dose to the surrounding normal structures(Kry et al., 2005). IMRT increases the volume of normal tissue exposed to some radiation but can reduce total dose received by critical structures (Kutcher et al 1989). Because high energy photons (greater than 10 MV) have dosimetric advantages in some situations because of their greater depth of penetration and skin-

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sparing potential, such energies are commonly used in 3D-CRT.With IMRT, however, high-energy photons may present more disadvantages than advantages .The introduction of technologically advanced radiotherapy, volume of healthy tissues receiving high doses will reduce (Pasquer et al., 2013; Wu et al., 2004; Brenner et al., 2000). Conversely, volume of healthy tissues receiving low doses will increase. On the other hand, delivery of a specified dose to the isocenter from a modulated radiation field by IMRT would require more monitor units (MUs) and longer treatment time. This will cause increased leakage radiation in the total body. VMAT uses a dynamic modulated arc to deliver IMRT. The VMAT technology simultaneously coordinates gantry rotation, MLC motion and dose rate modulation, facilitating highly conformal treatment and optimal sparing of the normal tissue near the target (Otto et al., 2008). Volumetric Modulated Arc Therapy (VMAT), based on the original investigation of K. Otto has been recently introduced in clinical practice in several institutes after an intensive validation at planning level, compared to IMRT or other approaches. Rapid Arc (RA), the Varian solution of VMAT, is implemented as the Progressive Resolution Optimization (PRO) algorithm in the Eclipse planning system by Varian Medical System (Palo Alto, California, USA). The optimisation process is based on an iterative inverse planning process aiming to simultaneously optimise the instantaneous multi leaf collimator (MLC) positions, the dose rate, and the gantry rotation speed to achieve the desired dose distribution (Yu et al., 2002; Shephard et al., 2007; Bortfelt et al., 2009; Sountoulides et al., 2010).

VMAT has the dual advantages of lower MUs and less scattered dose to the body (Wang et al., 2008; Ottolenghi et al., 2011). As the consequence of medical progress cancer patients have higher number of long term survivors after the treatments. Radiation-induced tumors in radiotherapy patients will become increasingly important as younger patients are treated.

Radiotherapy for prostate cancer has been linked to the late occurrence of second malignancies both in the true pelvis and outside the targeted area due to low-dose radiation scatter. Secondary malignancies following prostate irradiation include predominantly bladder cancer and, to a lesser extent, colon cancer (Ding et al., 2014; Kendall et al 2007; Nieder et al., 2008; Ruben et al., 2008; Zelefsky 2012; Budaus et al., 2012; Swamy et al., 2014). Those secondary radiation-induced bladder tumors are usually aggressive and sometimes lethal.

The aim of this study was to compare PTV coverage, organ at risk (OAR) and receiving 5 Gy of the volume (V5Gy), 2 Gy of the volume (V2Gy) ,1 Gy of the volume (V1Gy), monitor unit (beam on time) with 3D-CRT, IMRT and VMAT in the treatment of the prostate cancer.

Materials and Methods

CT datasets of 10 patient with localized prostate cancer (T1-2N0M0) who received IMRT treatment in our institution were used for this comparative planning study. All planning CT scans were obtained by using CT simulator (Philips Healthcare, The Nederlands) with 5-mm slice thickness, without a gap from the iliac crest to 8 cm below the ischial tuberosities. Patients were instructed to void the bladder and rectum about 1-1.5h before the CT simulation, according to their individual urinary conditions. The clinical target volume (CTV) was defined as the entire prostate in this study. a 5-mm margin was used to expand the CTV to the planning target volume (PTV), based on measured localization uncertainties, inter-user reproducibility and intra-fraction motion. For 6 MV, the beam margin, accounting for the beam penumbra, was set to be 0.5 cm from the PTV in the coplanar direction and 0.7 cm from the PTV for the direction perpendicular to the beam direction plane (along the z-direction). Normal structures including bladder, penile bulb, and rectal wall were outlined on the planning CT images. The contoured rectal wall extended from the bottom of the ischial tuberosities to the rectosigmoid flexure. The "normal tissue" volume was defined as the whole patient volume minus the PTV.

