

## RESEARCH ARTICLE

# Radiation-Induced Second Cancer Risk from External Beam Photon Radiotherapy for Head and Neck Cancer: Impact on in-Field and Out-of-Field Organs

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### Abstract

The purpose of this paper is to provide data on development of second primary cancers within or adjacent to tissue irradiated in the treatment of primary head and neck cancers using different techniques and modalities. **Materials and methods:** We selected five patients with HandN tumors located in base of the tongue for risk assessment. In order to examine the impact of choices of various planning techniques, numbers of beams and beam energy used in treatment plans - 7 and 9 field Intensity modulated radiotherapy (IMRT) plans using 6MV and 10 MV beam energies and a 6MV Volumetric modulated arc therapy (VMAT) plans were planned. Out-of-field measurements for secondary photon doses for the treatment plans were measured using diode-dosimeters and solid water slabs. Differential dose-volume histograms (DVH) for all 5 patients and 5 techniques, were exported and used to calculate organ equivalent dose (OAR), excess absolute risk (EAR), and life-time attributable risk (LAR) for in-field organs. **Results:** For all treatment plans, the DVH showed clinically acceptable values; adequate clinical target coverage and dose constraints were met for all organs at risk. There was a clear advantage for the VMAT plan; it provided superior organ at risk (OAR) sparing and adequate target coverage. VMAT has relatively low monitor units at  $0.93 \pm 0.034$  times 7F6. The average percentage scattered to prescription doses for the five patients at 15, 30, 45, 60 and 75 cm from the isocenter were  $0.9212 \pm 0.115$ ,  $0.2621 \pm 0.080$ ,  $0.1617 \pm 0.057$ ,  $0.0936 \pm 0.026$ ,  $0.0296 \pm 0.014$ , for VMAT. **Conclusion:** Organ-specific LAR was higher with VMAT compared to 7F6 for skin. 6-MV VMAT is an acceptable alternative to IMRT for HandN cancer and offers advantages in terms of sparing adjacent OAR.

**Keywords:** VMAT- LAR- EAR- SCR- H and N

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### Introduction

Patients undergoing radiation therapy have an increased risk of second malignancies as a result of radiation within the treatment field and the scatter away from the treatment field. The absolute risk of second malignancies caused by stray treatment radiation was found to be 1.4% for the patient surviving longer than 10 years beyond treatment (Kry et al., 2005). Cancer of the head and neck region remains an important cause of morbidity and mortality worldwide (Parkin et al., 2005). Surgery is the preferred treatment for many patients with early cancers, but primary radiation therapy (RT) is the treatment of choice for most patients with locally advanced cancers. The head and neck (HandN) is a complex region composed of dissimilar anatomical structures, each responding differently to irradiation: mucosal linings, skin coverings, subcutaneous connective tissue, salivary glandular tissue, teeth, cartilage, and bone. The use of

advanced radiotherapy planning and delivery techniques for HandN tumor helps in achieving dose escalation and better sparing of critical structures close to the target. The increased complexity of treatment techniques makes it vital to consider factors such as second cancer risk (SCR) while comparing and analyzing different planning methodologies.

With the average age of the radiation therapy (RT) patients decreasing and the advent of more complex treatment options comes the concern about the increased incidence of radiation-induced cancer. To date, there have been many data published on second cancer risk (SCR). Hall (2003) showcased the increased risk moving from 3-dimensional conformal radiotherapy (3DCRT) to intensity modulated radiotherapy (IMRT) and reported IMRT almost doubled the second cancer risk compared to 3DCRT. Chaturvedi (2007) showed that after RT, long-term survivors of cervical cancer presented with increased cancer risk. Kry (2005) reported a twofold to

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threefold increase in fatal secondary malignancy with IMRT based exclusively on photon scatter and neutron dose.

The purpose of this paper is to provide data on the development of second primary cancers within and adjacent to the volume of tissue irradiated in the treatment of primary head and neck cancer using different treatment techniques and modalities. In this study, we estimated and compared the second cancer risk of in-field and out of field organs for two treatment modalities - IMRT and VMAT. Overall, this paper emphasizes the importance of second cancer risk estimation and making careful treatment planning choices and decisions.

