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Proton Therapy Reduces Treatment-Related Toxicities for Patients with Nasopharyngeal Cancer: A Case-Match Control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon Therapy

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Abstract

Purpose: The physical properties of proton therapy allow for decreased dose delivery to nontarget structures. The purpose of this study was to determine if this translates into a clinical benefit by comparing acute and chronic morbidity between patients with nasopharyngeal carcinoma who are treated with intensity-modulated proton therapy (IMPT) and those treated with intensity-modulated radiation therapy (IMRT).

Materials and Methods: Patients receiving IMPT for nasopharyngeal cancer from 2011-13 were matched in a 2:1 IMPT to IMRT ratio. Matching criteria were, in order, T-stage, N-stage, radiation dose, chemotherapy type, World Health Organization classification, sex, and age.

Results: Ten patients treated with IMPT and 20 matched patients treated with IMRT were included. By the end of treatment, 2 IMPT-treated patients (20%) and 13 IMRT-treated patients (65%) required gastrostomy tube (GT) insertion ($P = .020$). Patients receiving IMPT had significantly lower mean doses to the oral cavity, brainstem, whole brain, and mandible. Increased mean dose to the oral cavity was associated with a higher rate of GT placement ($P < .001$), but mean dose to the brainstem, whole brain, and mandible was not. Partitioning analysis showed that no patient required GT insertion if the mean oral cavity dose was <26 Gy, but all patients with a mean oral cavity dose > 41.8 Gy required GT insertion. Treatment type (IMPT versus IMRT), induction chemotherapy (yes versus no), mean oral cavity dose, mean brainstem dose, and mean mandible dose were entered into the multivariable model. Only higher mean oral cavity dose remained significantly associated with higher GT rates on multivariable analysis

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(odds ratio, 1.31 [95% confidence interval, 1.09-1.69] per 1 Gy or Gy (RBE) excess to the oral cavity; $P = .003$).

Conclusion: Patients with nasopharyngeal cancer who are treated with IMPT have decreased rates of GT placement, which is likely due, in part, to better dose sparing of the oral cavity.

Keywords: proton; radiation therapy; nasopharyngeal carcinoma; gastrostomy tube; toxicity

Introduction

The preferred treatment for nasopharyngeal cancer (NPC) includes radiation and chemotherapy; although this strategy is effective, it comes at a price of considerable acute toxicities [1]. The use of radiation in conjunction with chemotherapy for the treatment of nasopharyngeal carcinoma is well established [1], but the preferred treatment modality shifted from older, 2-dimensional techniques to intensity-modulated radiation therapy (IMRT) techniques in the mid 2000s [2]. Even though IMRT is the current standard, there are still often high doses delivered to adjacent normal tissues in the path of the beams [3]. Treatment planning comparisons have shown that use of proton beam radiation (PBR) can result in better normal tissue sparing while maintaining effective target dose delivery [4–7].

The physical properties of PBR allow for sparing normal tissues beyond the range of the proton beam from unintended irradiation, which makes it an attractive modality to treat several head and neck cancers close to critical organs such as the brainstem [8]. Advances in techniques for delivering PBR, such as the development of highly conformal intensity-modulated proton therapy (IMPT), have broadened the range of possible treatment uses still further [9]. IMPT can be delivered with spot-scanning proton therapy, which has recently become available on a new generation of proton therapy delivery systems and does not require the dose-shaping compensators or apertures required for older passive scatter treatment delivery [10]. With spot-scanning proton therapy, a narrow proton spot scans in the lateral direction to create a field without introducing scattering elements outside of the beam path, while spots with different energies can be used to conform dose to target volumes that wrap around critical structures. Multifield optimization is a form of IMPT for which spots from all fields are inversely optimized simultaneously.

Dosimetric studies [11–14] have shown that IMPT reduces the dose to the spinal cord, parotid glands, and brainstem; and a small, retrospective clinical study [15] recently showed excellent response (93.3%) with low rates of grade 3+ acute toxicities. In particular, no patient in this series of 15 developed anterior mucositis greater than grade 1. This raised the question of whether the dosimetric advantages demonstrated by PBR could, in fact, lead to a clinically meaningful reduction in the acute toxicities associated with head and neck cancer treatment.

