Technical Note

Dosimetric, Radiobiological and Secondary Cancer Risk Evaluation in Head-and-Neck Three-dimensional Conformal Radiation Therapy, Intensity-Modulated Radiation Therapy, and Volumetric Modulated Arc Therapy: A Phantom Study

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Abstract

This analysis estimated secondary cancer risks after volumetric modulated arc therapy (VMAT) and compared those risks to the risks associated with other modalities of head-and-neck (H&N) radiotherapy. Images of H&N anthropomorphic phantom were acquired with a computed tomography scanner and exported via digital imaging and communications in medicine (DICOM) standards to a treatment planning system. Treatment plans were performed using a VMAT dual-arc technique, a nine-field intensity-modulated radiation therapy (IMRT) technique, and a four-field three-dimensional conformal therapy (3DCRT) technique. The prescription dose was 66.0 Gy for all three techniques, but to accommodate the range of dosimeter responses, we delivered a single dose of 6.60 Gy to the isocenter. The lifetime risk for secondary cancers was estimated according to National Council on Radiation Protection and Measurements (NCRP) Report 116. VMAT delivered the lowest maximum doses to esophagus (23 Gy), and normal brain (40 Gy). In comparison, maximum doses for 3DCRT were 74% and 40%, higher than those for VMAT for the esophagus, and normal brain, respectively. The normal tissue complication probability and equivalent uniform dose for the brain (2.1%, 0.9%, 0.8% and 3.8 Gy, 2.6 Gy, 2.3 Gy) and esophagus (4.2%, 0.7%, 0.4% and 3.7 Gy, 2.2 Gy, 1.8 Gy) were calculated for the 3DCRT, IMRT and VMAT respectively. Fractional esophagus OAR volumes receiving more than 20 Gy were 3.6% for VMAT, 23.6% for IMRT, and 100% for 3DCRT. The calculations for mean doses, NTCP, EUD and OAR volumes suggest that the risk of secondary cancer induction after VMAT is lower than after IMRT and 3DCRT.

Keywords: EBT2 FILM, imaging and radiation oncology core, intensity-modulated radiation therapy, three-dimensional conformal radiation therapy, thermoluminescent dosimeter, volumetric modulated arc therapy

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Introduction

In cancer patients treated with radiotherapy, secondary cancers are a frequent and well-known late effect.[1] However, the extent of the role of radiotherapy in the occurrence of secondary cancers is difficult to quantify because patients undergoing radiotherapy are often at high risk of a second cancer due to environmental risk factors or genetic predispositions.[2] Despite this uncertainty, there is clear evidence for the association between radiation exposure and cancer induction, especially from epidemiological studies of atomic survivors of the Bombing in Japan.[3,4] Furthermore, the importance of secondary cancer risk after radiations therapy has been recognized by several International organizations,

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including the International Commission on Radiological Protection, the National Council on Radiation Protection and Measurements (NCRP), and others.[5-9]

Little and Muir head distinguished the difference between nuclear bomb survivor sand patients treated by radiotherapy by the level of cell killing at doses higher than 2 Gy.[10] Other reports suggested a threshold of about 0.6 Gy in adults after fractionated radiotherapy and of 0.1 Gy in children after acute irradiation.[11] Schneider has applied a linear-quadratic model to estimate second cancer induction following radiation therapy.[12]

Currently, there are several ways to treat head-and-neck (H and N) cancer with ionizing radiation, including three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), and volumetric modulated arc radiotherapy (VMAT). Available IMRT delivery techniques may use multiple static beams, dynamically arced beams, or helically rotated beams. Many studies have been performed to evaluate IMRT techniques, and most have shown that IMRT is advantageous in terms of dose coverage of the planning target volume (PTV) and reduction of dose to normal tissues and organs at risks (OARs), although it is still debated whether or not this is true for H and N cancer.[13,14]

VMAT is a relatively new technique but is rapidly gaining popularity due to the efficiency of treatment delivery, the reduced treatment time and a smaller number of monitor units typically required. The radiobiological models describe the effects of the radiation treatment on cancer and healthy cells, and the radiobiological effects are generally characterized by the tumor control probability and normal tissue complication probability (NTCP).[15] Different planning and dosimetric studies have been published and reported that VMAT is found better than other techniques.[16-18]

The aim of this study was to calculate doses to OARs (brain and esophagus) and to estimate the secondary cancer risks after H and N VMAT compared to IMRT and 3DCRT. To avoid confounding issues linked to patient's anatomical characteristics and assess organ dose deposition precisely, we used a standardized the Imaging and Radiation Oncology Core (IROC -Houston) H and N anthropomorphic phantom based on realistic patient anatomy.