## Materials and Methods

### *Patient data and treatment planning*

We selected five patients with H and N tumor located at the base of the tongue (BOT) for risk assessment. The patient's age ranged from 42 to 58 years old with an average age of 51. All patients were stage II BOT cases. All these patients had undergone computed tomographic image scans (CT) using a Somatom CT scanner (Siemens medical solutions, USA) of the head for identification of the target and normal critical structures. Targets were defined in accordance with the report of the international commission on Radiation Units and Measurement (ICRU50). The gross tumor volume (GTV), clinical target volume (CTV), and organs-at-risk (OARs) were contoured on the planning CT scan. Planning target volume (PTV) were delineated with circumferential 5-mm margins to the CTV, in order to account for setup uncertainty. Critical structures included mandible, parotid glands, esophagus, cord, brain, lungs, and skin, with the remaining soft tissue delineated for risk analysis. Table 1 lists the patient characteristics, patient age, and size of the target volume.

Infinity linear accelerator with agility MLC (Elekta, Stockholm, Sweden) and Monte-Carlo based planning system Monaco v5.11 (Elekta, Stockholm, Sweden) was used for IMRT and VMAT planning. In order to examine the impact of making a choice between various planning techniques, number of beams and beam energy used in treatment plans - 7 and 9 fields IMRT plans using 6MV and 10 MV beam energies (7F6, 9F6, 7F10, 9F10) and a 6MV VMAT plans were created for each patient. Both IMRT and VMAT plans used dynamic MLC, prescribed to 58.1 Gy to elective nodes, 63 Gy to involved site and 70 Gy to primary volume in 35 fractions. All plans were prescribed to primary PTV volume so that  $\geq 95\%$  of the PTV received  $\geq 95\%$  of the prescription dose. For IMRT and VMAT plans, the dose was accurately calculated using Monte Carlo simulations. Due to the relatively low photon energy used for planning (6, 10MV); secondary neutron dose was irrelevant and was not considered in this study. All plans were created by a physicist and approved by a radiation oncologist and satisfied all clinical protocols and constraints. Differential dose-volume histograms (DVHs) for all 5 patients and 5 techniques, using 0.01 Gy bin widths for all OAR's, were exported and used to calculate organ equivalent dose (OED), excess absolute risk (EAR), and Life time attributable risk (LAR). Additionally, Bone

and soft tissue sarcoma and carcinoma risks within the scanned volume were also evaluated.

### *Scattered dose measurement*

Out-of-field measurements for secondary photon doses for the treatment plans were measured using diode-dosimeters (Sun nuclear - Standard (rf-IVD 2/IVD 2): 8/4) and solid water slabs. Diode-dosimeters have 27 nC / Gy sensitivity and had an active dimension of 1.4mm. The secondary doses were measured at different distances from isocenter (15, 30, 45, 60 and 75 cm). Doses at specific distances from the Isocenter at different lateral planes were taken to represent doses received by organs located at approximately those positions. Average diode readings obtained were corrected for temperature, pressure, and angle of incidence. This study methodology was proposed by Dong (2013), it allowed the derivation of representative doses per MU for each treatment plan which was then used to calculate an estimate of the total contribution from secondary scattered dose to various organs (esophagus, lung, stomach, bowel, and bladder) for all patient plans. The mean diode reading for each distance was converted to dose using a single nC-to-Gy calibration factor. The dose to each organ was determined by either diode measurement, DVH data, or from a combination of the both TLD measured and DVH calculated data.