Routine institutional image-based patient position verification protocols foresee 2D-2 D matching of orthogonal kV-MV images acquired with the On Board Imaging system installed at the accelerator with evaluation performed by radiographers and application of couch shifts if total vector length of displacement is smaller than 5 mm. Cone Beam CT is becoming part of our routine protocol and is now performed once a week in addition to the 2D-2 D matching (kV-MV) most common procedure.

3DCRT, IMRT and VMAT plans were developed using the Eclipse (Varian Medical System, Palo Alto, California, USA) Version 8.9 Treatment Planning System (TPS) with 6 MV for each patient. AAA (Analitical Anisotropic Algorithm, Varian Medical System, Palo Alto, California, USA) was used to compute the dose distributions. Inverse treatment plans for IMRT and VMAT were generated using the same dose-volume constraints for all plans. The dose constraints were set for the rectal wall, penile bulb, bladder, and unspecified normal structure Table 1.

3D CRT treatment planning

For the 3D-CRT radiotherapy planning, after counturing all normal structure and critical organ then 7 field treatment techniques was used. Beam arrangement 0, 45, 90, 135, 225, 270, 315 was used. Beam weighting was 4%, 12.9%, 22.2%, 12.9%, 12.9%, 22.2%, 12.9% respectively for gantry 0, 45, 90, 135, 225, 270,315. The prescribed dose was normalized to 100% at the isocenter, and 95% isodose surface covered the PTV. Figure 1. shows

Table 1. Dose-Volume Objectives for Treatment Planning

Structure	Criterion Dose(cGy)	%Volume
Planning target volume	7400 cGy	≤95%
Rectum	5000 cGy	< 40%
	6000 cGy	<17%
	7000 cGy	<15%
	7500 cGy	<8%
Bladder	5000 cGy	<50%
	7000 cGy	<30%
Penile bulb	4500 cGy	<50%
	3700 cGy	<70%
Femoral heads	5000 cGy	<5%

typical dose distribution for 3DCRT.

IMRT treatment planning

For the IMRT protocol, a five field dynamic multileaf collimator (DMLC) technique was used. The beam arrangement was as follows; a anterior (0), left anterior oblique (72), left posterior oblique (144), right posterior oblique (216) and right anterior oblique field (288). Inverse treatment planning by computer optimization was used. Inverse optimization were performed until the following planning goals were completely satisfied. As for PTV, D95 should generally be 95% of the prescription dose, maximum dose should be 107% or less, V90 should be 98% or higher and the mean dose will generally be 102% of the prescription dose. Figure 2 shows typical dose distribution IMRT for five field.

RapidArc (VMAT) treatment planning

Rotational IMRT (VMAT) planning is performed through inverse planning techniques in a similar to that of static gantry IMRT. This is further complicated due to increased number of dynamic variables involved during delivery. Varian's solution is the introduction of a new resolution-based optimization algorithm to aid in the inverse planning process. Although the clinical advantages of rotational techniques seem to be establishing themselves, a systematic process providing a turnkey solution for the inverse planning process is yet to be established. As a result, there is a strong correlation between the experience of the planner and the resulting plan quality.

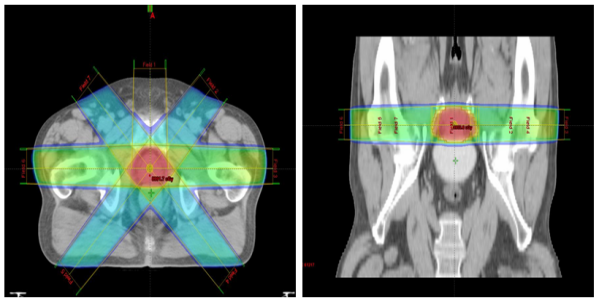

Figure 1. Axial (left) and Coronal (right) Isodose Distribution by 3DCRT of one Representative Patient were Shown

