INTERNATIONAL JOURNAL of PARTICLE THERAPY

Predicted Secondary Malignancies following Proton versus Photon Radiation for Oropharyngeal Cancers

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Abstract

Purpose: There has been a recent epidemic of human papillomavirus (HPV)–positive oropharyngeal cancer, accounting for 70% to 80% of diagnosed cases. These patients have an overall favorable prognosis and are typically treated with a combination of surgery, chemotherapy, and radiation. Because these patients live longer, they are at risk of secondary malignant neoplasms (SMNs) associated with radiation therapy. Therefore, we assessed the predicted risk of SMNs after adjuvant radiation therapy with intensity-modulated proton therapy (IMPT) compared with intensity modulated photon radiation therapy (IMRT) in patients with HPV- positive oropharyngeal cancers after complete resection.

Materials and Methods: Thirteen consecutive patients with HPV-positive oropharyngeal cancers treated with postoperative radiation alone were selected. All patients were treated with pencil beam scanning IMPT to a total dose of 60 Gy in 2 Gy fractions. The IMRT plans were generated for clinical backup and were used for comparative purposes. The SMN risk was calculated based on an organ equivalent dose model for the linear-exponential dose-response curve.

Results: Median age of the patient cohort was 63 years (range, 47-73 years). There was no difference in target coverage between IMPT and IMRT plans. We noted significant reductions in mean mandible, contralateral parotid, lung and skin organ equivalent doses with IMPT compared with IMRT plans ($P < .001$). Additionally, a significant decrease in the risk of SMNs with IMPT was observed for all the evaluated organs. Per our analysis, for patients with oropharyngeal cancers diagnosed at a national median age of 54 years with an average life expectancy of 27 years (per national Social Security data), 4 excess SMNs per 100 patients could be avoided by treating them with IMPT versus IMRT.

Conclusions: Treatment with IMPT can achieve comparable target dose coverage while significantly reducing the dose to healthy organs, which can lead to fewer predicted SMNs compared with IMRT.

Keywords: secondary malignancies; radiation therapy; protons; HPV-positive; oropharyngeal cancer

Submitted 05 Nov 2019
Accepted 03 Feb 2020
Published 22 April 2020

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Original Article

DOI
10.14338/IJPT-19-00076.1

http://theijpt.org

Introduction

The general trends in the epidemiology of head and neck cancers in United States have dramatically changed in the recent decades [1]. In particular, there has been a recent epidemic of human papillomavirus (HPV)–positive oropharyngeal cancer, accounting for 70-80% of diagnosed cases [2]. The HPV-positive oropharyngeal cancers have unique demographic, behavioral, and clinical characteristics. Unlike most head and neck cancers, they tend to occur in young- to middle-aged, white men (40-59 years) of higher socioeconomic status, who are typically nonsmokers and nondrinkers [3]. They are managed with a multimodality treatment approach comprising surgery, radiation and chemotherapy and have significantly better overall survival and failure-free survival compared with HPV- negative oropharyngeal cancers as well as cancers arising in other head and neck subsites [4].

Given their favorable prognosis and typical absence of high risk lifestyle behaviors (tobacco, alcohol), these patients live longer and are at an increased risk of secondary malignant neoplasms (SMNs) related to their initial cancer treatment. Radiation-induced SMNs typically occur in tissues adjacent to the target tumor volume but may also be associated with exposure to low doses of scatter and leakage radiation outside of the primary treatment field [5].

Intensity-modulated proton therapy (IMPT) has a particular advantage in this regard by sparing dose to the surrounding healthy tissues with its characteristic Bragg peak and steep dose fall-off [6]. Reduction of late toxicities, including SMNs, can, hence, improve the overall therapeutic benefit associated with IMPT [7, 8].

In this study, we evaluate the predicted excess absolute risk of SMNs after adjuvant radiation with IMPT compared with intensity modulated photon radiation therapy (IMRT) for patients with HPV-positive oropharyngeal cancer with an organ equivalent dose (OED) model for the linear-exponential dose-response curve. We hypothesized that by reducing radiation dose to healthy structures, IMPT would reduce the risk of SMNs compared with IMRT in this patient population.

