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Author for correspondence:
Salahuddin Ahmad, Department of Radiation Oncology, University of Oklahoma Health Sciences Center, and Stephenson Cancer Center, 800 NE 10th Street, SCC L100, Oklahoma City, OK 73104, USA.
E-mail: Salahuddin-ahmad@ouhsc.edu

Comparison of intensity-modulated proton therapy (IMPT) versus intensity-modulated radiation therapy (IMRT) for the treatment of head and neck cancer based on radiobiological modelling

My-Lien Nguyen[1], Kazi T. Afrin[2], Patrick Newbury[2], Christina Henson[2] and Salahuddin Ahmad[2]

[1]Department of Radiation Oncology, GenesisCare, 3175 Harbor Boulevard, Port Charlotte, FL 33952, USA and [2]Department of Radiation Oncology, University of Oklahoma Health Sciences Center, 800 NE 10th Street, SCC L100, Oklahoma City, OK 73104, USA

Abstract

Aim: The aim of our study is to retrospectively report the radiobiological aspects for intensity-modulated proton therapy (IMPT) against intensity-modulated radiation therapy (IMRT) for patients with head and neck cancer treated at our institution. A secondary goal is to reinforce current model-based approaches to head and neck cancer patient selection for IMPT.
Materials and Methods: Eighteen patients were evaluated with prescription doses ranging from 50 to 70 Gy delivered in 2 Gy per fraction. The dose volume histograms (DVH) were used to calculate equivalent uniform dose (EUD), tumour control probability (TCP) and normal tissue complication probability (NTCP) for biophysical comparison using mechanistic mathematical dose response models. Absolute values of TCP and NTCP were then compared between IMPT and IMRT.
Results: The dose models demonstrate a minimal radiobiological advantage for IMPT compared to IMRT in treating head and neck cancers. Absolute values of TCP were slightly higher, while absolute values of NTCP were slightly lower for IMPT versus IMRT.
Conclusions: Further studies are needed to determine if the radiobiological advantage indeed translates to a therapeutic advantage for patients.

Introduction

Head and neck cancer affects over 60,000 people and makes up about 4% of all cancers diagnosed in the United States.[1] Depending on the primary site of disease of head and neck cancer, treatment can vary widely ranging from surgery with or without adjuvant treatment, chemo-radiotherapy or even radiation alone. Traditionally, radiation therapy for head and neck cancers is delivered using intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) with photons either used definitively or in the adjuvant setting. Due to the side-effect profile of this treatment, other options have been explored including intensity-modulated proton therapy (IMPT), a potentially advantageous technique to treat head and neck tumours while sparing dose to organs at risk (OAR). The utilisation of IMPT for head and neck tumours is relatively new but has shown promise dosimetrically.[2]

In our previous study, we compared the dosimetric characteristics of patients treated at our institution[2] and found that both IMPT and IMRT had sufficient dose coverage to the target volume. IMPT, however, had a dosimetric advantage in the majority of OARs though both IMPT and IMRT plans met OAR planning objectives. We hypothesised that IMPT offers a dosimetric advantage to IMRT especially in the treatment of unilateral disease. Without further matched case comparisons, we could not draw a conclusion regarding the potential clinical benefits of IMPT.

There have been few retrospective studies that have shown the benefits of IMPT regarding radiobiological modelling when compared to IMRT. Chang et al. retrospectively looked at 4 head and neck cancer patients in the context of adaptive proton therapy (APT) with calculations of the tumour control probability (TCP) and normal tissue complication probability (NTCP). They found that there were benefits in TCP and NTCP with online APT in comparison to offline APT; however, there were no direct comparisons of APT with IMRT or VMAT.[3]

On the contrary, other studies have attempted to model the benefits of IMPT regarding patient selection. For example, Langendijk et al. developed a model-based approach where the NTCP was calculated in the first phase and integrated with an in silico comparative study

to estimate a clinical benefit to aid in patient selection.[4] Tambas et al. further looked at the first evidence of model-based selection of head and neck cancer patients in the Netherlands. Results from Tambas et al. showed that most patients were selected based on NTCP data regarding dysphagia-related toxicities with reduction in NTCP and OAR doses with the use of IMPT versus VMAT in all patients regardless of selection. Though time consuming, the use of modelling is feasible and fair when viewed in terms of patient selection.[5]

In the present study, we aim to reinforce model-based approaches based on TCP and NTCP for patient selection in the treatment with IMPT for head and neck cancers based on retrospective data by computing a radiobiological model to compare IMPT versus IMRT in our previous patient cohort. We used literature derived formulas to calculate equivalent uniform dose (EUD), TCP and NTCP to help guide us in determining the advantages of IMPT.