Materials and Methods

Treatment planning and phantom

All plans (3DCRT, IMRT, and VMAT) were generated in a Pinnacle treatment planning system (TPS, Philips, version 9.4 Fitchburg, WI, USA). VMAT treatment planning was done using clockwise and counter-clockwise dual arcs with angles 182°–178° and 180°–184°. Nine-field IMRT (beam angles: 200°, 240°, 280°, 320°, 0°, 40°, 80°, 120°, and 160°) the commonly used angles at MD Anderson Cancer Center, were used for IMRT, and four fields were used for 3DCRT (anterior-posterior, posterior-anterior, left lateral, and right lateral). The treatment plans were created with the guidance of an expert and followed MD Anderson standard guidelines.

The IROC H and N phantom were used in the dosimetric comparison among different H and N radiotherapy techniques (3DCRT, IMRT, and VMAT). Computed tomography (CT) images (1.5 mm slice thickness and slice interval) were taken from the Philips Brilliance 64-slice scanner (Philips Healthcare, Andover, MA, USA) containing 512 × 512 pixels in each slice. The CT imaging technique was 120 kV and 250 mA tube current. After the CT simulation, digital imaging and communications in medicine CT images were transferred to the TPS for contouring and planning preparation.

The anatomy structures, including PTV and OARs (brain and esophagus) were manually contoured as shown in Figure 1. The prescriptions and optimization objectives used for all treatment plans were based on the IROC phantom irradiation condition. The prescription dose was 66 Gy but to accommodate the range of dosimeter responses, a single fraction of 6.6 Gy was delivered to 90% of the region-of-interest mean dose to the PTV for all plans. This dose level was chosen to be consistent with the Radiation Therapy Oncology Group (RTOG) recommendations for this clinical radiotherapy. A primary goal of treatment planning was to ensure that PTV coverage was 90% of the prescription dose for each technique.

Three-dimensional conformal radiation therapy, intensity-modulated radiation therapy and volumetric modulated arc therapy delivery

A linear accelerator (Clinac 21iX, Varian Medical Systems, Palo Alto, CA, USA) was used for dose delivery. Six MV photon beams were used for all cases, and the adaptive convolve algorithm was used for the plan optimizations and dose calculations. Each plan used a maximum dose rate of 600 MU/min and was optimized with the direct machine parameter optimization algorithm for both IMRT and VMAT. To make fair comparisons, no modification was done throughout the optimization to the dose-volume constraints and weighting for IMRT and VMAT.

Dosimetric assessment

The mean and maximum doses and volumes receiving >20 and 38 Gy of OARs were calculated and compared among

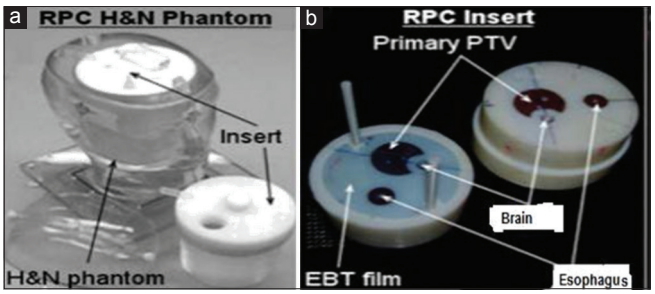

Figure 1: (a) Imaging and Radiation Oncology Core-Houston (formerly Radiological Physics Center) head-and-neck anthropomorphic phantom. (b) Standard imaging and radiation Oncology core insert that contains the simulated planning target volume and organs at risks

each technique. The lifetime probabilities of increasing fatal secondary malignancies were calculated using per Sievert (Sv) absorbed in OARs (brain and esophagus) using the NCRP Report 116. Mean doses were used for calculating fatal secondary risk in OARs due to the fact that they would be responsible for secondary malignancies according to a parallel study by Rehman *et al*. RTOG conformal index (CI) is defined as the volume of the PTV receiving the prescription dose divided by total volume of the PTV and its optimal value is 1 as shown in equation (1). Homogeneity index (HI) is defined as the dose received by 5% of the PTV divided by the dose received by 95% of the PTV. Its optimal value is equal to 1 as shown in Equation (2).