Materials and Methods

This study was approved by our institutional review board (No. 829031); 13 consecutive patients with AJCC 7th edition [9] stage III-IVA HPV- positive oropharyngeal cancers were selected under a waiver of informed consent. All patients were treated with transoral robotic surgery and selective neck dissection, followed by adjuvant radiation with IMPT to a dose of 60 Gy in 2-Gy fractions. Patients were excluded if they had indications for or had received adjuvant chemotherapy (positive margins, extracapsular extension), or had T3 or greater disease. Additionally, patients with bilateral nodal involvement (N2 and greater) were excluded. The patients were treated to 2 dose levels in 30 fractions using a dose-painting technique; 60 Gy in 2 Gy fractions to the postoperative tumor bed and high-risk neck nodes (typically ipsilateral), and 54 Gy in 1.8-Gy fractions to the low-risk neck nodes (typically contralateral). Demographic and treatment data were obtained from retrospective chart review. Additionally, 2-year local control, distant metastasis–free survival and overall survival were calculated for the patient cohort.

Treatment Planning

Healthy structures, representing organs at risk (OARs), were contoured for all patients. The definitions of treatment volume followed previously published guidelines [10]. All patients received treatment to the primary site and bilateral neck, with a standard postoperative dose and fractionation of a 60-Gy radiobiologic equivalent dose in 30 fractions [11, 12]. Proton beam therapy was planned and delivered via pencil beam scanning (PBS).

Clinically acceptable IMRT backup plans were generated for each patient at the time of treatment in case of IMPT downtime and were used for comparative purposes in the study. The same OARs and target constraints were used for the IMPT and IMRT plans. The constraints used are listed in Table 1. Finally, dose volume histograms of the planning target volume (PTV) and OARs were generated for IMPT and IMRT plans. Dosimetric data for all structures were extracted from Eclipse (Eclipse Foundation, Ottawa, Ontario, Canada), with a differential dose-volume histogram (DVH) data exported into MATLAB (MathWorks Inc, Natick, Massachusetts) for analysis.

Secondary Malignancy Calculation

Excess absolute risks of SMNs for IMRT and IMPT plans were calculated per previously reported models of organ-specific, radiation-induced cancer incidence based on the OED, as described by Schneider et al [13]. Additionally, the relative risk of SMNs was calculated as a ratio of the predicted SMNs with IMRT to IMPT.

Table 1. Planning constraints for intensity-modulated proton beam therapy (IMPT) and backup intensity-modulated photon radiation therapy (IMRT) plans.

Structure	Plan constraint
PTV	V95% = 100%
Mandible, PTV	Maximum < 60 Gy
Constrictors, PTV	Mean < 40 Gy
Esophagus, PTV	Mean < 20 Gy or ALARA
Larynx, PTV	Mean < 20 Gy or ALARA
Oral cavity, PTV	Mean < 20 Gy or ALARA
Lips - PTV	Mean < 20 Gy or ALARA
Parotid, contralateral	Mean < 20 Gy
Parotid, ipsilateral	Mean < 26 Gy

Abbreviations: PTV, planning target volume; ALARA, as low as reasonably achievable.

Differential DVHs were extracted in 0.01-Gy dose bins for each organ of interest to calculate the OED for each organ. The OED used here was defined by Schneider et al [13] as follows:

$$\text{OED} = \frac{1}{V}\sum_i DVH(D_i)D_i e^{-\alpha D_i}, \quad (1)$$

where V represents the total organ volume, D_i represents the dose of bin i, $DVH(D_i)$ is the volume receiving dose D_i, and α is a model-fitting parameter. Because of the inferior extent of the computed tomography scan not including the entire lungs, an average male and female lung volume was used. Based on the data presented by Schneider et al [13] for combined Hodgkin and atomic bomb survivor data, an α of 0.044 Gy^{-1} was chosen. The excess risk to each organ is presented in Vogel et al [14] as follows:

$$I^{org} = I_0^{org} De^{-\alpha D} = I_0^{org}\text{OED}^{org}, \quad (2)$$

where I_0^{org} is the organ-specific cancer incidence rate per 10 000 patients/y/Gy, as adapted from Dores et al [15] .

Specific organs assessed included the mandible, lung, parotids, trachea, larynx, esophagus, and skin. Additionally, a total in-field predicted risk of radiation-induced SMNs was calculated encompassing the above organs as well as including the irradiation within the body not solely limited to those organs.

