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Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer – A case matched analysis

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ABSTRACT

Background: Owing to its physical properties, intensity-modulated proton therapy (IMPT) used for patients with oropharyngeal carcinoma has the ability to reduce the dose to organs at risk compared to intensity-modulated radiotherapy (IMRT) while maintaining adequate tumor coverage. Our aim was to compare the clinical outcomes of these two treatment modalities.

Methods: We performed a 1:2 matching of IMPT to IMRT patients. Our study cohort consisted of IMPT patients from a prospective quality of life study and consecutive IMRT patients treated at a single institution during the period 2010–2014. Patients were matched on unilateral/bilateral treatment, disease site, human papillomavirus status, T and N status, smoking status, and receipt of concomitant chemotherapy. Survival analyzes were performed using a Cox model and binary toxicity endpoints using a logistic regression analysis.

Results: Fifty IMPT and 100 IMRT patients were included. The median follow-up time was 32 months. There were no imbalances in patient/tumor characteristics except for age (mean age 56.8 years for IMRT patients and 61.1 years for IMPT patients, p-value = 0.010). Statistically significant differences were not observed in overall survival (hazard ratio (HR) = 0.55; 95% confidence interval (CI): 0.12–2.50, p-value = 0.44) or in progression-free survival (HR = 1.02; 95% CI: 0.41–2.54; p-value = 0.96). The age-adjusted odds ratio (OR) for the presence of a gastrostomy (G)-tube during treatment for IMPT vs IMRT were OR = 0.53; 95% CI: 0.24–1.15; p-value = 0.11 and OR = 0.43; 95% CI: 0.16–1.17; p-value = 0.10 at 3 months after treatment. When considering the pre-planned composite endpoint of grade 3 weight loss or G-tube presence, the ORs were OR = 0.44; 95% CI: 0.19–1.0; p-value = 0.05 at 3 months after treatment and OR = 0.23; 95% CI: 0.07–0.73; p-value = 0.01 at 1 year after treatment.

Conclusion: Our results suggest that IMPT is associated with reduced rates of feeding tube dependency and severe weight loss without jeopardizing outcome. Prospective multicenter randomized trials are needed to validate such findings.

The prognosis of oropharyngeal cancer (OPC) has improved in the past decades, especially in terms of locoregional control and overall survival, likely due to the increased proportion of human papillomavirus (HPV)-related tumors. It is now widely accepted that HPV infection is a major causal factor for OPC, especially among non-smoking, non-drinking patients [1–3], and is responsible for the increase in OPC incidence that is observed worldwide, and notably in North America and Europe. Patients with HPV-positive OPC are usually younger, have fewer comorbid conditions, and more often present with lower T status but advanced N status

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[4], and have an improved prognosis compared with patients with HPV-negative disease [5].

Radiotherapy, with or without chemotherapy, is the treatment of choice for most patients with early [6,7] and advanced [8–10] OPC because it allows organ preservation and avoids the morbidity associated with surgical procedures. Avoiding long-term sequelae of radiation or chemoradiation is particularly important for patients with OPC as the combination of younger HPV-positive patients with improved disease control outcomes means survivors have the potential to live with the side effects and complications of treatment for many years. Because it maintains dose levels to the tumor, this strategy could be of interest in all OPC tumors regardless of HPV status.

Proton therapy, because of its intrinsic physical properties, has the ability to reduce the integral dose delivered to the patient while maintaining highly conformal target coverage. Dosimetric studies have shown that intensity-modulated proton therapy (IMPT) allowed dose reductions for various normal tissue structures, including the contralateral submandibular and parotid glands, oral cavity, spinal cord and brainstem, as well as the volume of normal tissue receiving doses of 10, 30, and 50 Gy [11] and in a pediatric population [12,13]. We previously reported a dosimetric comparison of the first 25 oropharyngeal cancer patients treated with IMPT at our institution and found that mean doses to the anterior and posterior oral cavity, hard palate, larynx, mandible and esophagus were significantly lower with IMPT than with IMRT comparison plans generated for the same patients, as were doses to several central nervous system structures involved in the nausea and vomiting response [14].

Although dosimetric analyses can be hypothesis-generating, analyzing comparative clinical outcomes including safety and efficacy of IMPT relative to photon-based IMRT is critical. Therefore, the aim of this study was to report the first case-matched analysis of patients with OPC treated with IMPT or IMRT at a single center from 2010 through 2014.