### *Risk Modeling - out of field organs*

Various risk models have been developed to predict second cancer incidence (Schneider 2008). When the doses are less than 2Gy, the dose-response relationship is a linear function of risk; therefore cancer incidence is directly proportional to the mean dose of the organ. However, when the dose was greater than 2 Gy and distribution is heterogeneous, the relationship is no longer linear. The relationship curve will vary linear exponentially because of the sterilization of mutated cells. In this study, plateau dose response model is used to model SCR for out of field organs. The plateau dose relationship accounts for repopulation process due to fractionation. In OED calculations of the out-of-field organs, we used measured values directly, or the mean value at that distance, because it was measured during treatment.

$$OED = \frac{1}{V} \sum_i V_i \left[ \frac{1 - \exp(-\delta D_i)}{\delta} \right] \quad (1)$$

Where, V is the total volume,  $V_i$  is the volume element and  $D_i$  is the dose element.  $\alpha$  and  $\delta$  are used to determine the organ-specific dose response curve. Parameters  $\alpha$  and  $\delta$  are estimated from the combined fit of atom bomb data and Hodgkins data.  $\delta$  value of 0.139 Gy<sup>-1</sup> was used for calculation. The effective OED was calculated by summing up the OED in the various organs of interest multiplied by their corresponding weighting factors.

### *Risk Modeling - In field organs*

To calculate the risk of second malignancies, all corresponding DVHs using 0.01 Gy bin widths were extracted from Monaco planning system and exported to the software developed for risk modeling. This formulation used in this study has been previously

used in several studies to estimate the in-field organ dose. According to this concept, dose distributions that caused the same radiation-induced cancer incidence had the same OED. It also accounts for the effects of cell sterilization and repopulation at higher dose levels. The OED for carcinoma and sarcoma induction was used to approximate the risk for a radiation-induced second cancer is written as follows (Schneider et al., 2008; Schneider et al., 2011).

$$\text{OED}_{\text{carcinoma}} = \frac{1}{N} \sum_i \exp(-\alpha' i D_i) \frac{\exp(-\alpha' D_i)}{-\alpha' R} (1 - 2R + R^2 \exp(-\alpha' D_i) - [1 - R]^2 \exp[-\frac{\alpha' R}{1-R} D_i]) \quad (2)$$

$$\text{OED}_{\text{sarcoma}} = \frac{1}{N} \sum_i \exp(-\alpha' i D_i) \frac{\exp(-\alpha' D_i)}{-\alpha' R} (1 - 2R + R^2 \exp(-\alpha' D_i) - [1 - R]^2 \exp[-\frac{\alpha' R}{1-R} D_i] - \alpha' R D_i) \quad (3)$$

$$\alpha'_i = \alpha + \beta D_i \cdot \frac{d_F}{D} \quad (4)$$

Where R is the repopulation parameter,  $d_F$  is dose per fraction, D the total dose,  $\alpha'$  is the cell kill parameter,  $\alpha$  and  $\beta$  varies for each organ and are derived from data based on Atomic bomb survivors.

For each organ of interest, the OED derived from DVH of all 5 study patients were used to find the mean OED. The mean OED values were then combined with organ - dependent parameters to estimate the EAR. Equation 5 was used for EAR assessment.

$$\text{EAR}(D, e, a, s) = \rho(D) \cdot \beta \cdot \exp(\gamma_e [e^{-30}] + \gamma_a \ln[\frac{a}{70}]) \cdot (1 \pm s) \quad (5)$$

Where, the excess absolute risk (EAR) is factorized into a function of dose  $\rho(D)$ ,  $\gamma_e$ ,  $\gamma_a$  are model parameters and the attained age (a) at exposure (e).  $\beta$  is the slope of the dose-response curve in low dose region, s is used to include gender specificity and is set to - 0.17 (male). The model parameters used in the calculation model is listed in Table 2.

The lifetime attributable risk (LAR), gave the percentage likelihood in excess of the baseline risk of second malignancy happening during one's lifetime and, was calculated using EAR (per 10 000 PY) as a function of point dose (Louise et al., 2015). It could be considered an effective means of calculating the risk because it takes the patient age at the time of treatment and predicted lifespan into account.

$$\text{LAR}(D, e, a) = \int_{e+L}^a \text{EAR}(D, e, a, s) \cdot [\frac{S(a)}{S(e)}] \cdot (da) \quad (6)$$

The integration was performed over an attained age from a latent period of solid cancer induction after the exposure (L = 5 years) to 70 years of age. The ratio  $S(a)/S(e)$  defines the probability of surviving from age at exposure to the attained age, which was obtained from life table for the US population.