Statistical Analysis

Statistical analysis was performed with a paired sampled t test for pairwise comparisons. A $P < .05$ was considered statistically significant. All statistical analysis was performed in MATLAB (version 2018a).

Results

The median age of the patient cohort was 63 years (range, 47-73 years), and 11 patients (85%) were men. Most patients had AJCC 7th edition [9] stage IVA disease (11 of 13; 85%) (Table 2). Two-year local control, distant metastasis–free survival, and overall survival were 92%, 100%, and 100%, respectively.

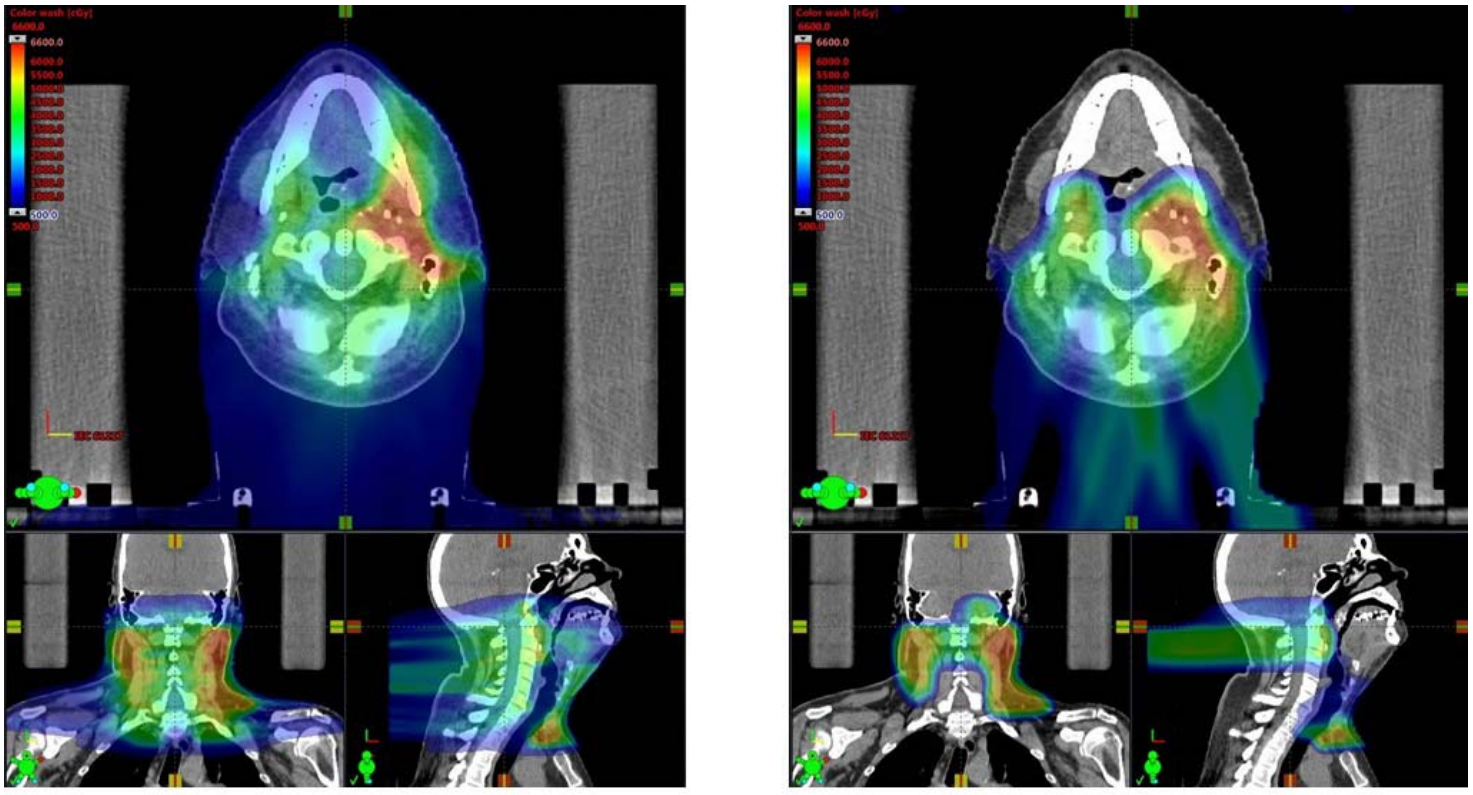
There was no statistically significant difference in target coverage between IMPT and IMRT plans ($P > .5$). We noted significant reduction in the dose to the OARs with IMPT compared with the IMRT plans (Figure 1). For example, the mean dose to the mandible, contralateral parotid, and lung with IMPT plans was 11.2, 12.2, and 2.2 Gy, respectively, compared with IMRT plan mean doses of 28.1, 16.9, and 5.8 Gy, respectively ($P < .001$) (Table 3).