Materials and Methods

Previously, we looked at 21 patients treated with pencil-beam scanning proton therapy at our institution from January 2019 to August 2020. Back-up IMRT plans were created for all 21 patients at the time of treatment planning. For IMRT, gross tumour volume (GTV) and clinical target volume (CTV) were contoured with expansion of CTV by 3 to 5 mm to create the planning target volume (PTV) to account for setup and motion uncertainties with dose prescribed to the PTV with at least 95% of the volume receiving 100% of the prescription dose. The CTV to PTV expansion for IMRT varied by provider and site treated. With this goal achieved, at least 99% of CTV was covered by 100% of the prescription dose. For IMPT, GTV and CTV were contoured, and CTVs were used for proton plans. To consider the setup uncertainties, robustness-based optimisation technique with uncertainty value of 5 mm in all directions and 3.5% range uncertainty were used to achieve 99% of CTV coverage by 100% of the prescription dose. This made the comparison between IMRT (PTV) and IMPT (CTV) valid and justified although there was provider variation of CTV to PTV expansion for IMRT which does not translate to the robustness-based uncertainty value of 5 mm used in IMPT planning. In addition, the proton prescription dose incorporated the relative biological effectiveness (RBE) of 1.1 which usually was termed as GyRBE.

For intents of radiobiological modelling, we excluded three patients given their treatment fractionation (>2 Gy/fraction). This left us with 18 patients to be evaluated. Prescription doses ranged from 50 to 70 Gy delivered in 25–35 fractions. Treatment planning was performed using the Varian Eclipse[6] treatment planning system and RaySearch RayStation[7] treatment planning system for IMRT and IMPT, respectively.

Equivalent uniform dose

In general, radiation doses delivered to target volumes are inhomogeneous which introduces issues when comparing dose distributions among treatment plans. The concept of EUD was presented to combat this issue. The EUD is defined as the homogenous absorbed dose which, when delivered, eliminates the same number of clonogenic cells as the actual inhomogeneous clinically absorbed dose delivered. EUD as defined by Niemierko[8] is as follows:

$$EUD = \frac{N_f}{D_{ref}} * \left(-\frac{\alpha}{\beta} + \sqrt{\left(\frac{\alpha}{\beta}\right)^2 + 4\frac{D_{ref}}{N_f}\left(\frac{\alpha}{\beta} + D_{ref}\right)\left(\frac{\ln(A)}{\ln(SF_2)}\right)} \right) \quad (1)$$

where the parameter A is defined as

$$A = \frac{\sum_{i=1}^{n} v_i * p_i * SF_2^{\left(\frac{D_i}{D_{ref}}\right)\frac{\left(\frac{\alpha}{\beta}+\frac{D_i}{N_f}\right)}{\left(\frac{\alpha}{\beta}+D_{ref}\right)}}}{\sum_{i=1}^{n} v_i * p_i} \quad (2)$$

where N_f is the number of fractions, D_{ref} is the reference dose of 2 Gy, α/β is the ratio of radiosensitivity parameters in the linear quadratic model of cell survival, SF_2 is the clonogenic cell survival fraction at a dose of 2 Gy which is assumed to be 0.5 in this study, D_i is the dose being received by each partial volume segment, v_i is the local volume of clonogens and p_i is the local density of clonogens. EUDs were calculated using Equation 1 for IMPT and IMRT plans. Using the linear quadratic model, the α/β ratio is defined as the dose at which linear and quadratic components of cell killing are equivalent. The α/β value for head and neck cancer was assumed to be 10.