Material and methods

Patient population and matching strategy

From 2011 to 2014, 50 adult OPC patients receiving spot-scanning IMPT with curative intent were included in an institutional review board-approved observational study in which clinical outcomes were prospectively recorded. Participants provided study-specific informed consent. Although tumor outcomes and toxicity for this population have been reported, a comparative analysis could not be performed at that time [15]. For comparative purposes, IMRT patients were selected from our institutional database which included 512 consecutive patients with OPC treated with IMRT from 2010 to 2012.

IMRT patients were matched with IMPT patients based on factors that influence treatment volumes and expected toxicity during or after radiotherapy. A 2:1 ratio was used to increase statistical power. These factors were, in order: laterality of treatment (unilateral vs bilateral), disease site (tonsil vs base of tongue), p16/HPV status (positive vs negative, missing data being considered as any category), T status (T1–T2 vs T3–T4), N status (N0–N1 vs N2–N3), receipt of concomitant chemotherapy, and smoking status. For smoking status, the cut-off chosen was 5 pack-years (PY, ($\leqslant$5 vs >5 PY) because of difficulty in matching when using the more widely used cut-off of 10 PY. Further matching was attempted on age, but even when a large age matching range was used (case age ±10 years), the addition of this criterion resulted in the loss of a significant number of patients. We therefore decided not to match on age but to investigate the age distribution between the two groups and to adjust the toxicity analyses using this factor.

Treatment

The vast majority of OPC cases managed at our institution are treated with a radiation therapy-based approach, and these results have previously been reported [16]. Before therapy was begun, all patients underwent multidisciplinary evaluation within our institution and all cases were presented at our head and neck cancer multidisciplinary tumor board for individualized treatment recommendations regarding the sequence and combination of treatment modalities. All patient underwent nutritional counseling and follow-up during and after treatment. Gastrostomy (G-) tube placement was based on a reactive approach, with the decision made after discussion among the patient, the treating radiation oncologist, and the dietician. Reasons for G-tube insertion varied but often included weight loss, inability to maintain oral nutrition, and dehydration.

Detailed treatment processes were previously described [15,17,18] and are briefly summarized below. All patients underwent non-contrast computed tomography (CT) simulation while immobilized in the supine position with full-length thermoplastic mask, bite block with or without an oral stent, and a posterior customized head, neck and shoulder mold for IMPT patients. During our Head and Neck Radiation Oncology Planning and Development Clinic, all IMRT and IMPT patients were examined by at least two radiation oncologists and target volumes were peer-reviewed for quality assurance purposes [19]. Gross tumor plus margins were prescribed a dose of 66 Gy for small volume disease and 70 Gy for more advanced disease, and elective regions received 54–63 Gy. For IMPT patients, a relative biological effectiveness (RBE) value of 1.1 was used. Carefully selected patients with well-lateralized tonsil cancers underwent ipsilateral neck irradiation [20,21].

IMPT planning was performed with an Eclipse proton therapy treatment planning system (version 8.9, Varian Medical Systems, Palo Alto, California). Typically 3 beams were used for whole-field bilateral neck IMPT plans: a left and right anterior oblique and single posterior beam. Multi-field optimization was used for bilateral treatments, and single-field optimization was used for unilateral cases. The robustness of each treatment plan was also considered to evaluate the sensitivity to uncertainties associated with variations in patient setup and proton beam range in each patient [22,23]. Plan-specific quality assurance measurements were made before treatment delivery [24]. Daily kilovoltage image guidance was used for all patients. Verification CT scans were obtained at week 1 and 4 of therapy and adaptive re-planning was considered if inadequate doses were delivered to the targets or the organs at risk.

IMRT planning was performed with a Pinnacle planning system (Philips Medical Systems, Andover, MA). Treatment was delivered with a static gantry approach. The template for patients treated to both sides of the neck used 9 beams set equidistant through 360 degrees. Plans for patients treated to only one side of the neck involved a template using 7 beams equidistant through a 190 degree arc. Beam angles and number were modified during the optimization process. In general, IMRT was used to treat the primary tumor and upper neck nodes, whereas the lower neck below the isocenter was treated with an anterior beam, with a larynx and/or full midline block. A "whole-field" IMRT approach was used for situations in which the patient's anatomy or primary tumor location created concerns that tumor might be under-dosed using the "split-field" approach. IMRT was delivered with Varian (Varian Medical Systems, Palo Alto CA) linear accelerators as 6-MV photons with daily image guidance [18]. No systematic re-planning was performed for IMRT patients. Appropriate recommendations from the International Commission on Radiation Units and Measurements were followed [25,26].