Additionally, a decrease in both the excess absolute risk as well as relative risk of SMNs with IMPT was observed for all evaluated organs. The highest relative risk of SMNs was observed for the lung (relative risk, 12.8; 95% CI, 2.48-23.1), and the highest absolute excess risk was observed for the skin (absolute risk, 1.97; 95% CI, 1.81-2.12). In total, 16.2 excess cases of SMNs per 10 000 patients/y were predicted for treatment with IMRT compared with IMPT (Table 4).

Per our analysis, for patients with oropharyngeal cancers diagnosed at a national median age of 57 years [19] with an average life expectancy of 27 years (per national Social Security data), 436 excess SMNs per 10 000 patients/y could be avoided by treating them with IMPT versus IMRT. The median age of our patient cohort was 63 years, slightly older than the

Table 2. Patient characteristics.

Characteristics	Data
Age at diagnosis, y, median (range)	63 (47–73)
Gender, No. (%)	
Male	11 (85)
Female	2 (15)
Stage (AJCC 7th edition), No. (%)	
T1	4 (31)
T2	9 (69)
N1	2 (15)
N2a	4 (31)
N2b	7 (54)
III	2 (15)
IVA	11 (85)
Smoking history, No. (%)	
Never	8 (62)
$<$ 10 pack-yrs	3 (23)
$\geq$ 10 pack-yrs	2 (15)
Radiation dose, Gy	60



(a) (b)

Figure 1. Representative example of (a) intensity modulated radiation therapy and (b) pencil beam proton beam therapy plans for a patient treated with adjuvant radiation for human papillomavirus–positive oropharyngeal cancer.

Table 3. Dose statistics for organs at risk of interest for intensity-modulated proton beam therapy (IMPT) and intensity-modulated photon radiation therapy (IMRT) treatments.

	PBT			IMRT			
Organ	Average	Range	SD	Average	Range	SD	*P* value
Esophagus maximum, Gy	51.9	35.5-62.7	8.8	53.2	41.7-63.1	5.2	.39
Esophagus mean, Gy	12.1	5.0-24.9	6.1	14.9	8.2-22.4	4.7	.07
Larynx maximum, Gy	61.5	55.6-63.7	2.2	61.9	56.2-66.0	3.0	.37
Larynx mean, Gy	21.9	15.2-30.1	4.7	23.3	18.5-33.1	4.1	.29
Mandible maximum, Gy	60.5	56.7-63.2	1.6	61.0	57.0-65.5	2.4	.48
Mandible mean, Gy	11.2	5.3-21.1	4.8	28.1	17.7-37.2	4.5	< .001
Ipsilateral parotid maximum, Gy	63.6	61.5-66.1	1.2	64.2	62.7-65.8	0.9	.07
Ipsilateral parotid mean, Gy	25.1	16.9-42.2	6.8	25.5	19.4-38.7	5.5	.72
Contralateral parotid maximum, Gy	57.7	54.8-62.9	2.2	57.9	55.6-60.2	1.4	.79
Contralateral parotid mean, Gy	12.2	4.3-18.8	3.7	16.9	10.6-22.5	2.9	< .001
Skin maximum, Gy	64.4	62.8-66.0	0.9	63.7	61.2-65.5	1.0	.16
Skin mean, Gy	7.1	4.5-10.9	1.8	11.9	8.5-20.3	3.7	.002
Trachea maximum, Gy	56.3	47.9-62.8	5.7	57.6	45.6-63.2	4.9	.44
Trachea mean, Gy	20.3	10.5-36.2	7.6	20.3	12.0-37.1	6.2	.98
Lung mean, Gy	2.2	0.04-6.7	2.1	5.8	2.4-18.2	3.6	< .001
Lung V20 Gy, %	4.2	0.0-13.7	4.5	9.5	1.9-44.0	9.1	< .001
Lung V5 Gy, %	8.0	0.1-18.9	6.4	24.0	7.9-77.3	16.0	< .001

Abbreviations: V, volume.

literature reported median age. Per the Social Security life-expectancy tables, these more-elderly patients are expected to live 22 additional years. This corresponds to 358 excess SMNs per 10 000 patients/y for patients' treatment with IMRT versus IMPT.