Few clinical data regarding the use of PBR for NPC exist, and no currently published clinical studies have described the use of IMPT in the treatment of NPC. As patients with NPC often experience acute treatment-related nausea, vomiting, mucositis, and weight loss necessitating management with hospital admission, intravenous fluids, or gastrostomy tube (GT) placement, the purpose of this study was to determine if patients treated with IMPT had significantly less acute and chronic morbidity during radiation therapy when compared to case-matched controls treated with IMRT.

Materials and Methods

Study Cohort

Between 2011 and 2013, a total of 10 patients with NPC were enrolled in a prospective observational study and treated at a single institution. Between 2011 and 2013, a total of 93 patients treated with IMRT for NPC were identified in an institutional database. Patients treated with IMPT were matched in a 2:1 ratio with patients receiving IMRT. Matching criteria were, in order, T-stage, N-stage, radiation dose, chemotherapy type, World Health Organization classification, sex, and age. This study was conducted with approval from the institutional review board.

Data Collection

Patient charts were reviewed to determine pretreatment characteristics, tumor characteristics, treatment details, tumor control, and survival. Objective metrics during treatment, such as weight, diet, and GT placement, were also recorded from the medical record. Acute toxicities were assessed weekly during radiation by the treating physician and were documented according to the Common Terminology Criteria for Adverse Events, version 4.0 [16]. Weights before treatment and weekly during treatment

were obtained from the medical record. Dates of GT insertion and removal were recorded, when applicable. Results of clinical swallow study or modified barium swallow study before, during, and after treatment were recorded. Chronic toxicities were defined as those occurring or persisting for more than 90 days after completion of therapy.

Simulation and Radiation Treatment Planning

All patients underwent simulation for radiation treatment planning purposes, which consisted of fabrication of a custom thermoplastic mask and bite block for immobilization in the supine position, followed by noncontrast computed tomography imaging. Eclipse proton therapy treatment planning system (version 8.9, Varian Medical Systems, Palo Alto, California) was used for IMPT plans, and Pinnacle treatment planning system (version 9.0, Koninklijke Philips N.V., Amsterdam, Netherlands) was used for IMRT plans. Typically, 3 fields from 3 different beam directions (combing gantry/couch angles) were used for full-field IMPT plans, and a monoisocentric technique was used to match IMRT plans to low neck anterior-posterior fields. The 3 beam angles used for full-field IMPT plans included a posterior beam, a left anterior oblique beam, and a right anterior oblique beam with slight superior-inferior (couch kick 15°–20°). The treatment planning system then simultaneously optimized the spot intensities from all fields, using an optimization algorithm with the objective of covering 95% of the planning target volume with the prescribed dose while minimizing dose to the adjacent organs at risk.

The prescribed dose to clinical target volume 1 (CTV1) (defined as gross disease plus a 1-cm margin) was 70 Gy for IMRT plans or 70 Gy relative biological equivalent (RBE) for IMPT plans, (RBE = 1.0 for photons and 1.1 for protons) to be given in 33 to 35 fractions of 2 to 2.12 Gy or Gy (RBE) per fraction; the dose to the CTV2 (encompassing the high-risk nodal volume adjacent to gross disease in the neck) was 63 Gy or Gy (RBE) in 1.9 Gy or Gy (RBE) fractions; and the dose to CTV3 (encompassing uninvolved nodes in the neck considered to be at risk of harboring subclinical disease) was 57 Gy or Gy (RBE) in 1.7 Gy or Gy (RBE) fractions. For patients treated with IMRT, a 3- to 5-mm planning target volume expansion was added to the CTV volumes for set-up uncertainties. Daily orthogonal 2-dimensional kilovoltage x-ray images were compared with digitally reconstructed radiographs generated by the treatment planning system from simulation computed tomography images to align the patient for image guidance. The delineation of planning target volumes for IMPT-treated patients was done in a similar fashion as for IMRT-treated patients.

Organs at risk with specified dose constraints were contoured for treatment planning, including the brainstem, spinal cord, cochleas, salivary glands, oral cavity, and larynx. All contours in all cases were reviewed for quality assurance by a team of head and neck radiation oncology experts before treatment planning. Mean doses to the oral cavity, brainstem, whole brain, and mandible were recorded for each patient for analysis. The mandibular dose was used as a surrogate for dose to the anterior oral cavity, as the mandible has been described as a nontarget structure subject to beam path toxicities, such as anterior oral mucositis, when treating head and neck cancer with IMRT [3].