Data collection and endpoint definition

All data were prospectively recorded for the IMPT cohort and retrospectively collected for the IMRT cohort. The data collected consisted of baseline patient and tumor characteristics, including smoking status (PY), comorbid conditions according to the Charlson comorbidity index [27], p16 status, tumor outcomes, acute/late toxicity including emergency room visits, and unplanned hospitalizations. Patient weight, placement of a G-tube during or after radiation therapy, patient-rated fatigue or dry mouth (both of which were rated on a 0–3 scale from none to severe) were recorded prospectively in the radiation oncology medical records at each visit, making the coding process more reliable and reducing the rate of missing data. Fewer than 5% of data were missing for all endpoints except for weight loss and fatigue at 1 year after treatment. Toxicity grades considered were peak grade during radiotherapy and toxicity that persisted at 3 months and at 1 year after treatment. Toxicity at 2 years after treatment was recorded but not analyzed because of missing data resulting from the relatively short follow-up time.

Survival times were calculated from the end of radiotherapy to the date of the first event of interest. Events were defined as follows: death from any cause for overall survival (OS), death from any cause or disease recurrence for progression-free survival (PFS), and locoregional or distant recurrence for locoregional control and distant control. Patients were censored at their last follow-up date.

Statistical analysis

Follow-up was calculated by inverting the censoring indicator and applying the Kaplan–Meier method [28]. The distribution of categorical variables between IMPT and IMRT patients were compared with chi-square tests. Survival distributions between IMPT and IMRT were compared with log-rank tests. Survival curves and estimates of survival at specific time points were computed with the Kaplan–Meier method. Multivariate survival analyses were done with Cox regression and included all variables with $p < 0.30$ in univariate analysis, along with the case (IMPT)/control (IMRT) status. The toxicity endpoints (including the composite endpoint of G-tube and grade 3 weight loss) and the statistical analysis plan were predefined before the statistical analysis, in an effort to inform the endpoint of a future phase III trial. Toxicity rates are reported as the frequency and percentage of patients with toxicity information at a specified time point. IMPT and IMRT patients were further compared by multivariate logistic regression, which included age dichotomized at 60 years as a covariate. Duration of G-tube placement was compared between IMPT and IMRT patients with log-rank tests using the removal of feeding tube as an event and censoring patients who died with a feeding tube in place. All p-values reported are 2-sided and a $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using SAS software (Release 9.3; SAS Institute, Cary, NC, USA).

Results

Patient, tumor and treatment characteristics are presented in Table 1. No imbalances were found between the two groups in any covariate apart from patient age (p-value = 0.01). Median age (range) was 61 years (37–84) for IMPT patients and 55.5 years (34–78) for IMRT patients. Patients had few comorbidities (Charlson comorbidity index of 0–1 in 89.3%). Most tumors were locally advanced (N2–N3 in 80%). Most tumors were HPV-positive, with only three HPV-negative tumors and 16 patients with unknown HPV status. Approximately 43% of the patients received induction chemotherapy and two-thirds received concurrent chemotherapy. Unilateral radiotherapy was delivered to 20% of the patients.

Table 1
Patient, tumor and treatment characteristics.