## Results

### Treatment plans

For all treatment plans, the DVH showed clinically acceptable values; it met adequate clinical target coverage and dose constraints for all organs at risk. There was a clear advantage for the VMAT plan; it provided superior

OAR sparing and adequate target coverage. The monitor units increased with increasing number of fields (or Arcs) and PTV size, which was in agreement with the study reported by Dong (2013). VMAT has relatively fewer monitor units (MU) as  $0.93 \pm 0.034$  times of 7F6.

### Risk from scattered beam – Out of field organs

The secondary scattered dose decreased as the distance from the in-field region increased. VMAT has a relatively low secondary dose around the target area. The average percentage scattered dose to prescription dose for five patients at 15, 30, 45, 60 and 75 cm from the Isocenter is  $0.9571 \pm 0.099$ ,  $0.2873 \pm 0.079$ ,  $0.1870 \pm 0.042$ ,  $0.1015 \pm 0.020$ ,  $0.0319 \pm 0.012$  for 7F6, 0.9848  $\pm$  0.092, 0.3051  $\pm$  0.078, 0.1926  $\pm$  0.049, 0.1095  $\pm$  0.028, 0.0344  $\pm$  0.025, for 9F10 and 0.9212  $\pm$  0.115, 0.2621  $\pm$  0.080, 0.1617  $\pm$  0.057, 0.0936  $\pm$  0.026, 0.0296  $\pm$  0.014, for VMAT respectively. The measured dose values were used to calculate OED using plateau dose response model. The ratios of OED, which depicts the relative risk of esophagus, lungs, stomach, bowel, and bladder cancer for each plan with respect to 7F6 is shown in Figure 3.

### Risk from primary beam - in-field organs

The relative OED with respect to 6MV 7 field IMRT plan (7F6) for all OARs based on DVH study were shown (Figure 2). The VMAT plan had the most conformal dose distribution out of all plans studied, thus resulted in significant risk reduction in organs such as brain and brain stem. VMAT plan resulted in higher risks of second cancer for soft tissue, skin, and mandible and was within 12.7%,

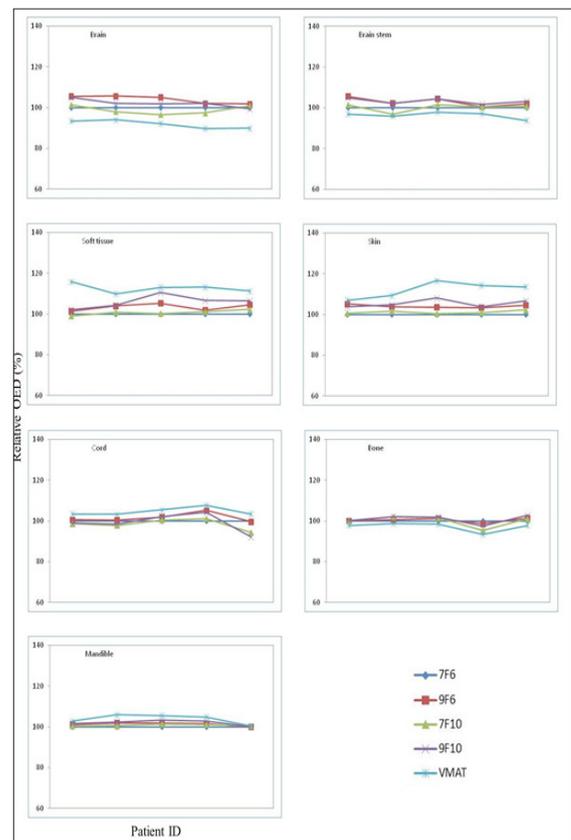


Figure 1. Relative Percentage OED of Organs for Different Plans Calculated from Differential DVH Data