Statistical Analysis

Descriptive statistics were used to summarize toxicity and tumor response data. The Pearson χ^2 test was used for between-group comparisons of categorical variables. The Kruskal-Wallis test was used for between-group comparisons of continuous numeric variables. The Cochran Armitage trend test was used for between-group comparisons of ordinal variables. Factors with a P value $<.2$ in the bivariable analyses were retained in the multivariate model. In the multivariate model, nominal logistic regression was used to adjust for all variables simultaneously. $P < .05$ was considered significant, and all tests were 2-sided. Recursive partitioning was used as an exploratory analysis to evaluate dose to normal structures and GT insertion. Analyses were performed with JMP (SAS Institute Inc, Cary, North Carolina).

Results

Patient and Tumor Characteristics

Patient characteristics for the 10 patients with NPC who were treated with IMPT and the 20 case-matched patients treated with IMRT are summarized in **Table 1**. Most patients underwent induction chemotherapy (N = 8, 80% IMPT-treated patients and N = 15, 85% IMRT-treated patients) and concurrent chemotherapy (N = 10, 100% IMPT-treated patients and N = 18, 90% IMRT-treated patients). There were no significant differences between the groups by any of the matching criteria. Median follow-up was 21.6 (interquartile range [IQR], 13.6-28.6 months) and 25.8 (IQR, 17.2-36.7 months) months for the IMPT and IMRT groups, respectively.

Table 1. Comparison of patient characteristics between those treated with IMPT for NPC and matched patients treated with IMRT.

	IMPT (N = 10)	IMRT (N = 20)	*P* value[a]
Age at RT, median (IQR), y	45 (18-55)	51 (39-59)	.194
Sex, N (%)			1
Male	7 (70)	14 (70)	
Female	3 (30)	6 (30)	
T-stage, N (%)			.930
T1	4 (40)	8 (40)	
T2	2 (20)	3 (15)	
T3	2 (20)	3 (15)	
T4	2 (20)	6 (30)	
N-stage, N (%)			.468
N0	1 (10)	4 (20)	
N1	3 (30)	3 (15)	
N2	6 (60)	10 (50)	
N3	0 (0)	3 (15)	
WHO grade, N (%)			.519
I	0 (0)	2 (10)	
II/III	9 (90)	15 (75)	
Unknown	1 (10)	3 (15)	
RT dose, median (IQR)	70 (70-70) Gy (RBE)	70 (70-70) Gy	.480
Induction chemotherapy, N (%)			.526
Platinum/taxane	8 (80)	13 (65)	
Platinum/taxane/cetuximab	0 (0)	2 (10)	
None	2 (20)	5 (25)	
Concurrent chemotherapy, N (%)			.255
Platinum	10 (100)	17 (85)	
Cetuximab	0 (0)	1 (5)	
None	0 (0)	2 (10)	
Adjuvant chemotherapy, N (%)			.32
Platinum/taxane	1 (10)	0 (0)	
None	9 (90)	20 (100)	

Abbreviations: IMPT, intensity-modulated proton therapy; NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; RT, radiation therapy; IQR, interquartile range; WHO, World Health Organization.

[a]The Pearson χ^2 test was used for between-group comparisons of categorical variables. The Kruskal-Wallis test was used for between-group comparisons of continuous numeric variables. The Cochran Armitage trend test was used for between-group comparisons of ordinal variables. $P < .05$ was considered significant, and all tests were 2-sided.

Radiation Dose to Oral Cavity, Whole Brain, Brainstem, and Mandible

Patients who received IMPT had significantly lower mean doses to the oral cavity, brainstem, whole brain, and mandible (**Table 2**). The **Figure** shows representative sagittal (**Figure A**) and axial (**Figure B**) IMPT and IMRT plans for the same patient, along with dose subtraction to show unnecessary radiation that is spared when using IMPT.