Patient characteristics		Entire cohort, *n* (%)	IMPT, *n* (%)	IMRT, *n* (%)	*p*
Age	⩽60 years	90 (60)	23 (46)	67 (67)	0.01
	>60 years	60 (40)	27 (54)	33 (33)	
Sex	Female	22 (14.7)	8 (16)	14 (14)	0.74
	Male	128 (85.3)	42 (84)	86 (86)	
Tobacco status	0 Pack-Years	70 (46.7)	25 (50)	45 (45)	0.35
	0–10 Pack-Years	21 (14)	4 (8)	17 (17)	
	>10 Pack-Years	59 (39.7)	21 (42)	38 (38)	
Charlson comorbidity index	0–1	134 (89.3)	45 (90)	89 (89)	0.90
	⩾2	16 (10.7)	5 (10)	11 (11)	
Tumor site	Tonsil	81 (54)	27 (54)	54 (54)	1.00
	Base of tongue	69 (46)	23 (46)	46 (46)	
P16 status	Positive	131 (87.3)	44 (88)	87 (87)	0.98
	Negative	3 (2)	1 (2)	2 (2)	
	Unknown	16 (10.7)	5 (10)	11 (11)	
T Status	T1–T2	120 (80)	40 (80)	80 (80)	1.00
	T3–T4	30 (20)	10 (20)	20 (20)	
N-Status	N0–N1	30 (20)	10 (20)	20 (20)	1.00
	N2–N3	120 (80)	40 (80)	80 (80)	
Induction chemotherapy	Yes	64 (42.7)	20 (40)	44 (44)	0.64
	No	86 (57.3)	30 (60)	56 (56)	
RT laterality	Bilateral	120 (80)	40 (80)	80 (80)	1.00
	Unilateral	30 (20)	10 (20)	20 (20)	
Concurrent chemotherapy	Yes	96 (64)	32 (64)	64 (64)	1.00
	No	54 (36)	18 (36)	36 (36)	
	Cisplatin	39 (41)	13 (41)	26 (41)	
	Carboplatin	11 (11)	6 (19)	5 (8)	
	Cetuximab	42 (44)	11 (34)	31 (48)	
	Taxane	4 (4)	2 (6)	2 (3)	
Neck dissection	Not performed	115 (76.7)	41 (82)	74 (74)	0.50
	Pre radiotherapy	14 (9.3)	3 (6)	11 (11)	
	Post radiotherapy	21 (14)	6 (12)	15 (15)	

Matched variables were unilateral/bilateral treatment, disease site, HPV status, T and N status, smoking status and receipt of concomitant chemotherapy. The cut-off used for matching on smoking status (⩽5 PY) was different from the one presented in the table because of difficulties in matching using the 10 PY cut-off. For p16 matching, patients with unknown p16 status could be considered either p16 positive or negative.

Median follow-up time was 32 months (range 2–55) for the entire cohort, 29 months (range 8–49) for the IMPT group and 33 months (range 2–55) for the IMRT group. Owing to differences in the inclusion period, the number of living patients censored before 2 years of follow-up after treatment was 21 (42%) in the IMPT group and 13 (13%) in the IMRT group. Twelve patient deaths were recorded, two in the IMPT group and ten in the IMRT group. OS rates at 3 years were 94.3% in the IMPT group and 89.3% in the IMRT group. Results from the Cox regression are reported in Table 2. In univariate analyses, only advanced T status and the insertion of a G-tube at the acute phase were associated with decreased OS, with hazard ratios (HR) of 3.1 (95% confidence interval (CI): 0.98–9.8, p-value = 0.05) and 6.61 (95% CI: 1.8–24.4, p-value = 0.005), respectively. In multivariate analyses, the insertion of a G-tube at the acute phase was the only significant factor affecting OS, with a HR of 4.96 (95% CI: 1.1–23.0, p-value = 0.04). The HR between IMPT and IMRT in multivariate analysis was 0.55 (95% CI: 0.12–2.5, p-value = 0.44).

Twenty-two events (recurrence or death) were observed, 7 in the IMPT group and 15 in the IMRT group, leading to a 3-year PFS rate of 86.4% in the IMPT group and 85.8% in the IMRT group, corresponding to a HR of 1.02 (95% CI: 0.41–2.54, p-value = 0.96). The results from the PFS analysis are presented in Table 3. PFS curves according to

Table 2
Univariate and multivariate analyses for overall survival.