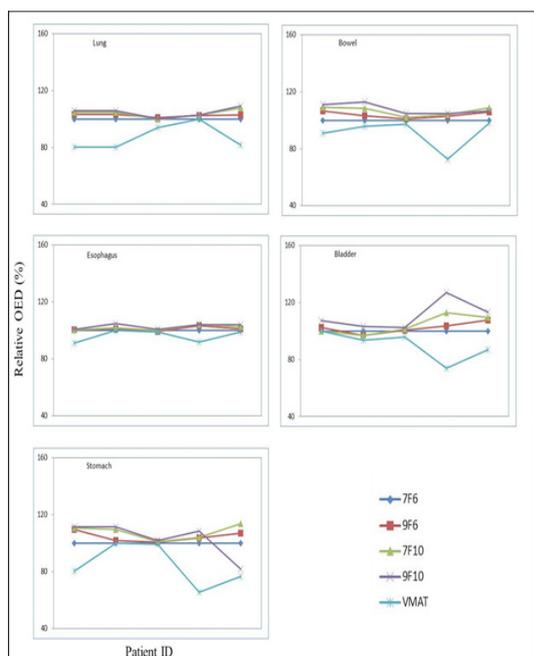


Figure 2. Relative Percentage OED of Organs for Different Plans, at Different Distance from Isocenter

Table 1. Patient Information

ID	Sex	Age	Stage	Volume (cm <sup>3</sup> )		
				PTV 70	PTV 63	PTV 58.1
HN1	M	42	II	325	478	755
HN2	M	47	II	251	356	652
HN3	M	52	II	357	520	855
HN4	M	56	II	208	323	608
HN5	M	58	II	268	378	678

12.2%, and 3.8% of that of 7F6 respectively.

The EAR (combining all organs EAR) estimated with the mechanistic model for all the organs studied, ranged from 4.9 – 6.5 per 10,000 persons per year (PY) for 7F6 and 9F10 respectively (Figure 3). Number of fields (7 fields and 9 fields) used in planning did not create significant impact on EAR, the absolute difference between 7F6 and 9F6 were low ranging from 0.2 - 0.4 per 10,000 PY, whereas energy difference (6MV and 10 MV)

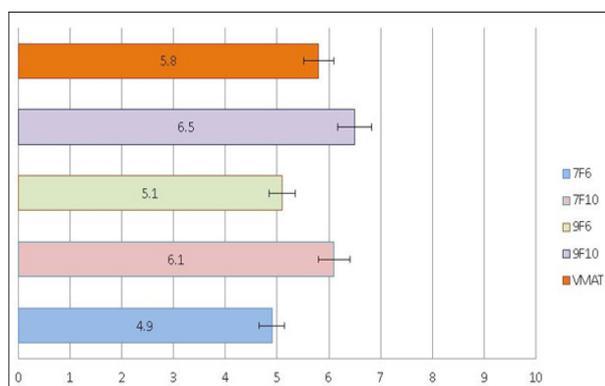


Figure 3. EAR Based on All Organs Studied (per 10,000 person-Year)

had a significant impact on EAR with absolute difference between 7F6, 7F10, and 9F6, 9F10 were ranging from 1.0 – 1.5 per 10,000 PY and 1.2 – 1.7 per 10,000 PY respectively.

The absolute risks (LAR based on EAR) for all considered cases are given in table 3-4. Table 3 provides LAR normalized per MU (%/MU) for organ at risk for five different treatment plan considered. The LAR data showed a strong dependence on age at exposure. The LAR decreased as a function of age at exposure. Figure 4 provides the percentage risk (LAR %) of cancer incidence for all organs studied. As seen in the figure, for most organs 9F10 plan resulted in the largest risk, However, for some organs like skin and soft tissue, the VMAT plan