$$CI = \frac{V_{prescribed}}{V_{PTV}} \quad (1)$$

$$HI = \frac{D_{5\%}}{D_{95\%}} \quad (2)$$

Dose-volume histogram evaluation

Dose-volume histograms (DVHs) were used to provide quantitative comparisons among the different spine radiotherapy techniques (3DCRT, IMRT, and VMAT). Therefore to ensure an unbiased comparison for successive computation of various indices, all mean DVH data for the studied H and N techniques were gathered from Pinnacle[3] with a bin size of 0.05 Gy. PTV and OAR DVHs for different H and N radiotherapy techniques were calculated.

The brain and esophagus NTCP were calculated using the Lyman-Kutcher-Burman algorithm[19] using the following equations.

$$NTCP = \frac{1}{2\pi}\int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \quad (3)$$

and

$$t = \frac{D - TD_{50}(v)}{mTD_{50}(v)} \quad (4)$$

In Eq. (4), $v = V/V_{ref}$ and $TD_{50}(v) = TD_{50}(1)\, v^{-n}$, as suggested by Burman *et al*.[20] The NTC*P* values in this study were calculated using an in-house software running on a MATLAB™ platform (The MathWorks, Natick, MA, USA).[21] The equivalent uniform dose (EUD) for the brain and esophagus were calculated using the following equation:

$$EUD = (\sum v_i D_i^{1/n})^n \quad (5)$$

In Eq. (5), v_i and D_i were volume and dose with the number of voxel equal to i in the differential DVH. The values of n for the brain and esophagus are equal to 0.25 and 0.06 according to the Lyman-Kutcher-Burman algorithm.

Results

In this study, all 3DCRT, IMRT, and VMAT plans satisfied a minimum of 90% prescribed PTV coverage and a goal of achieving the minimum dose to the OARs using the IROC H and N phantom. Dosimetric comparisons of treatment plans for all techniques are shown in Figure 2. It is seen from the isodose lines that the VMAT plan delivered lower doses to the OARs, namely, brain and esophagus than the 3DCRT and IMRT plans.

The DVH for the PTV is shown in Figure 3a while the DVHs for the OARs such as the brain, and esophagus are shown in Figure 3b and c. It can be seen that VMAT delivered lower doses than the other two techniques. CI was calculated for 3DCRT, IMRT, and VMAT plans and their values were 0.90, 0.91, and 0.95. Results of HI were 1.08, 1.16, and 1.06 for 3DCRT, IMRT, and VMAT plans, respectively.

Table 1 compares the mean and maximum doses to the OARs for estimating the risk of stochastic and deterministic effects using 3DCRT, IMRT, and VMAT techniques for HN radiotherapy. Mean and maximum doses in OARs were lower for VMAT as compared to other techniques. The maximum doses to the brain and esophagus were greater in 3DCRT than IMRT, and significantly smaller when using VMAT.

For comparison with representative patient treatments, Table 1 reports the doses to OARs that would be received for a prescription dose of 66 Gy.

To estimate the secondary cancer risk, Table 2 evaluates the analogous volumes of OARs receiving >20 Gy and 38 Gy from the different H and N radiotherapy techniques.

The volumes of esophagus and brain organs are shown in Table 2 and lifetime secondary cancer risk for such organ are shown in Table 3. The probability of lifetime secondary cancer risk per Sv was taken from the NCRP Report No. 116.[7] Mean doses to OAR were used for the calculation of secondary cancer risk. The NTCP and EUD for the brain and esophagus were calculated and shown in Table 4.

Table 1: Maximum and mean doses to organs at risk for three-dimensional conformal therapy, intensity-modulated radiation therapy, and volumetric modulated arc therapy for head-and-neck radiotherapy

OARs	VMAT		IMRT		3DCRT	
	Mean dose (Gy)	Maximum dose (Gy)	Mean dose (Gy)	Maximum dose (Gy)	Mean dose (Gy)	Maximum dose (Gy)
Esophagus	14	23	17	29	37	40
Brain	21	40	21	42	31	56

Doses are based on PTV prescribed dose of 66 Gy. OARs: Organs at risk, 3DCRT: Three-dimensional conformal therapy, IMRT: Intensity-modulated radiation therapy, VMAT: Volumetric modulated arc therapy, PTV: Planning target volume