Tumour control probability

The TCP is the probability of tumour eradication for a given total dose of radiation. The TCP can be calculated from data obtained from the dose volume histogram (DVH) for each treatment plan. TCP[9–11] is calculated using the following formula:

$$TCP = e^{-N * SF_2^{\left(\frac{D}{D_{ref}}\right)\frac{\left(\frac{\alpha}{\beta}+\frac{D}{N_f}\right)}{\left(\frac{\alpha}{\beta}+D_{ref}\right)}}} \quad (3)$$

where N is the number of clonogenic tumour cells that equals clonogenic cell density (CCD) times target volume, D is the EUD and the remaining terms have been defined as above. In this study, we have used three different values: 2000/cc, 20000/cc and 200000/cc for CCD. We calculated the TCPs for the three values of N and SF_2 of 0.5 using Equation 3.

Normal tissue complication probability

NTCP is based on tolerance dose data for an OAR using conventional fractionation (2 Gy/fraction at 5 fractions per week). It is a measure of the probability that a dose of radiation will have an undesirable effect on an OAR. NTCP is calculated using the following formula[12–15]:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{t^2}{2}} dt \quad (4)$$

where the variable t is defined as

$$t = \frac{D - TD_{50}(\vartheta)}{m * TD_{50}(\vartheta)} \quad \vartheta = \frac{v}{v_{ref}} \quad TD(\vartheta) = TD(1)\,\vartheta^{-n} \quad (5)$$

ϑ is the fraction of the organ irradiation, TD_{50} is the tolerance dose[16] which would lead to a 50% complication probability, v_{ref} is the reference volume for TD50, m is a parameter which determines the slope of the complication probability versus the dose curve and n is a parameter which characterises the volume

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Table 1. TD50, *m* and *n* values used to calculate NTCP for each critical structure

	Larynx	Parotid	Optic Structure	Brainstem	Oral Cavity	Cochlea
TD50 (Gy)	80	46	65	65	68	46.5
m	0.075	0.18	0.14	0.14	0.11	0.35
n	0.110	0.70	0.25	0.16	0.06	1.00

Table 2. Patient number (PN), prescription dose (PD), minimum dose (MID), mean dose (MND), maximum dose (MXD) and equivalent uniform dose (EUD) all in GyRBE for IMPT and Gy for IMRT, target volume (TV) in cc for the treatment of 18 head and neck patients

PN	PD	TV for IMPT	TV for IMRT	MID IMPT	MID IMRT	MND IMPT	MND IMRT	MXD IMPT	MXD IMRT	EUD IMPT	EUD IMRT
1	60	221.90	330.24	50.38	54.18	63.87	62.02	61.53	64.70	61.53	61.04
2	60	303.50	396.19	51.42	54.44	63.36	61.08	67.11	64.08	61.56	60.48
3	60	125.20	176.80	57.81	42.68	61.64	61.65	64.21	65.35	61.38	61.20
4	60	71.90	109.91	57.38	54.06	62.12	60.93	64.84	63.45	61.78	60.32
5	60	112.70	187.59	50.76	57.73	63.78	61.95	67.39	64.43	61.44	61.57
6	60	53.50	102.84	55.23	57.43	63.48	62.02	66.31	66.12	62.60	61.52
7	66	92.50	167.36	60.59	60.01	70.08	68.06	72.61	70.92	68.73	67.14
8	66	162.10	380.45	54.73	42.69	70.19	71.05	73.80	77.61	66.83	62.07
9	66	10.50	24.34	64.36	64.05	70.58	68.17	72.92	70.68	69.94	67.75
10	66	94.70	94.70	60.07	48.00	70.48	69.69	73.88	73.43	68.90	63.44
11	50	39.40	40.33	41.83	43.92	51.94	50.87	55.86	53.49	50.27	50.25
12	70	5.80	5.69	67.28	68.58	74.97	72.03	77.84	75.96	73.86	71.79
13	70	14.00	20.40	68.94	67.63	73.88	70.88	77.51	72.62	73.25	70.72
14	70	31.80	50.52	51.04	65.70	60.70	71.33	79.68	74.28	59.03	70.82
15	70	86.10	85.50	64.29	67.50	74.05	72.21	78.82	76.42	72.00	71.61
16	66	9.00	8.95	65.22	64.17	69.15	66.64	71.44	67.78	66.57	67.49
17	70	116.10	192.48	58.42	50.69	75.85	72.10	78.38	77.80	67.96	63.52
18	66	2.60	7.00	62.54	65.31	69.17	68.30	70.76	68.30	69.80	66.50
Average	57.91	57.15	67.18	66.10	71.10	69.30	65.41	66.40			