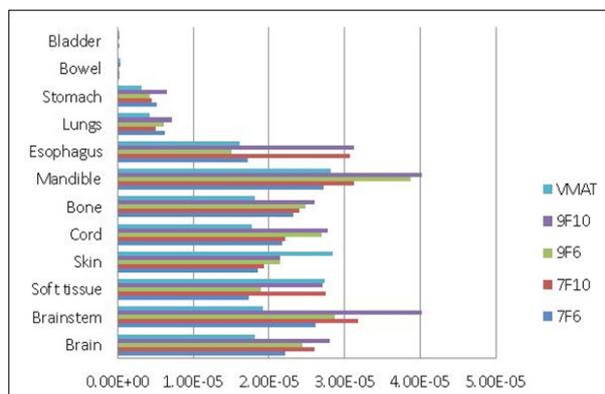


Figure 4. Estimates of LARs of Cancer Incidence (%)

Table 2. OED and EAR Calculation Parameters (Schneider et al., 2011) and Source of Dosimetric Data

Organ	$\alpha$	$\beta$	R	$\alpha/\beta$	$\gamma_c$	$\gamma_a$	Source of dose	Position from Isocenter
Sarcoma (Soft tissue)	0.067	0.2	0.5	3	-0.013	-0.56	DVH	-
Sarcoma (Bone)	0.06	0.6	0.5	3	-0.013	-0.56	DVH	-
Brain	0.018	0.7	0.93	3	-0.024	2.38	DVH	-
Soft tissue	0.044	8.2	0.15	3	-0.037	1.7	DVH / Diode	-
Bone	0.067	0.2	0.5	3	-0.013	-0.56	DVH	-
Cord	0.018	0.7	0.93	3	-0.024	2.38	DVH	-
Esophagus	0.06	-	0.5	3	-0.002	1.9	DVH / Diode	15
Lung	0.06	-	0.83	3	0.002	4.23	DVH / Diode	30
Stomach	0.46	5.2	0.46	3	-0.002	1.9	Diode	45
Bowel	0.001	10	0.09	3	-0.056	6.9	Diode	60
Bladder	0.033	0.73	0.56	3	-0.056	6.9	Diode	75

Table 3. Average LAR as a Function of Organ and Age at Exposure (Yr) for the Five Patients Considered

	Organ	7F6	7F10	9F6	9F10	VMAT
LAR (% / MU)	Brain	2.21E-05	2.61E-05	2.45E-05	2.81E-05	1.81E-05
	Brainstem	2.62E-05	3.18E-05	2.87E-05	4.02E-05	1.92E-05
	Soft tissue	1.74E-05	2.75E-05	1.90E-05	2.71E-05	2.74E-05
	Skin	1.85E-05	1.94E-05	2.15E-05	2.15E-05	2.85E-05
	Cord	2.18E-05	2.21E-05	2.70E-05	2.78E-05	1.78E-05
	Bone	2.32E-05	2.41E-05	2.49E-05	2.60E-05	1.82E-05
	Mandible	2.72E-05	3.12E-05	3.87E-05	4.02E-05	2.82E-05
	Esophagus	1.72E-05	3.07E-05	1.51E-05	3.12E-05	1.62E-05
	Lungs	6.20E-06	5.10E-06	6.11E-06	7.20E-06	4.20E-06
	Stomach	5.21E-06	4.51E-06	4.21E-06	6.51E-06	3.21E-06
	Bowel	2.02E-07	1.72E-07	2.77E-07	3.92E-07	3.02E-07
	Bladder	1.02E-07	2.14E-07	1.11E-07	2.17E-07	2.06E-07

Table 4. Absolute LAR (%) of Sarcoma and Carcinoma for the Five Patients Considered