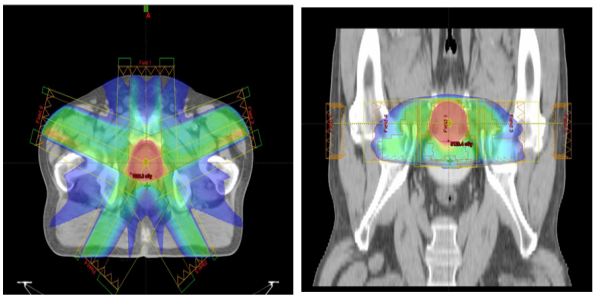

Figure 2. Axial (left) and Coronal (right) Isodose Distribution by 5 field IMRT of one Representative Patient were Shown

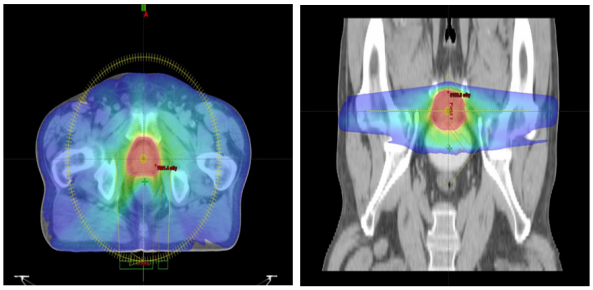

Figure 3. Axial (left) and Coronal (right) Isodose Distribution by VMAT of One Representative Patient were Shown

Once all the contours have been created, a single arc field is set with a collimator rotation of 45. All VMAT plans require some degree of collimator rotation to reduce the cumulative effects of tongue and grove leakage throughout gantry rotation, and to allow spatial modulation in the transverse plane. The jaws are set to be open to largest PTV throughout the entirely of the gantry rotation, with an extra margin of approximately 10 mm. The above two parameters may then be automatically optimized in TPS and upper version. The arc is set to run from 179 through to 181 in a counterclockwise (CCW) direction or from 181 through to 179 in a clockwise (CW) direction and the of the irradiating beam is 6 MV. The above field setup allows the optimization algorithm the largest range of parameters, so that the change of the best plan being produced is maximized. Although the target volume is deep, the fact that radiation is entering the patient from all angles, a beam energy of 6 MV is adequate to produce dose coverage without the increased neutron dose that will result from higher energy beams (19,20). Following optimization, dose calculation is done using the optimized MU value and the AAA dose calculation alghorithm with a dose grid size of 2.5 mm. the dose distribution is then evaluated and the DVHs examined for the planer ability to meet any dose constraints. If target volume coverage does not meet ICRU 83 criteria, there may be a need to renormalize the whole plan by adjusting the plan normalization value, usually by no more than 1-2%.Figure 3. shows typical dose distribution VMAT for one arc.

During planning, the primary goal was to achieve similar PTV coverage for all techniques and, the secondary goal was to reduce OAR doses as much as possible individually. Conformity index (CI) and homogeneity index (HI) were used for PTV coverage.

Dose Volume Histograms (DVHs) were used to compare treatment plans including PTV, OAR, V5%, V2% and V1%. MUs were compared between three treatment techniques.

For statistical analyses the Kruskal-Wallis test was used. All computations were performed using the SPSS program (SPSS Inc., Chicago, IL). A p-value below 0.05 was considered significant.

Results

In term of the OAR, the Dose-Volume objectives were easily met in all cases (Table 2). Table 2 shows, summary of Conformity Index, Homogeneity Index, Rectum V70%,V50%,V20, Bladder V70%, V50% and V20% were shown for 3D-CRT, IMRT and VMAT.