dependence of the complication probability. We compared the NTCP for IMPT and IMRT for the following OARs: larynx, contralateral parotid, optic structures, brainstem, oral cavity and cochlea using Equation 4. Typical values of parameters TD_{50}, *m*, *n* for different OARs used to calculate *t*-values are available in the literature.[15,17,18] The values used in the present study are given in Table 1.

Results

The patient number (PN), target volume (TV), prescription dose (PD) and comparisons of minimum dose (MID), mean dose (MND), maximum dose (MXD) and EUDs between IMPT and IMRT, for all patients are shown in Table 2. The average mean doses were 67.18 GyRBE and 66.10 Gy; average minimum doses were 57.91 GyRBE and 57.15 Gy and average maximum doses were 71.10 GyRBE and 69.30 Gy for IMPT and IMRT, respectively. In general, for most of the patients, the mean and maximum doses were higher for IMPT than IMRT. This could potentially suggest hotspots in the IMPT plan that are unintentional. However, despite the higher overall doses in IMPT, the average EUD dose was lower for IMPT (65.41 GyRBE) compared to IMRT (66.40 Gy). The average EUD for IMPT fell between average minimum and mean doses, whereas the average EUD for IMRT was higher than average mean dose.

The TCPs for both IMPT and IMRT treatment plans were calculated using equation 3 with SF_2 of 0.5, α/β of 10 and CCD of 2000/cc, 20000/cc and 200000/cc. The clonogenic cell counts were estimated by multiplying target volume with the CCDs. The ratio of average IMPT TCP against IMRT TCP was found to be slightly greater than 1 and increased with the increase in CCDs. The ratio varied from 1.0001 to 1.008. Table 3 shows this trend.

With the mechanistic formula shown in equations 4 and 5, NTCPs were calculated for larynx, contralateral parotid, optic structures, brainstem, oral cavity and cochlea. The average maximum dose for OARs from 18 patients is shown in Table 4. The ratio of the average maximum dose of OARs for IMRT against IMPT ranged from 1.014 to 1.039. This indicates that the maximum dose for OARs were higher in IMRT compared to IMPT by 1.4% to 3.9%. Thus, OARs were getting higher maximum dose in IMRT compared to IMPT.

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Table 3. The ratio of tumour control probability (TCP) for IMPT and IMRT (TCP(IMPT)/TCP(IMRT)) assuming clonogenic cell density (CCD) of 2000/cc, 20000/cc and 200000/cc, respectively. The mean ratios are 1.0001, 1.0010 and 1.0080, respectively

Patients	Ratio for CCD 2000/cc	Ratio for CCD 20000/cc	Ratio for CCD 200000/cc
1	1.0002	1.0018	1.0183
2	1.0003	1.0031	1.0312
3	1.0001	1.0007	1.0069
4	1.0001	1.0012	1.0115
5	1.0001	1.0007	1.0068
6	1.0000	1.0007	1.0069
7	1.0000	1.0002	0.9976
8	1.0004	1.0040	1.0064
9	1.0000	1.0000	1.0002
10	1.0000	1.0005	1.0055
11	1.0001	1.0007	1.0067
12	1.0000	1.0000	1.0000
13	1.0000	1.0000	1.0001
14	0.9999	0.9986	0.9862
15	1.0000	1.0000	1.0000
16	1.0000	1.0000	1.0000
17	1.0005	1.0046	1.0526
18	1.0000	1.0000	1.0001
Average	1.0001	1.0010	1.0080

Table 4. Average maximum doses and the ratios; *t*-values and NTCP ratios for OARs due to IMRT and IMPT techniques