	Organ	7F6	7F10	9F6	9F10	VMAT
HN1	Bone sarcoma	0.02	0.06	0.16	0.26	0.36
	Soft tissue sarcoma	0.42	0.74	0.72	0.81	1.23
	Soft tissue carcinoma	1.06	1.92	1.45	2.08	4.08
HN2	Bone sarcoma	0.04	0.05	0.12	0.2	0.45
	Soft tissue sarcoma	0.38	0.71	0.74	0.95	1.41
	Soft tissue carcinoma	1.23	2.02	2.34	2.98	4.56
HN3	Bone sarcoma	0.05	0.05	0.08	0.11	0.55
	Soft tissue sarcoma	0.53	0.69	0.95	1.16	1.62
	Soft tissue carcinoma	1.54	2.42	2.65	3.45	4.85
HN4	Bone sarcoma	0.01	0.06	0.26	0.39	0.23
	Soft tissue sarcoma	0.21	0.41	0.56	0.88	1.02
	Soft tissue carcinoma	0.81	2.15	2.89	3.51	3.45
HN5	Bone sarcoma	0.02	0.08	0.09	0.2	0.31
	Soft tissue sarcoma	0.24	1.23	1.45	1.51	1.54
	Soft tissue carcinoma	1.04	1.89	2.71	3.78	3.98

had the highest associated risk. The absolute attributable risk for bone sarcoma was lower with the 7F6 plan and was significantly higher with VMAT plan.

## Discussion

The aim of our study was to evaluate radiation-induced second cancer risk following clinically relevant linear accelerator based external radiotherapy techniques. The criteria for selecting the best possible treatment plan for HandN cancer included several factors, like the choice of beam energy, the number of treatment fields, and the choice between treatment planning and delivery

techniques like IMRT or VMAT. The study results presented are entirely based on detailed Monte Carlo simulations and dosimetrically measured data. Many epidemiological studies reported second primary cancer risks following radiotherapy. Brenner (2000) showed that the likelihood of developing second cancer depended on both the entire irradiated volume and on the volume of the high-dose region. Ruben (2008) reported carcinogenesis in both nearby and distant tissues. Our study examined the second cancer risk to both organs inside and outside the primary beam from different clinically relevant radiation treatments for HandN cancer.

The dose homogeneity within the PTV was slightly improved by the VMAT technique when compared with all IMRT plans, although the difference was not statistically significant between 9 field IMRT plan (9F10) and VMAT. The volume of 10Gy volume (V10Gy) and 5Gy volume (V5Gy) were statistically significant lower for 7F6 ( $24.1 \pm 6.1\%$ ,  $34.2 \pm 3.4\%$ ) than 9F10 ( $30.2 \pm 5.9\%$ ,  $41.8 \pm 4.1\%$ ) and VMAT ( $31.2 \pm 6.8\%$ ,  $43.1 \pm 5.7\%$ ) respectively. V10Gy and V5Gy for VMAT were higher than IMRT. With advanced radiotherapy techniques like IMRT and VMAT, patients are exposed to small volumes of high dose due to conformal dose distribution, and large volumes of normal tissue are exposed to a lower dose due to leakage and scatter radiation from treatment head. Many published dosimetric studies report that the VMAT treatment plans generally use fewer MUs compared to stationary fields IMRT plans (Brenner et al., 2000; Yoo et al., 2010). This substantial reduction in the number of MU helped in minimizing the whole body integral dose, with consequently less risk of radiation-induced carcinogenesis and thus second cancers. Our study results are in contrast to the relationship between the number of MU and whole body integral dose. VMAT compared to other IMRT techniques had relatively low monitor units, but delivered an overall higher integral dose. Yoo (2010) reported similar higher levels of whole body integral dose with VMAT compared with IMRT.

In the last decade, IMRT and VMAT have been increasingly utilized to treat HandN cancer to permit more conformal dose distribution and dose escalation. Various studies reported the impact of these novel

treatment techniques on increased second cancer risk. Kim (2011) presented the secondary radiation doses of intensity-modulated radiotherapy and proton therapy in patients with lung and liver cancer and Vanhavere (2004) measured the secondary scattered dose of IMRT at 20–50 cm from isocenter, ranging from 5.8 and 1.0 mGy per Gy, though the secondary risk from their measurement was not presented. However, in this study, we measured the scattered dose from 15–75cm and used plateau dose-response model to convert measured dose values to OED, to predict SCR.