Discussion

We demonstrate that, for patients with HPV-positive oropharyngeal cancer, the predicted risk of SMNs is significantly reduced statistically for treatment with IMPT compared with IMRT. Although both modalities afforded good target coverage, IMPT plans were able to achieve improved healthy-tissue sparing. This reduction in integral dose led to a predicted decrease of 436 additional cases of SMNs for every 10 000 patients/y (or 4 per 100 patients/y) for treatment with protons instead of photons.

In this study, we evaluated patients with HPV-positive oropharyngeal cancers; all of whom would be categorized as early stage (stage 1) under AJCC 8th edition [17] staging system. Additionally, all but 2, of these patients (11 of 13; 85%) who had $\geq$ 10 pack-year smoking history, would be categorized as "low risk" per the Radiation Therapy Oncology Group phase 3 trial (RTOG 0129) with a projected 3-year overall survival of 93% [19]. This overall favorable prognosis as well as the low prevalence of exposure to tobacco/alcohol underscores the importance of reducing treatment-related toxicity in this population. The benefit of protons in reducing acute and chronic treatment-related toxicities and patient-related quality-of-life measures has been demonstrated in several institutional case series [16, 18]. The demonstrated reduction in the risk of SMNs is an additional advantage of protons. However, this benefit is age dependent, with a greater decrease in risk observed for younger

Table 4. Predicted risk of secondary malignant neoplasms per 10 000 patients/y.

Modality	Mandible	Lung	Parotid	Trachea	Larynx	Esophagus	Skin	In field total
IMPT	0.95	0.13	2.18	1.4	2.00	2.21	1.25	26.7
IMRT	2.16	0.92	3.17	1.77	2.34	3.19	3.22	42.9
Excess absolute	1.20	0.79	0.98	0.37	0.34	0.98	1.97	16.2
95% CI	1.06-1.34	0.16-1.42	0.85-1.11	0.31-0.42	0.25-0.43	0.81-1.15	1.81-2.12	14.7-17.6
Relative risk	2.39	12.8	1.48	1.28	1.18	1.48	2.65	1.62
95% CI	2.04-2.73	2.48-23.1	1.37-1.59	1.21-1.23	1.12-1.23	1.26-1.59	2.42-2.88	1.53-1.71

Abbreviations: IMPT, intensity-modulated proton beam therapy; IMRT, intensity-modulated photon radiation therapy.