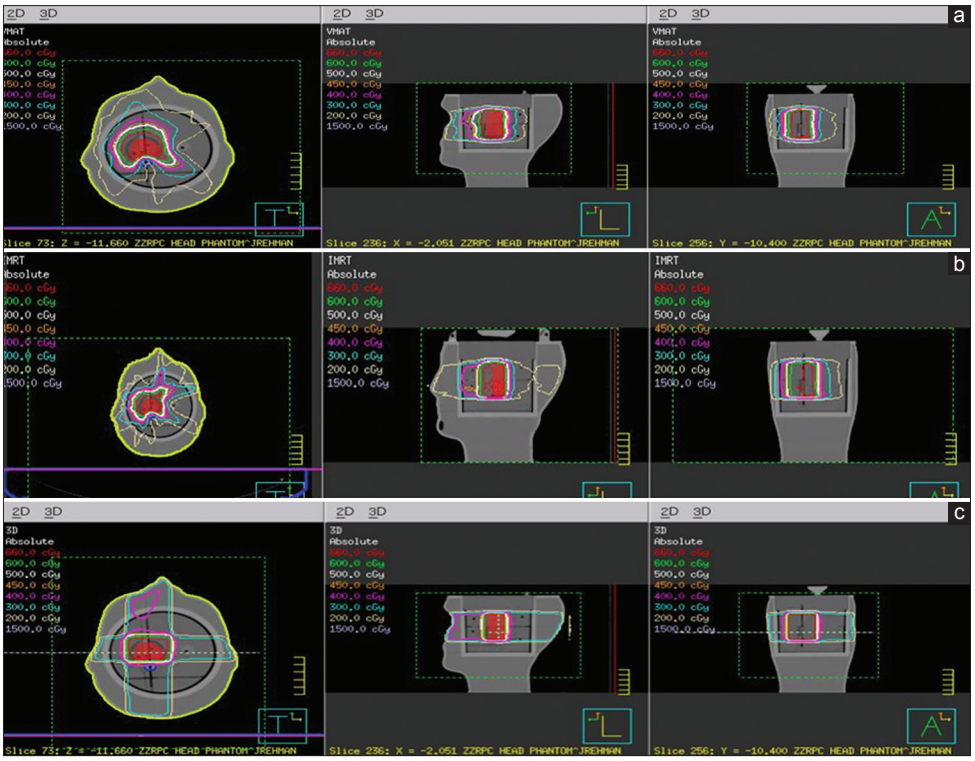

Figure 2: Head-and-neck axial, sagittal, and coronal (left to right) images of (a) volumetric modulated arc therapy, (b) intensity-modulated radiation therapy, and (c) three-dimensional conformal radiation therapy, with absolute isodose lines of 660, 600, 500, 450, 400, 300, 200, and 150 cGy. These isodose values correspond to the doses delivered to the phantom, and were intended to represent patient doses of 66 Gy, etc