Patient characteristics		Univariate		Multivariate	
		HR (95% CI)	*p*	HR (95% CI)	*p*
RT type	IMRT	1		1	
	IMPT	0.42 (0.09–1.91)	0.26	0.55 (0.12–2.5)	0.44
Age	⩽60 years	1		–	
	>60 years	1.6 (0.50–4.89)	0.44	–	
Sex	Female	1		–	
	Male	1.71 (0.22–13.2)	0.61	–	
Tobacco status	0 PY	1		–	
	0–10 PY	1.63 (0.3–8.9)	0.57	–	
	>10 PY	1.73 (0.49–6.1)	0.39	–	
Charlson comorbidity index	0–1	1		1	
	⩾2	3.2 (0.87–11.9)	0.08	3.39 (0.81–14.1)	0.09
Tumor site	Tonsil	1		–	
	Base of tongue	1.17 (0.38–3.6)	0.79	–	
P16 status	Positive	1		–	
	Negative	NA		–	
	Unknown	1.61 (0.35–7.4)	0.54	–	
T Status	T1–T2	1		1	
	T3–T4	3.1 (0.98–9.8)	0.05	1.36 (0.35–5.4)	0.65
N-Status	N0–N1	1		1	
	N2–N3	2.97 (0.38–23.1)	0.30	1.38 (0.14–13.4)	0.78
Induction chemotherapy	No	1		1	
	Yes	2.66 (0.80–8.8)	0.11	1.96 (0.52–7.4)	0.32
RT laterality	Bilateral	1		–	
	Unilateral	NA		–	
Concurrent chemotherapy	No	1		1	
	Yes	3.02 (0.66–13.8)	0.15	1.16 (0.20–6.8)	0.91
Neck dissection	Not performed	1		–	
	Pre radiotherapy	1.03 (0.13–8.3)	0.98	–	
	Post radiotherapy	2.06 (0.55–7.8)	0.28	–	
Acute G-tube insertion	No	1		1	
	Yes	6.61 (1.8–24.4)	0.005	4.96 (1.1–23.0)	0.04
Weight loss at 3 months after RT	<20%	1		–	
	⩾20%	0.86 (0.11–6.8)	0.88	–	

NA: not assessed. Hazard ratios (HRs) were not estimated for HPV-negative or unilateral RT patients because of the very low numbers of patients/events in these groups.

treatment group are shown in Fig. 1. In both univariate and multivariate analyses, advanced age (HR = 2.70; 95% CI: 1.10–6.90; *p*-value = 0.04) and the insertion of a G-tube at the acute phase (HR = 3.09; 95% CI: 1.19–8.00; *p*-value = 0.02) were associated with decreased PFS. T status was close to significance in the univariate (*p*-value = 0.08) but not in the multivariate analysis.

Overall, 15 locoregional relapses, 5 in the IMPT and 10 in the IMRT group, were observed. Eight distant relapses were observed, 1 in the IMPT group and 7 in the IMRT group. Three-year locoregional control rates were 91.0% for IMPT patients and 89.7% for IMRT patients. Three-year distant control rates were 97.8% for IMPT patients and 93.5% for IMRT patients. No significant differences were found between the IMPT and IMRT groups with respect to locoregional control (HR = 1.03; 95% CI: 0.35–3.02; *p*-value = 0.96) and distant control (HR = 0.33; 95% CI: 0.04–2.74; *p*-value = 0.30). In the univariate analysis, locoregional control was significantly decreased by advanced T status (*p*-value = 0.04) and acute G-tube insertion (*p*-value = 0.03). Probably because of the low rate of events, no significant factor was found in the multivariate analysis for either of these endpoints.

The association between acute G-tube placement and survival was studied. The PFS curves according to acute G-tube placement are shown in Supplementary Fig. 1. Patients receiving a G-tube during radiotherapy had a longer history of tobacco smoking (*p*-value = 0.03), a higher Charlson comorbidity index (*p*-value = 0.03), more advanced T and N status (*p*-values = 0.01 and 0.07), more frequent bilateral treatment (*p*-value < 0.001), use of induction chemotherapy (*p*-value = 0.07) and concurrent chemotherapy (*p*-value < 0.001), and a longer treatment duration (by a mean 2 days; 43 vs 41 days, *p* = 0.0002). Sensitivity analyses for PFS were done for this group without using acute G-tube placement as a variable and yielded comparable results as the initial analyses, with no statistically significant difference between the IMPT and IMRT groups (HR: 0.82; 95% CI:0.32–2.1; *p*-value = 0.67).

No significant differences were found in acute grade 3 or higher dermatitis or mucositis between the IMPT and IMRT patients (*p*-values = 0.15 and 0.90). Toxicity endpoints between treatment groups are described in Table 4. The median duration of G-tube placement was 2.8 months in the IMPT group and 4.8 months in the IMRT group (*p*-value = 0.12). The age-adjusted OR for the use of a G-tube were 0.53 (95% CI: 0.24–1.15; *p*-value = 0.11) during treatment and 0.43 (95% CI: 0.16–1.17; *p*-value = 0.10) at 3 months after treatment. Grade 3 weight loss at 1 year after treatment may have been more prevalent in the IMPT group, with an OR of 0.28 (95% CI: 0.08–1.05; *p*-value = 0.06). When considering the predefined composite index of G-tube use or grade 3 weight loss, the ORs at 3 months and 1 year after treatment were 0.44 (95% CI: 0.19–1.0, *p*-value = 0.05) and 0.23 (95% CI: 0.07–0.73, *p*-value = 0.01). Patient-reported grade 2 or higher xerostomia at 3 months was less common among the IMPT patients, with an OR of 0.38 (95% CI: 0.18–0.79, *p*-value = 0.009). No differences were found between the two groups in grade 2 or higher patient-reported fatigue at any time, in the frequency of emergency room visits, or in unscheduled hospitalizations.