IMRT and VMAT provided very similar and highly

Table 2. Summary of DVH Analysis, CI (Conformity Index) and HI(Homogeneity Index) for three Techniques (3D-CRT, IMRT and VMAT)

	3D-CRT (mean±SD)	IMRT (mean±SD)	VMAT (mean±SD)	P Value
Rectum				
V20%	41,3±14,4	40,9±10,2	48,8±16,3	0,48113
V50%	16,9±9,3	14,4±4,8	15,9±5,8	0,80097
V70%	6,3±3,8	5,9±2,1	5,6±2,4	0,91718
Bladder				
V20%	24,2±17,3	49,4±13,1	53,5±16,6	0,0055
V50%	11,8±7,6	20,3±7,7	18,7±8,0	0,04226
V70%	7,0±4,4	8,9±5,4	8,1±5,0	0,37608
CI	1,978±0,665	1,428±0,070	1,086±0,005	
HI	1,182±0,031	1,078±0,029	1,068±0,008	

Table 3. Comparison of Low doses from Planning Data (V1%, V2% and V5%) by 3DCRT, IMRT and VMAT

	3D-CRT (mean±SD)	IMRT (mean±SD)	VMAT (mean±SD)	P Value
V1%	37,5±9,5	46,9±7,1	48,2±6,0	0,01666
V2%	22,9±6,9	33,2±5,9	35,7±4,8	0,00178
V5%	14,1±4,6	22,8±4,3	26,2±3,9	0,00015

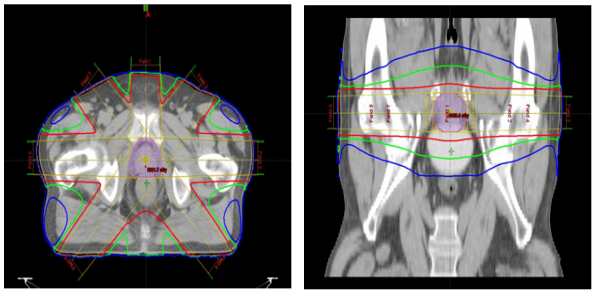

Figure 4. Axial and Coronal Low dose Isodose Distribution (1,2,5 Gy) by 3DCRT of one Representative Patient

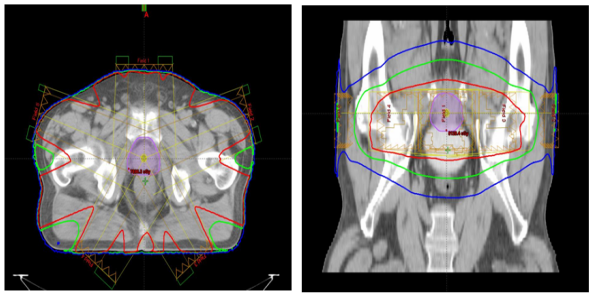

Figure 5. Axial and Coronal Low dose Isodose Distribution (1,2,5 Gy) by IMRT of one Representative Patient

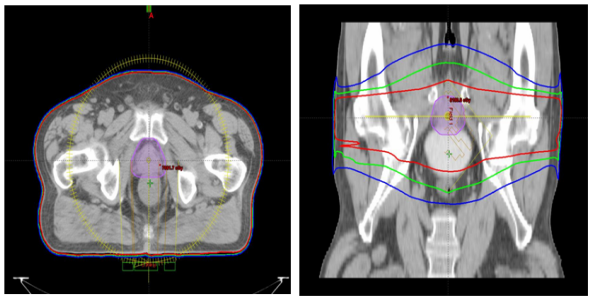

Figure 6. Axial and Coronal Low dose Isodose Distribution (1,2,5 Gy) by VMAT of one Representative Patient

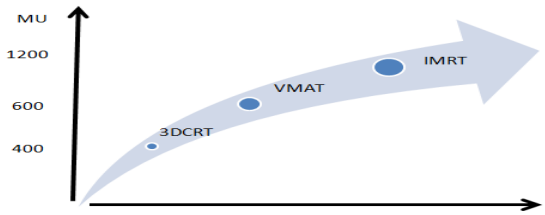

Figure 7. Comparison of MUs for three Diffrerent (3D-CRT,IMRT,VMAT) Planning Results

conformal plans that complied well with OAR Dose-Volume constraints. Although some dosimetric difference were statistically significant, they remain small difference. VMAT provided a more homogeneous dose distribution, where as 3D-CRT enabled less low dose region. For rectum, VMAT was able to provide a higher V20% than IMRT and 3D-CRT (48,8±16,3, 40,9±10,2 and 41,3±14,4 respectively; p:0,48. For Bladder, V20% (24,2±17,3) is lower for 3D-CRT than IMRT(49,4±13,1) and VMAT(53,5±16,6); p:0,0055.