Gastrostomy Tube Placement

Gastrostomy tube placement was not triggered by strictly standardized criteria but instead the decision was made after discussion between the patient, treating radiation oncologist, and dietician. Reasons for GT insertion varied and often included weight loss and dehydration. By the end of radiation treatment, 2 patients (20%) treated with IMPT required GT insertion either during or after treatment, compared with 13 patients (65%) treated with IMRT ($P = .020$) (**Table 3**). Among those who required GT, there was no significant difference in the median length of time the GT was in place (IMPT, 5.3 months, IQR 4-9 months versus IMRT, 3.2 months, IQR 2.5-7.3 months; $P = .230$). Bivariable analysis was performed by evaluating the association of GT placement with age, sex, T-stage, N-stage, induction chemotherapy, radiation type, and mean radiation dose to the oral cavity, brainstem, whole brain, and mandible (**Table 4**). Increased mean dose to the oral cavity was associated with a higher rate of GT placement, but mean dose to the brainstem, whole brain, and mandible was not. Partitioning analysis showed that

Table 2. Comparison of mean dose to nearby critical structures between those treated with IMPT for NPC and matched patients treated with IMRT.

	IMPT (IQR)	IMRT (IQR)	*P* value[a]
Mean oral cavity dose, median (IQR)	17.3 Gy (RBE)	40.6 Gy	<.001
	(12.2-24.2)	(33.7-42.5)	
Mean brainstem dose, median (IQR)	26.7 Gy (RBE)	34.2 Gy	.002
	(23.2-28.7)	(29.9-38.5)	
Mean whole brain dose, median (IQR)	6.53 Gy (RBE)	10.94 Gy	<.001
	(4.89-8.34)	(9.2-12.93)	
Mean mandible, median (IQR)	32.62 Gy (RBE)	42.65 Gy	.020
	(20.38-42.09)	(38.05-47.28)	

Abbreviations: IMPT, intensity-modulated proton therapy; NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; IQR, interquartile range.
[a]The Kruskal-Wallis test was used for between-group comparisons of continuous numeric variables. $P < .05$ was considered significant, and all tests were 2-sided.

no patient required GT insertion if the mean oral cavity dose was <26 Gy, but all patients with a mean oral cavity dose > 41.8 Gy required GT insertion. Treatment type (IMPT versus IMRT), induction chemotherapy (yes versus no), mean oral cavity dose, mean brainstem dose, and mean mandible dose were entered into the multivariable model. Only higher mean oral cavity dose remained significantly associated with higher GT rates on multivariable analysis (odds ratio, 1.31 [95% confidence interval, 1.09-1.69] per 1 Gy or Gy (RBE) excess to the oral cavity; $P = .003$).

Common Terminology Criteria for Adverse Events, Version 4.0, Acute and Chronic Toxicities

Among the IMPT-treated patients, 5 patients experienced a total of 9 common terminology criteria (CTC) grade 3 acute toxicities, whereas among IMRT-treated patients, 18 patients experienced a total of 30 CTC grade 3 acute toxicities ($P = .015$).