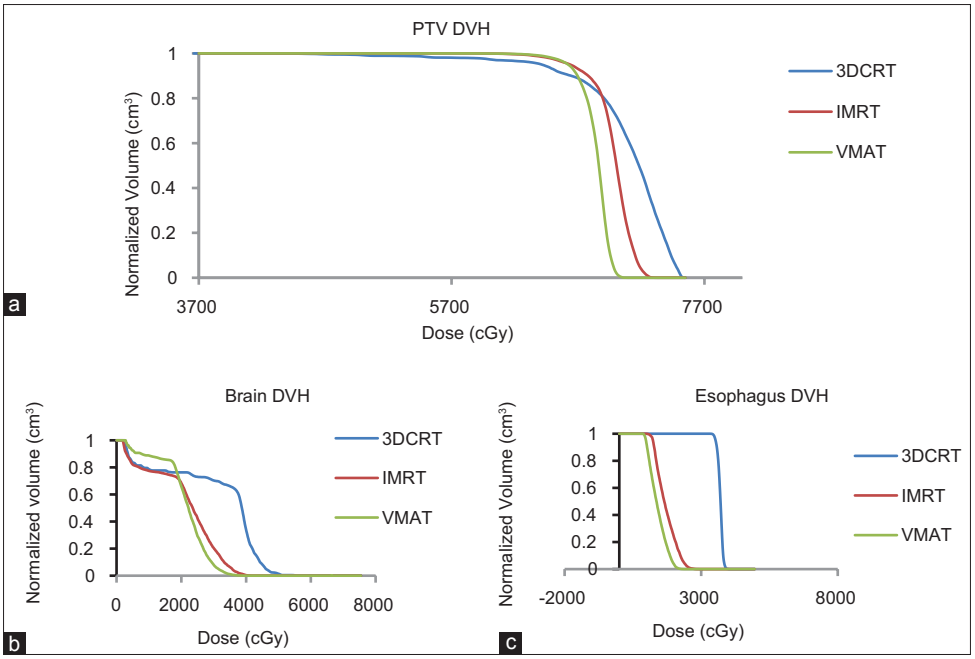

Figure 3: Cumulative dose-volume histograms of planning target volume (a) brain (b), and esophagus (c) for treatment plans using three-dimensional conformal radiation therapy, intensity-modulated radiation therapy and volumetric modulated arc therapy

Discussion

Dose-volume histograms

Figure 3a shows the DVHs for the PTV for three delivery techniques. The dose range in Figure 3a started from 37 Gy rather than 0 Gy to focus on the drop-off region of the DVH curve. PTV coverage was found to be same 90% for each technique, i.e., 3DCRT, IMRT, and VMAT by using normalization method for fair comparison. DVHs for the OARs including brain and esophagus showed that doses delivered by

Table 2: Volumes of organs at risk receiving doses greater than the secondary cancer risk thresholds of 20 Gy and 38 Gy

OARs	VMAT (percentage volume)		IMRT (percentage volume)		3DCRT (percentage volume)	
	>20 Gy	>38 Gy	>20 Gy	>38 Gy	>20 Gy	>38 Gy
Esophagus	3.6	0	23.6	0	100	11.5
Brain	65.8	0.1	68.3	1.7	76.4	57.6

VMAT: Volumetric modulated arc therapy, IMRT: Intensity-modulated radiation therapy, 3DCRT: Three-dimensional conformal therapy, OARs: Organs at risk

Table 3: Lifetime secondary cancer risk for organs at risk by head-and-neck radiotherapy technique

OARs	Probability (%/Sv)	VMAT (%)	IMRT (%)	3DCRT (%)
Esophagus	0.30	4.2	5.1	11.1
Brain	0.50	10.5	10.5	15.5

VMAT: Volumetric modulated arc therapy, IMRT: Intensity-modulated radiation therapy, 3DCRT: Three-dimensional conformal therapy, OARs: Organs at risk, Sv: Sievert

Table 4: Normal tissue complication probability and equivalent uniform dose of organs at risk

OARs	VMAT		IMRT		3DCRT	
	NTCP (%)	EUD (Gy)	NTCP (%)	EUD (Gy)	NTCP (%)	EUD (Gy)
Esophagus	0.4	1.8	0.7	2.2	4.2	3.7
Brain	0.8	2.3	0.9	2.6	2.1	3.8

VMAT: Volumetric modulated arc therapy, IMRT: Intensity-modulated radiation therapy, 3DCRT: Three-dimensional conformal therapy, OARs: Organs at risks, NTCP: Normal tissue complication probability, EUD: Equivalent uniform dose

VMAT were lower than those by IMRT and 3DCRT as shown in Figure 3b and c.

Dose-volume indices

Lee *et al*. have developed and compared a smart-arc based technique with conventional radiotherapy for spine craniospinal irradiation using 23.4 Gy per 13 fractions.[18] They reported a median CI of 1.22 (1.09–1.45) and 1.04 (1.03–1.07) and suggested a noteworthy reduction of mean and maximum doses to the heart, thyroid, esophagus, optic nerves, and eyes when compared to conventional plans. In our study, CI for VMAT plan was 0.95 and was closest to unity, which showed that VMAT plan was more conformal than other plans. The mean and maximum doses were also lower in most OARs. HI for VMAT plan was found to be 1.06 and was the lowest than other plans that indicated VMAT was more homogeneous than other techniques. In general, extremely conformal and homogeneous dose distributions were attainable with VMAT due to its high angular sampling rate of radiation beams.[22] The variation of parameters depends on different weightings and priorities used during planning. One goal of this study was to generate highly conformal plans, with an acceptable small compromise of dose homogeneity.