3D-CRT has shown statistically significant lower V5%, V2% and V1% than IMRT and VMAT dose distribution. Also Table 3 shows V5%:5Gy receving of the volume, V2%:2Gy receiving of the volume, V1%:1Gy receiving of the volume. Also V5%, V2% and V1% are shown as planning data in Figures 4-6. In Figure 4, receiving 5Gy of the volume (V5%) is red; receiving 2 Gy of the volume is green and receiving 1 Gy of the volume is blue. Figure 4 for 3D-CRT;Figure 5 for IMRT planning data; Figure 6 including VMAT planning data.

Comparison of MUs between three treatment techniques was shown in Figure 7

An advantage of IMAT plans over IMRT is that patient MUs are reduced by more than half from to 604±56 to1216±129. In addition, treatment delivery time is considerably shortened, from about 3-4 minutes for IMRT to 1 minute approximately for VMAT with a single gantry rotation.

Discussion

Many radiation-induced second cancers appear to occur in organs and tissues in the high-dose volume, but some may also appear in the low dose volumes. There are pronounced differences in the types of radiation-induced second cancers between children, young adults and elderly patients treated with radiotherapy (Ottolenghi et al., 2011).

The risk of radiotherapy-induced second cancers after radical radiotherapy of most adult cancers is well below 1% .The risk of dying from uncontrolled local recurrences within a few years after radiotherapy is much higher than the risk of developing a second cancer 10 or 20 y later. In adult cancer patients, more than 90 % of second cancers occurring after radiotherapy are the consequence of increased life expectancy due to cure from the first cancer (Ottolenghi et al., 2011).

Improvement in early cancer detection and advances in therapy have resulted in increasing number of cancer survivors. Prostate cancer is the most common malignancy

among men. Radiation therapy is an important part in the treatment of prostate cancer.

Radiotherapy is associated with a modest increase in secondary cancers. In the treatment of prostate cancer, the risk of dying from a secondary radiation-induced bladder cancer may be greater than the risk of dying from the primary prostatic tumor following surgery or watchful waiting (Yu et al., 2002).

The risk of second malignencies using IMRT technique higher photon doses than the 3D CRT (Wang et al., 2008).

In the last few years, IMRT and VMAT have been increasingly utilized to treat prostate cancer to permit more conformal dose distribution and dose escalation. On the other hand, volums of normal tissue to low doses of radiation with IMRT and VMAT are larger than conventional conformal techniques. Hall and Wuu are one of the first to discuss how a shift from 3D-CRT to IMRT may result in an increase in second malignancies(Hall et al., 2003). Because IMRT uses more radiation fields, thus involving a bigger volume of normal tissue that is exposed to lower doses and IMRT requires the accelerator to be powerd for longer MUs, resulting in more total body dose due to scatter radiation. The amount of secondary radiation generated is a linear function of the amount of MUs. IMRT is associated with a 3 to 5 higher number of monitor units compared with conventional treatment. The potential cancer induction maximum in the 1-5 Gy range would make an impact in multi field therapy. Organ specific dose volume histograms could be helpful for risk assessment. Prospective and uniform out-of-field dosimetry during planning would be preferable over dose reconstruction.

In this study, IMRT and VMAT provided very similar and highly conformal plans for tumor coverage than 3D-CRT. The dose homogenity within the PTV was slightly improved by the VMAT technique when compared with IMRT, although the difference was not statistically significant. By contrast, V5Gy, V2Gy and V1Gy were statistically significant lower for 3D-CRT (14,1±4,6%, 22,9±6,9%, 37,5±9,5%) than IMRT (22,8±4,3%, 33,2±5,9%, 46,9±7,1%) and VMAT (26,2±3,9%, 35,7±4,8%, 48,2±6%) respectively. V5Gy, V2Gy and V1Gy for VMAT were higher than IMRT. We found MUs 421±29 for 3D-CRT, 1216±129 for IMRT (five field) and 604±56 for VMAT (one 360º rotation).