Discussion

This comparative clinical study of patients with OPC treated with IMPT or IMRT suggests that IMPT may achieve toxicity reduction while preserving tumor control. Our study showed that IMPT,

Table 3
Univariate and multivariate analyses for progression free survival.

Patient characteristics		Univariate		Multivariate	
		HR (95% CI)	*p*	HR (95% CI)	*p*
RT type	IMRT	1		1	
	IMPT	1.02 (0.41–2.54)	0.96	1.00 (0.39–2.6)	0.99
Age	⩽60 years	1		1	
	>60 years	3.08 (1.28–7.41)	0.01	2.7 (1.1–6.9)	0.04
Sex	Female	1		–	
	Male	1.43 (0.33–6.12)	0.63	–	
Tobacco status	0 PY	1		–	
	0–10 PY	0.94 (0.19–4.51)	0.93	–	
	>10 PY	2.14 (0.85–5.37)	0.10	–	
Charlson comorbidity index	0–1	1		1	
	⩾2	2.35 (0.79–7.04)	0.13	1.83 (0.6–5.8)	0.31
Tumor site	Tonsil	1		–	
	Base of tongue	1.03 (0.44–2.4)	0.94	–	
P16 status	Positive	1		–	
	Negative	NA		–	
	Unknown	1.25 (0.37–4.3)	0.72	–	
T Status	T1–T2	1		1	
	T3–T4	2.27 (0.91–5.64)	0.08	1.15 (0.40–3.31)	0.80
N-Status	N0–N1	1		–	
	N2–N3	1.11 (0.37–3.3)	0.85	–	
Induction chemotherapy	No	1		–	
	Yes	1.38 (0.60–3.2)	0.45	–	
RT laterality	Bilateral	1		–	
	Unilateral	0.57 (0.16–1.92)	0.36	–	
Concurrent chemotherapy	No	1		–	
	Yes	1.37 (0.55–3.37)	0.50	–	
Neck dissection	Not performed	1		–	
	Pre radiotherapy	1.12 (0.25–4.96)	0.88	–	
	Post radiotherapy	2.18 (0.83–5.8)	0.11	–	
Acute G-tube insertion	No	1		1	
	Yes	3.27 (1.39–7.66)	0.006	3.09 (1.19–8.00)	0.02
Weight loss at 3 months after RT	<20%	1		–	
	⩾20%	0.91(0.21–3.93)	0.90	–	

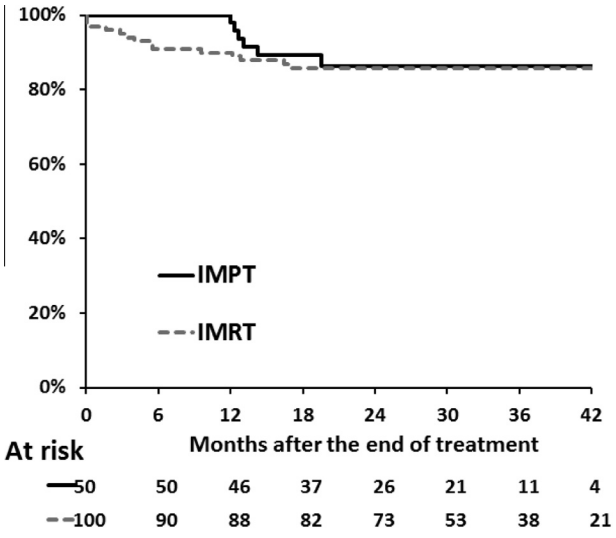

Fig. 1. Progression free survival according to type of ionizing radiation (IMPT vs IMRT).

when compared with IMRT, achieves similar cure rates, by both OS and disease control measures, after a median follow-up time of nearly 3 years. With regard to toxicity, IMPT may have resulted in a reduction of G-tube rates during the acute phase, at 3 months, and 12 months. When using a pre-planned composite endpoint of G-tube or grade 3 weight loss, IMPT was associated with significantly reduced rates of toxicity at both 3 months and 12 months after treatment.