Figure 3 show the secondary scattered dose measurement of five patients for IMRT (7F6, 7F10, 9F6, 9F10) and VMAT. The secondary scattered dose decreased as the distance from the in-field region was increased as reported by Dong (2013). VMAT plan had a relatively lower scattered dose especially away from the target area and we found that the declining slope of the secondary scattered dose for 9F6 and 9F10 was similar and steeper than VMAT. VMAT had a relatively low OED for most of the out of field organs compared to the other modalities and this OED difference from modality decreases when the position of the organ gets further away from the field edge.

Comparing the different plans analyzed in this study, organ-specific LAR was significantly lower using VMAT than 9F10. This was in agreement to the study done by Rehman (2015), who reported on lower doses to OAR close to the PTV using 6 MV VMAT. This could be explained by the fact, that the VMAT plan used 6MV and the irradiated volumes for HandN cancer had the advantage of a highly conformal treatment technique for the PTV, whereas 9F10 added a larger low dose bath to organs away from the target volume when with compared to VMAT. It should be noted that 9F10 plan used 10 MV and as a consequence had increased transmission and leakage through treatment unit head, contributing to increasing in SCR.

The risk of second cancer incidence for 9F10 and VMAT were analogous. 9 field IMRT plans covered large sections of the tissue as like VMAT plan. Increasing the number of fields from 7 to 9 did not have a dramatic effect in terms of increased second cancer risk (SCR). However, changing beam energy from 6MV to 10MV had a significant impact on SCR. In this work, EAR was used to quantify radiation-induced cancer.

HN1, aged 42, demonstrated the largest relative LAR, especially for bone sarcoma compared to all other patients, which showed there was a solid relationship between patient risk and age at the time of radiotherapy (Louise et al., 2015). The mechanistic risk model used in this study allowed for direct translation of patient dosimetric data into lifetime second cancer risk. The absolute risks (LAR), for all patients considered, are given in table 3 - 4. The highest risk was found for HN3 based on soft tissue carcinoma model was 4.85% for VMAT and the IMRT plan values for the same are 1.54% for 7F6, 2.42% for 7F10, 2.65% for 9F6 and 3.45% for 9F10. The absolute risk parameters are always associated with uncertainties, and these are often associated with the lack of sufficient data to base the model parameters (Schneider 2011). In this study, it was eliminated to an extent with the usage

of mechanistic modeling for risk calculation which incorporates the impact of cell repopulation kinetics.

In conclusion, for clinically comparable treatment plans, the risk of second malignancy should be an important selection criteria for treatment plans. The current study provides the model and organ-dependent excess radiation induced risk for both in-field and out of field organs attributable to HandN cancer. We compared secondary scattered doses and OED which is related to radiation-induced SCR. We established that the secondary dose depended on the distance from the Isocenter. The secondary dose and OED from VMAT were less than the secondary dose from conventional IMRT. The secondary dose and OED became similar between IMRT and VMAT as the distance from the field edge increased. VMAT resulted in reduced relative second cancer risk in all organs except skin and soft tissue close to PTV. In-depth Monte Carlo simulations showed 6MV, seven fields IMRT plan (7F6) had the lowest associated risk, followed by 9F6 and VMAT plan.

The LAR of radiation-induced SCR was significantly lower when using VMAT than when using 9F10. The difference was apparent in the organs such as the brain, brainstem, and mandible. Organ-specific LAR was higher with VMAT compared to 7F6 for skin and as expected, the increase in beam number with IMRT increases skin exposure and hence skin-specific SCR risk. The absolute attributable risk for bone sarcoma was significantly higher with VMAT plan. There was a solid relationship between patient risk and age at the time of radiotherapy.

In terms of overall SCR, 6-MV VMAT is an acceptable alternative to IMRT for HandN cancer and offers advantages in terms of sparing adjacent OAR. The relatively low levels of absolute lifetime risks support the use of VMAT with 6MV photons as a viable treatment modality for advanced HandN cancer. However, improvements in estimation and long-term validation of risk models are required before affirming these outcomes. We strongly recommend using the difference between cumulative LAR, when we need to select between VMAT and IMRT plans. Despite the importance of radiation-induced second cancer which is a late effect, the primary goal of cancer control should never be compromised.

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