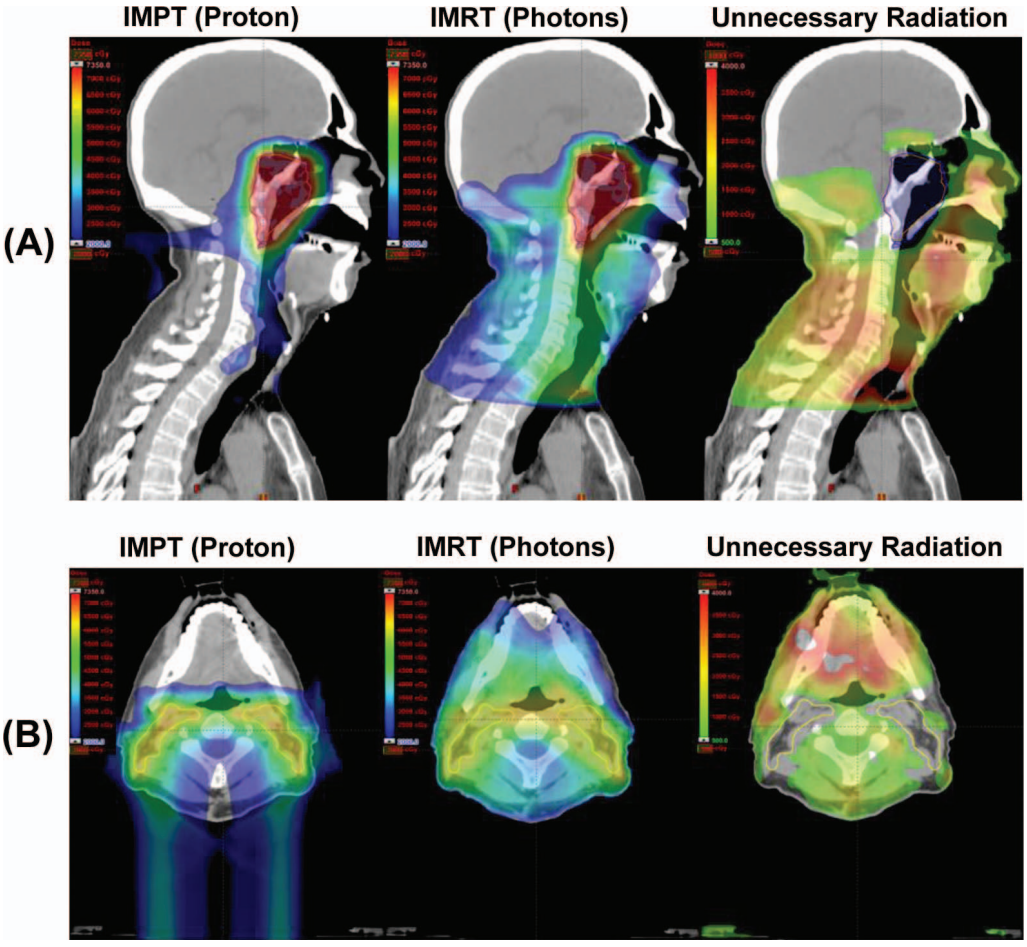

Figure. Representative sagittal (A) and axial (B) IMPT and IMRT plans for the same patient with nasopharyngeal carcinoma. (A) The dose distribution of the IMPT plan; the center panels show the dose distribution of the comparative IMRT plan. (B) The result of a dose subtraction in order to show unnecessary radiation that is spared when using IMPT as compared to IMRT. Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy.

Table 3. Comparison of acute toxicities between those treated with IMPT for NPC and matched patients treated with IMRT.

	IMPT	IMRT	*P* value[a]
Percentage of body weight lost during treatment before gastrostomy tube placement, median (IQR)	5.7 (4.5-11.2)	7.6 (6.1-12.1)	.333
Feeding tube during or after treatment, No. (%)			.020
Yes	2 (20)	13 (65)	
No	8 (80)	7 (35)	
Gastrostomy tube duration, median (IQR), mo	5.3 (4-9)	3.18 (2.5-7.3)	.230
Swallowing dysfunction after treatment, No. (%)			.175
Yes	0 (0)	3 (15)	
No	8 (80)	12 (60)	
Unknown	2 (20)	5 (25)	

Abbreviations: IMPT, intensity-modulated proton therapy; NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; IQR, interquartile range.

[a]The Pearson $\chi 2$ test was used for between-group comparisons of categorical variables. The Kruskal-Wallis test was used for between-group comparisons of continuous numeric variables. $P < .05$ was considered significant, and all tests were 2-sided.

All 30 patients experienced some degree of acute radiation dermatitis. Of the IMPT-treated patients, 1 (10%) developed grade 1 dermatitis, 4 (40%) developed grade 2 dermatitis, and 4 (40%) developed grade 3 dermatitis. Of the IMRT-treated patients, 7 (35%) developed grade 1 dermatitis, 8 (40%) developed grade 2 dermatitis, and 5 (25%) developed grade 3 dermatitis. There was no significant difference in the severity of skin toxicity by treatment type ($P = .412$). No patient in either treatment group experienced grade 4 or 5 acute toxicities.

Table 4. Factors associated with gastrostomy tube placement in patients treated with IMPT for NPC and matched patients treated with IMRT.