These clinical results are consistent with a recent case-matched analysis of patients with nasopharyngeal carcinoma published by our institution [29] and a recent comparative study in patients receiving ipsilateral head and neck radiotherapy [30], and the rates of G-tube placement are within the range of those reported in randomized trials [31]. One unexpected finding in the current study is that acute G-tube placement was a significant adverse prognostic factor for OS and PFS. An analysis of G-tube placement demonstrated strong associations with many adverse features, including greater intensity of treatment as measured by bilateral radiation and use of chemotherapy, more advanced disease, and smoking with have a higher incidence of comorbidities. G-tube placement was also associated with a small (mean 2 days) but statistically significant longer treatment duration, potentially affecting treatment outcome. Therefore, it is likely that G-tube placement is a proxy for advanced disease and more intensive treatment rather than a causal factor for future disease progression. Nevertheless, reducing the need for feeding tube placement during radiotherapy and at the chronic phase could be an important goal to reduce toxicity and improve patient quality of life [32].

The limitations of this study are related to the retrospective coding of IMRT patients, which is known to underestimate toxicity relative to prospective coding. However, the main endpoints, G-tube and weight loss, were limited to the use of objective measures that were captured at the time of occurrence. Further, patient-reported levels of fatigue and dry mouth were collected on a regular basis and in a consistent fashion during the entire period of accrual. The prospective coding of IMPT patients, who were all included in quality of life evaluation cohorts, ensures high quality data. The practice regarding feeding tube placement at our institution is reactive and involves the patient along with several

Table 4
Toxicity analysis for pre-planned endpoints between IMPT and IMRT at various time points, adjusted for patient age (dichotomized at 60 years).

Endpoint	During RT				3-months post RT				1 year post RT			
	IMPT *n* (%)	IMRT *n* (%)	OR (95% CI)	*p*	IMPT *n* (%)	IMRT *n* (%)	OR (95% CI)	*p*	IMPT *n* (%)	IMRT *n* (%)	OR (95% CI)	*p*
G-tube presence	12 (24)	38 (38)	0.53 (0.24–1.15)	0.11	6 (12)	23 (23)	0.43 (0.16–1.17)	0.10	1 (2)	7 (7.8)	0.16 (0.02–1.37)	0.09
Weight loss > 20% compared to baseline	–	–	–	–	4 (8.3)	13 (13.5)	0.64 (0.19–2.11)	0.46	3 (6.7)	17 (19.3)	0.28 (0.08–1.05)	0.06
G-tube OR weight loss > 20%	–	–	–	–	9 (18)	34 (34)	0.44 (0.19–1.0)	0.05	4 (8)	22 (24.7)	0.23 (0.07–0.73)	0.01
Patient rated xerostomia grade 2–3	–	–	–	–	21 (42)	60 (61.2)	0.38 (0.18–0.79)	0.009	21 (42)	42 (47.2)	0.63 (0.30–1.33)	0.23
Patient rated fatigue grade 2–3	39 (78)	84 (86.6)	0.49 (0.20–1.23)	0.13	20 (40.8)	34 (36.2)	1.1 (0.53–2.27)	0.80	7 (14.6)	17 (22.1)	0.5 (0.18–1.36)	0.17
Emergency room visit	16 (32)	32 (32)	0.95 (0.45–2.0)	0.89	–	–	–	–	–	–	–	–
Unscheduled hospitalization	10 (20)	21 (21)	0.92 (0.39–2.2)	0.84	–	–	–	–	–	–	–	–

OR represent the risk of toxicity in IMPT patients compared to IMRT patients. OR was not calculated for G-tube presence at one year post treatment because no patient was present in the IMPT group, but a *p*-value was calculated using a chi-2 Fisher exact test.
Abbreviations: CI, confidence interval; ND, not determined; OR, odds ratio; RT, radiotherapy.

clinicians [33]. It might be argued that the use of feeding tube might have been discouraged in IMPT patients, but this would have likely translated into increased weight loss, which was not observed. Also, even though the placement of a feeding tube might be physician-biased, feeding tube dependency in the long run, at 3 months and 1 year, is a strong surrogate for chronic swallowing dysfunction and/or functional limitations on taste and saliva production with negative implications for quality of life [32,34]. Reducing these late side effects is an important goal, especially given the high survival rates observed in patients with HPV-positive disease.