Mean doses, maximum doses and volumes of organs at risks receiving >20 and 38 Gy

The mean dose to esophagus was higher for both 3DCRT and IMRT than VMAT. Lower mean doses were seen for both OARs for VMAT than other techniques. The 3DCRT yielded largest maximum doses in the esophagus (40 Gy), and brain (56 Gy) as compared to IMRT and VMAT techniques. It is also revealed that VMAT delivered the lowest maximum doses to the esophagus (23 Gy), and brain (40 Gy) as shown in Table 1.

Hall and Wuu highlighted that the risk increased with a linear proportionality to dose between low doses and moderate doses (from 0.1 to 3 Gy).[1,6] Little differentiated between A-bomb survivors and patients treated by radiotherapy to the role of cell killing at doses higher than 2 Gy, but the investigation of Rubino *et al*. did not offer verification for a role of cell killing. Some other studies advised a threshold of about 0.6 Gy in adults after fractionated radiotherapy and after acute irradiation in children at 0.1 Gy.[23] We consequently choose volumes receiving >20 and 38 Gy for comparison in our analysis to find the best technique for reducing secondary cancer risk among 3DCRT, IMRT, and VMAT for OARs because from 1 to 19 Gy, all techniques remained almost the same. For VMAT, it can be seen in Table 2 that only 3.6% of the volume of esophagus received dose > 20 Gy. This is smaller than IMRT and 3DCRT having 23.6% and 100% of the volumes of esophagus receiving doses > 20 Gy, respectively. There were only very small volumes of esophagus receiving higher doses > 38 Gy from VMAT (0.1%) and IMRT (1.7%) as shown in Table 2.

Normal tissue complication probability and equivalent uniform dose of the organs at risks

In Table 4, it can be seen that the NTCP of the esophagus and brain are ranged from 0.4% to 4.2% for the 3DCRT, IMRT, and VMAT technique. These small NTCP values of OARs showed that the critical organ sparing in these three radiation dose delivery techniques are better. However, the NTCP of the esophagus and brain for the IMRT and VMAT are about 3–10 times smaller than those for the 3DCRT, revealing that the intensity modulated techniques can provide better critical organ sparing than the traditional conformal method. Comparing the IMRT and VMAT plans, it is seen that the NTCP for the esophagus and brain in the VMAT plans (0.4% and 0.8%) are slightly smaller than the IMRT (0.7% and 0.9%). This shows that the VMAT technique is slightly better than IMRT in the critical organ sparing for the H and N plans. In addition, the

NTCP results were agreed well with the EUD, in which the EUD of the OARs for the 3DCRT are higher than those of the IMRT and VMAT, and the EUD of the esophagus and brain are found smallest (1.8 and 2.3 Gy) when using the VMAT technique.

Secondary cancer risk estimation

The majority of dosimetry studies have previously focused on dose in regions far away from the target volume because the dose close to the target appears to be essential when treating primary cancer. On the other hand, most cancer incidence data are based on second cancers found close to the target volume due to the obvious reason that there is a greater chance for a second cancer to occur in these regions that receive relatively higher dose levels. Hall showed that the risk of cancer increases with a linear proportionality to dose between low doses and moderate doses (from 0.1 to 3 Gy).[24]

The maximum doses to OARs in this study were lower after VMAT than 3DCRT. The additional uncertainty of the risk estimation was based on the different dose rate and time schedule, which is fractionated application over 6 weeks versus single dose. However, in this study, the estimated risk for secondary cancer in the respective OARs was considerably lower after VMAT and IMRT as compared to 3DCRT as shown in Table 3. The probability per Sv was taken from the NCRP Report #116.

We have calculated the secondary risk cancer from mean doses of OARs in all techniques. The calculated doses to the OARs in this study were considerably lower with VMAT than with 3DCRT and IMRT. Therefore, the estimated risk for secondary cancer should be considerably lower with VMAT for H and N radiotherapy.

Conclusions

This is to the best of our knowledge the first report about the estimation of H and N second cancer risk using VMAT. In comparison with IMRT and 3DCRT, the calculated mean and maximum doses for OARs were lower for VMAT, as were the volume of OARs treated at high doses (>20 Gy). These doses to OARs were verified using film and TLD dosimetric systems. NTCP and EUD values of the OARs were found the smallest in VMAT, although both VMAT and IMRT technique have higher critical organ sparing than the 3DCRT. This would suggest that the risk of secondary cancer induction after VMAT is lower than after IMRT or 3DCRT in H and N cancer.

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Conflicts of interest

There are no conflicts of interest.

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