	Odds ratio for GT requirement	95% confidence interval	*P* value[a]
Age at initiation of radiation[b]	0.987	0.940-1.03	.586
Sex			
Female	Reference	Reference	-
Male	1.50	0.325-7.47	.606
T-stage			
T1	Reference	Reference	-
T2	4.20	0.399-99.89	.240
T3	1.87	0.285-13.50	.514
T4	1.87	0.285-13.50	.514
N-stage			
N0	Reference	Reference	-
N1	0.333	0.022-3.72	.374
N2	0.762	0.082-5.96	.795
N3	2.00	0.118-58.73	.633
Induction chemotherapy			
No	Reference	Reference	-
Yes	0.278	0.035-1.52	.143
Radiation type			
IMPT	Reference	Reference	-
IMRT	9.33	1.74-75.66	.008
Mean dose to oral cavity[c]	1.16	1.06-1.32	<.001
Mean dose to the brainstem[c]	1.12	0.995-1.29	.062
Mean dose to the whole brain[c]	0.986	0.562-1.14	.840
Mean dose to the mandible[c]	1.07	0.984-1.17	.124

Abbreviations: IMPT, intensity-modulated proton therapy; NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; GT, gastrostomy tube.

[a]The Pearson χ^2 test was used for between-group comparisons of categorical variables. The Kruskal-Wallis test was used for between-group comparisons of continuous numeric variables. The Cochran Armitage trend test was used for between-group comparisons of ordinal variables. $P < .05$ was considered significant, and all tests were 2-sided.

[b]Unit odds ratio per year.

[c]Unit odds ratio per Gy or Gy (RBE).

Reported long-term toxicities were also few. Among the IMPT-treated patients, there were 3 patients who experienced a total of 5 chronic grade 3 toxicities, whereas among IMRT-treated patients, there were 3 patients who each experienced 1 chronic grade 3 toxicity ($P = .542$). Two patients in the IMRT group required tympanostomy tube placement owing to chronic middle ear effusions after radiation. Two patients in the IMRT group developed temporal lobe radionecrosis. Both patients were asymptomatic, and neither has required any treatment. Two patients in the IMPT group also developed temporal lobe radionecrosis. One patient was asymptomatic and was observed, and the other patient developed neurologic symptoms and experienced full resolution of those symptoms upon treatment with bevacizumab.

Weight Loss and Swallowing Dysfunction

The median percentage body weight lost from the beginning to the end of radiation was 5.7% (IQR, 4.5%-11.2%) in the IMPT group and 7.6% (IQR, 6.1%-12.1%) in the IMRT group ($P = .333$). Eight patients in the IMPT group and 15 in the IMRT group had a clinical swallowing evaluation by a speech pathologist or a modified barium swallow study during and after treatment. No patients in the IMPT group developed documented swallowing dysfunction, defined as oropharyngeal dysphagia with or without penetration and/or aspiration, and 3 patients (15%) in the IMRT group developed swallowing dysfunction ($P = .175$; **Table 3**).

Control and Survival Outcomes

At the time of last follow-up, there had been no documented local failures in the IMPT group and 1 in the IMRT group. One patient in each of the IMPT group and the IMRT group developed distant metastatic disease. Additionally, 1 patient in the IMPT group died of unknown causes with diffuse metastatic disease, and 1 patient in the IMRT group died of aspiration pneumonia and respiratory insufficiency shortly after completing chemoradiation.

Discussion

This is a retrospective case-control study comparing acute toxicities between patients with NPC who were treated with IMPT and matched patients treated with IMRT. Not only did we find IMPT to be a safe and well-tolerated method of treating patients with NPC, we found significantly lower rates of GT placement during and after treatment among patients treated with IMPT. In an effort to propose a mechanism for decreased GT requirement, we evaluated mean dose to the oral cavity as well as the brainstem for both groups and found mean oral cavity dose to be significantly higher in those requiring GT.

In the current study, we showed that a significantly decreased mean dose to the oral cavity and brainstem was achieved in patients treated with IMPT, compared to case-matched controls treated with IMRT. Several dosimetric studies [4–7] have shown the advantage PBR affords in the sparing of nearby organs at risk, but it has yet to be confirmed whether this dosimetric benefit translates into a clinically meaningful one. We showed decreased rates of GT placement in patients treated with IMPT, and the overall acute and long-term toxicity profile of IMPT for NPC appears to be safe and well tolerated. Although the use of PBR has been described for the treatment of several head and neck subsites [17], few studies describing its use in the treatment of NPC have been published to date.