The second limitation is the absence of matching on age. Because increasing age is known to be associated with increasing acute and late toxicity [35,36], and especially feeding tube dependence, toxicity analyses were all age-adjusted. However, the IMPT patients were significantly older than their IMRT counterparts, most likely because approval of IMPT for older patient is easier because they are covered by Medicare. This age difference should favor IMRT patients in terms of toxicity and, notably, late feeding tubes. In our group, age above 60 years was found to be associated only with increased patient-reported xerostomia level at 3 months and at 1 year after treatment. Nevertheless, although patients were matched on several factors, the presence of unmeasured confounding factors or selection bias cannot be ruled out. This study remains hypothesis-generating and needs prospective independent validation.

Several outcomes of interest that might differ between treatment groups, either subjective or objective, such as osteoradionecrosis, late mucosal or neuromuscular toxicity, or acute nausea, could not be collected rigorously from the IMRT group or because of the relatively short follow-up time of this study, and have not been analyzed. Other important items, such as full patient-reported outcomes or utility metrics, would be of interest, and some have been collected from the IMPT group but unfortunately were not available from the IMRT group.

One major unanswered question relates to the selection of patients for proton therapy. We anticipate, based on predicted toxicity, that some subgroup of patients will have improved swallowing and salivary function with IMPT compared with IMRT [34,37,38]. The present study does not provide insight into this issue of patient selection, but rather suggests that differences in toxicity pattern can be detected in a non-selected OPC patient population. The allocation of this scarce and expensive resource based on expected patient benefit is a reasonable option that will, however, require prospective validation.

Indeed, in the current context of debate about the costs associated with technology improvements in radiation oncology, and especially the cost of proton therapy, this report sheds new light on the potential value of IMPT for treating OPC. Although the delivery of proton therapy is about two to three times more expensive than the delivery of IMRT [39,40], reducing treatment toxicity in the acute, subacute, and chronic phases is a major goal for patients with OPC that could lead to increased quality of life, improved job return, and decreased healthcare utilization if costs are considered over the entire disease cycle [39]. Value is defined as the outcomes that matter most to the patients divided by the cost of care [41]. Evaluating value therefore requires an investigation of which outcomes matter to patients. Late dysphagia has been found to be a major correlate of decreased quality of life [42], and before and after treatment patients prioritize swallowing abilities among other functional outcomes [43]. Scientific literature about patient preferences in head and neck oncology is scarce outside of larynx preservation [44] but when asked about their preferences, head and neck cancer patients ultimately prioritize survival over quality of life [45]. It might be hypothesized, although this remains to be proven, that the reduction of subacute and chronic side effects observed after IMPT could reduce some of the costs associated with the delivery of this advanced technique [39].

Designing a comparative study of IMPT versus IMRT for head and neck cancer is challenging. It is widely accepted that patient-reported outcomes should be the measure of interest [46,47], but no set of such outcomes is currently accepted as standard by the medical community for head and neck cancer patients, although several tools have been developed for this purpose. Also, clinically meaningful differences in patient-reported outcomes for remains to be evaluated. As no literature is available on such outcomes for head and neck patients treated with proton therapy, no statistical hypothesis or sample size calculation is feasible. In this context, our study suggests that the chronic presence of a feeding tube or a significant weight loss from baseline is a reasonable composite study endpoint that could be meaningful both for patients and physicians. The systematic collection of patient-reported outcomes and objective radiographic swallowing data (via modified barium swallow studies) at baseline, during treatment, and at follow-up as secondary endpoints would then provide the basis for evaluating patient-reported differences between these two treatments and the basis for evaluating the value of IMPT.

In conclusion, this case-matched analysis of patients with OPC treated with either IMPT or IMRT suggests, although additional

follow-up and patients are needed, that IMPT provides similar tumor control and lower rates of subacute and late swallowing-related morbidity than IMRT, as measured by the rate of feeding tube dependency and/or severe weight loss. Given their potential consequences in terms of treatment selection, it is essential that our findings be replicated through prospective multicenter trials, ideally prospective such as the ongoing phase 2–3 randomized trial NCT01893307, or by using a model based approach, as advocated in Europe, and incorporate cost-effectiveness analysis as well as patient-reported outcomes.

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Conflict of interest

The author declare no conflicts of interest regarding the topic under consideration.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.radonc.2016.05.022.

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