There are so many articles published about comparision 3D-CRT and IMRT, VMAT techiques for lots of cancer treatment (Swamy et al., 2014; Ding et al., 2014). Some authors have reported dosimetric comparisons of 3D-CRT, IMRT and VMAT for prostate treatment (Romanenko et al., 2003; Xu et al., 2008), direct comparison with our study is difficult. They use different comparison parameter. The comparison mostly was for PTV and OAR. There is not for volume of low dose radiation such as V5Gy, V2Gy, V1Gy. All studied intensity modulated techniques yield treatment plans of significantly improved quality and higher MUs when compared to 3D-CRT. Palma et al. compared 3D-CRT, Dynamic IMRT and arc therapy using Varian's Rapid Arc. They reported better treatment efficiency for the arc therapy (491.6 and 454.2 MUs for constant and variable dose rate respectively) vs.788.8 MUs for Dynamic IMRT. They also reported overall similar dose distributions with slight advantages regarding dose to OAR and conformity for the plans with variable dose rate during rotation. A detailed analysis of dose exposure to non PTV normal tissue was not performed (Palma et al., 2008). Zelefsky et al. reported for prostate patients (1.8 Gy/fraction) approximately 700 MUs for dynamic IMRT and 300 MUs for 3D-CRT (Zelefsky et al., 2008). Shaffer et al. reported 949 MUs for VMAT and 1814 MUs for nine field IMRT with a integrated boost to the CTV (120% of PTV) (Shaffer et al., 2009). Wolff et al. reported for prostate treatment 252±8 MUs for 3DCRT, 544±56 MUs for step-and-shoot IMRT, 386±29 MUs for (one 360º rotation) VMAT and 371±34 for (one 360º rotation and two 100º rotation) VMAT (Wolff et al., 2009) .Tsai et al. compared treatment and dosimetric advantages between VMAT, step-and-shoot IMRT and Helical Tomotherapy (HT). They reported, all VMAT, IMRT and HT plans were to meet the goals for PTV and the constrain for organs. Also, they reported, the mean MUs 309.7 for VMAT, 336.1 for step-and-shoot IMRT and 3368 for HT (Tsai et al., 2011). The studies show that arc therapy has similar coverage of PTV and doses of normal tissue with IMRT (step-and-shoot or dynamic). Arc therapy had significintly lower MUs than IMRT. It means shorter beam on time. Modulated arc therapy carries less risk of including secondary tumors. The risk of developing a second malignancy increased 0.4%, 1% and 2.8% for 3D-CRT, step-and-shoot IMRT and HT by 6MV photon irradiation respectively (Xu et al., 2008). Also importantly modulated arc therapy with its shorter treatment time may be less affected by intrafractional movement.

A lot of studies suggest that IMRT results in increased secondary cancer risk. This has often been attributed to an increase in MUs requirements and head leakage (Followill et al., 2003). Indeed, it has been shown that, compared to 3D-CRT IMRT does result in increased leakage. Moreover, increased beam on time results in increased collimator head scatter, both of which contribute to an increase in out-of-field dose .

Studies involving proton treatments have consistently shown reduced secondary cancer risks compared to 3D-CRT and IMRT, largely because a reduction in exit doses results in a reduction in the volume of normal tissues irradiated, thus resulting in improved conformity. Similarly, the risk of secondary cancer has been shown to be lower with proton arc therapy compared to photon VMAT (Rechner et al., 2012).

The risk of second malignencies using IMRT technique have been estimates to be 2 or 3 times higher than that after conventional radiation therapy (Murray et al., 2013).

In conclusion, this study confirms that VMAT has slightly better conformity and homogeneity but VMAT has upper volume of low doses than IMRT. VMAT spread low doses of radiation to larger areas of normal tissue. VMAT had lower MUs than IMRT.Lower MUs reduce the risk of second malignancy. If target coverage and normal tissue sparing are comparable between different treatment techniques, the risk of second malignancy should be a important factor in selection of the treatment.

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