Our toxicity data compare favorably with those in other small, single-institution case series from Loma Linda and Massachusetts General Hospital [18, 19] although GT rates were not reported. Massachusetts General Hospital is currently conducting a phase II study evaluating combined proton-photon therapy to 70 Gy (RBE) in 35 daily fractions given with concurrent cisplatin and fluorouracil [20]. Preliminary results from 23 consecutive patients with stage III to IVB NPC in this trial were presented in abstract form in 2012. A 3-dimensional (3D) technique was used, with 2 posterior oblique fields used to spare the parotids with no exit dose into the oral cavity. Toxicities included hearing loss (29%) and weight loss (38%). Surprisingly, GT placement was high in this group (48%) [21]. However, these data have not yet been published in manuscript form, and doses to nearby critical structures were not given in the abstract. The local control rate at 28 months' follow-up was 100%; the 2-year disease free survival rate was 90% and the overall survival rate, 100% [21]. Temporal lobe necrosis was not specifically mentioned in these publications, so we cannot compare their incidence of this toxicity with the finding that 2 IMRT- and 2 IMPT-treated patients developed radionecrosis in our cohort. Temporal lobe necrosis has been described in the setting of IMRT, and dosimetric studies have suggested a dose constraint of D (0.5 cm^3) = 69 Gy [22]. D (0.5 cm^3) is defined as the dose received by 0.5 cm^3. Doses to the temporal lobe in excess of this constraint are often necessary to obtain adequate target coverage for NPC; however, for the patients treated with IMPT, uncertainties regarding the neurologic RBE may have also played a role.

The abovementioned previously published series used a 3D conformal, passive scatter proton technique. The use of IMPT has not been previously described for NPC, but we recently reported in abstract form our results from 25 patients with oropharyngeal cancer who were treated with IMPT [23]. Patients treated with IMPT experienced less nausea, vomiting, mucositis, and hearing problems after treatment than historic controls treated with IMRT. Twenty percent of patients treated with IMPT required a GT compared with 48% of patients treated with IMRT ($P = .037$) [23], and these results are similar to what we report in the current cohort.

Toxicity reduction for patients undergoing radiation for NPC merits investigation, as toxicity from treatment can be life-threatening and/or quality-of-life threatening. Dehydration and poor oral intake are the leading reason for hospital admission during treatment, and significant weight loss during and after treatment has been identified as a predictor of poor outcomes [24]. Gastrostomy tube placement can help significantly with hydration and nutrition, but the placement of a GT does necessitate a minimally invasive procedure associated with a mortality rate of 2.2%, a major complication rate of 7.4%, and a minor complication rate ranging from 1% to 30% [25]. From a health care system–wide standpoint, there is also considerable cost associated with GT placement and use. One study published in 2001 estimated that the direct charges associated with GT use for 1 year amounted to $31,832 [26], and these charges are likely even higher in the current era.

There are several factors leading to GT requirement in patients undergoing radiation to the head and neck, including mucositis [27, 28], xerostomia [2], dysphagia, dysgeusia [29], and nausea [30–32]. We showed that patients who required GT placement had higher mean radiation doses to the oral cavity. A systematic review comparing IMRT versus 2-dimensional to 3D radiation therapy showed a trend toward superiority of IMRT regarding acute mucositis [33]. Our data suggest it may be possible to reduce dose to the oral cavity even further with IMPT.

To our knowledge, our study is the first of its kind reporting clinical outcomes and toxicities for patients with NPC who are treated with multifield optimization IMPT. Another strength of our study is our ability to match and compare these cases to those of patients treated in the same era at the same institution with IMRT. These results are novel, and hypothesis generating, but subject to the limitations similar to those of other single-institution retrospective series. Patients were selected to receive IMPT on the basis of many factors such as tumor size and extent, patient and physician motivation, as well as insurance approval. Additionally, the placement of GT in these patients was not triggered by standardized criteria and was also subject to patient and physician preference. The lack of a defined threshold for GT placement (ie, 10% loss of body weight or failure to maintain 50% of calculated nutritional requirements [34]) could have confounded our results.

Conclusion

Patients with NPC who receive treatment with IMPT have a meaningful reduction in acute toxicity as evidenced by decreased rates of GT placement. Analysis of mean dose to the oral cavity suggests that this may be partially attributable to the ability of IMPT to spare dose to this organ at risk. Partition analysis showed no patient required GT placement below the threshold of 26 Gy mean dose to the oral cavity, suggesting this may be a reasonable dose constraint to strive for when generating either IMRT or IMPT plans. Future prospective trials in NPC will provide further data comparing additional toxicity endpoints between IMPT and IMRT.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.
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