	Max doses (Gy)		Ratios	*t* values		NTCP ratios
OAR	IMRT	IMPT	IMRT/IMPT	IMRT	IMPT	IMRT/IMPT
Larynx	60.63	59.81	1.014	−4.64	−7.89	>1000
Parotid	61.37	59.11	1.038	−4.37	−4.5	1.4
Cochlea	60.56	54.7	1.107	−2.06	−2.75	24
Brain Stem	62.07	59.81	1.038	−5.65	−6.63	27
Optic Structure	62.08	59.77	1.039	−6.32	−6.85	8
Oral Cavity	62.07	59.81	1.038	−4.64	−5.93	16.7

The *t*-values calculated using equation 5 for OARs were negative as shown in Table 4. Higher negative values were calculated for IMPT compared to IMRT for all OARS indicating lower NTCP values for IMPT. The absolute values of NTCPs for both techniques were very small but the ratios of NTCPs for IMRT against IMPT were clearly higher as shown in Table 4. For example, for the parotid, IMRT had an NTCP that was 1.4 times higher when compared to that of IMPT. Similarly for the brainstem, IMRT had a NTCP that was 27 times higher when compared to that of IMPT. Thus, the NTCP values for IMPT are much lower when compared to IMRT values for all OARS.

Discussion

In this manuscript, we have estimated EUD, TCP and NTCP values for IMPT and IMRT based treatment planning for head and neck cancer radiation therapy. Our analysis suggests that both treatment approaches are reasonable. Based on our results, IMPT improved absolute TCP when compared to IMRT. However, the difference in TCP in the two modalities is minimal which makes it difficult to draw conclusions regarding tumour control benefits of IMPT. IMPT based treatment plans also resulted in relatively lower NTCP values for all OARS indicating less normal tissue complications with IMPT. Even though the relative differences in NTCPs were large, the absolute values of the NTCPs were also so small that any rational statement based on this absolute value comparison is difficult to make.

Though the absolute differences in TCP and NTCP seen in our retrospective study between IMPT and IMRT is small, we reinforce the model-based approaches created by the Dutch to justify patient selection for IMPT in head and neck cancer patients. IMPT, overall, has a radiobiological benefit that with appropriate patient selection can be utilised to benefit head and neck cancer patients. Defining a threshold for when IMPT utilisation is justified (for example, a 10% NTCP reduction via the Langendijk et al model-based approach[4]) becomes a more difficult topic that needs further exploration via clinical prospective trials.

In our patient cohort, overall mean and maximum doses are higher for IMPT than IMRT. Though this is likely due to hotspots as mentioned earlier, a limitation of our study is that we do not use this to further explore the topic of dose escalation. In an in silico study, Jakobi et al. found that dose escalation via a simultaneous integrated boost (SIB) method increased TCP with both IMRT and IMPT plans with only a small increase in NTCP for aspiration.[19] It would be of further benefit to explore this topic prospectively to see if dose escalation is warranted and safe in the head and neck patient population.

We based our calculations of EUD, TCP and NTCP on mechanistic modelling derived from literature. Though we believe that this is an appropriate representation for head and neck cancers, this is but an estimate of actual tumour killing and normal tissue complications.

This study along with our previous one does not take into account clinical data comparing matched patients receiving IMPT versus IMRT. In the future, we plan to further explore this topic with matched clinical controls to determine the possible therapeutic advantages of IMPT when compared to IMRT. This would also help in determining a TCP or NTCP threshold that would clinically correlate with the benefits of IMPT. We also await the results from randomised trials such as NCT01893307, which compares IMRT to IMPT for the treatment of stage III-IVB oropharyngeal cancer. We hope that one day there will be a similar trial conducted in patients who are receiving unilateral radiation to the head and neck region.

Conclusions

Our study demonstrates that there is a theoretical biological advantage of IMPT in treating head and neck cancers, which reinforces the use of model-based approaches in patient selection for IMPT. Utilisation of proton therapy, especially IMPT, will certainly be

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one of the most popular techniques of treatment for head and neck cancer as proton therapy grows in the field of radiation therapy. IMPT is preferable in treating select patients in which dose delivered to surrounding critical structures is of concern and can be minimised with the use of IMPT. Further studies will need to be performed with matched clinical controls to determine if the advantages for IMPT indeed translate to therapeutic advantage for patients.

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