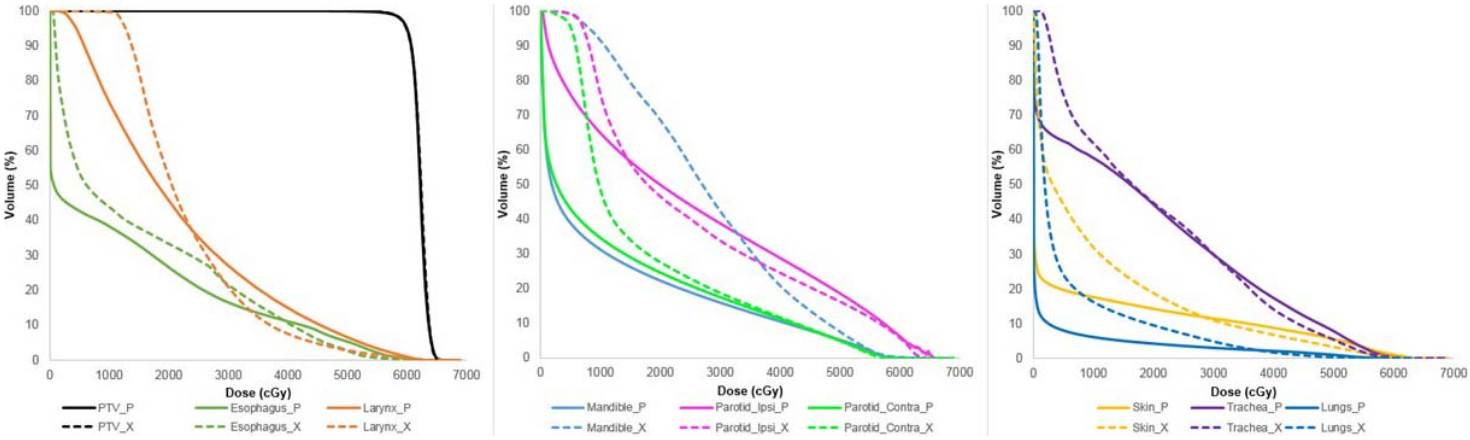


Figure 2. Mean dose-volume histogram of intensity-modulated proton beam therapy (IMPT) and intensity-modulated photon radiation therapy (IMRT) plans. Doses to organs at risk were averaged across all patients.

patients, which should be factored into determining the cost effectiveness of the treatment modality. Improvement in toxicity cost coupled with the benefit of reduction in SMNs with protons, can further improve the cost effectiveness of IMPT, offer higher-quality adjusted life years, and improve the overall therapeutic ratio of this modality.

In our analysis, the largest absolute decrease in the risk burden of SMNs was observed for skin, with a predicted absolute decrease of 1.97 cases per 10,000 patients/y. This is likely secondary to the low-dose photon bath in the volumetric arc therapy/IMRT plans and, hence, a greater predicted risk of secondary malignancies.

Several studies have indirectly addressed the issue of secondary malignancies in patients with HPV-positive oropharyngeal cancer [20–22]. Morris et al [20] conducted a population-based cohort study evaluating the risk of secondary malignancies in patients with primary head and neck squamous cell carcinomas. They found that the risk of SMNs among the head and neck sites was the highest for hypopharyngeal cancers and lowest for laryngeal cancers. Additionally, they noted that the pattern of SMNs varied based on the location, for example, the most common site for oral cavity and oropharyngeal cancers was head and neck, whereas, for patients with laryngeal and hypopharyngeal cancers, the lung was more common. Although the information about the HPV status was lacking in that analysis, they noted an overall decline in the risk of SMNs from oropharyngeal cancers likely because of the lack of high-risk behaviors and field cancerization. Other work by Thiagarajan and Iyer [23] has explored the incidence of radiation-induced sarcomas in long-term survivors of head and neck cancers. In contrast to the above study, radiation-induced sarcomas do not exhibit any subsite predilection and were found to arise in any irradiated tissue of mesenchymal origin.

Data evaluating the risk of SMNs between protons and IMRT in patients with head and neck cancers are sparse. Yoon et al [24] calculated the secondary dose delivered to tissues outside the specified target volume in phantom models with ion chambers and CR-39 detectors during IMRT and proton radiation for head and neck cancers. They then calculated the organ-specific radiation-induced SMN risk by applying an organ equivalent model, similar to our analysis; however, they evaluated only 3 organs: stomach, lung, and thyroid. They found that the average OEDs were, in general, higher for IMRT than they were for protons. Additionally, their results suggested that the estimated SMN risk using the scattering mode for proton therapy was, on average, less (although not statistically significant) and did not exceed that of conventional IMRT. Additionally, PBS proton beam therapy, which was used in this analysis, is hypothesized to further reduce the risk of secondary malignancies because the out-of-field neutron dose produced by a scanned proton beam is estimated to be $>$ 100 times less than that generated by a scattered proton beam [25].

Our study has several limitations. Given the few patients, the conclusions drawn are hypothesis generating and require validation with a larger cohort with long-term clinical follow-up. The SMN risk calculation is based on the OED model, which is based on secondary malignancies in patients with Hodgkin disease treated with radiation therapy [13]. However, dose reconstruction in that model is limited by older treatment-planning systems with reduced accuracy. Additionally, the influence of chemotherapy, as well as that of genetic susceptibility, is not accounted for in this model. However, we have applied this model for relative comparison between different treatment techniques for radiation, and such unknown factors should apply in a similar manner to both evaluated treatment modalities. Another possible source of uncertainty is the unknown shape of the dose-response relationship. In this model, linear, linear-exponential, and plateau models were used. The real dose-response

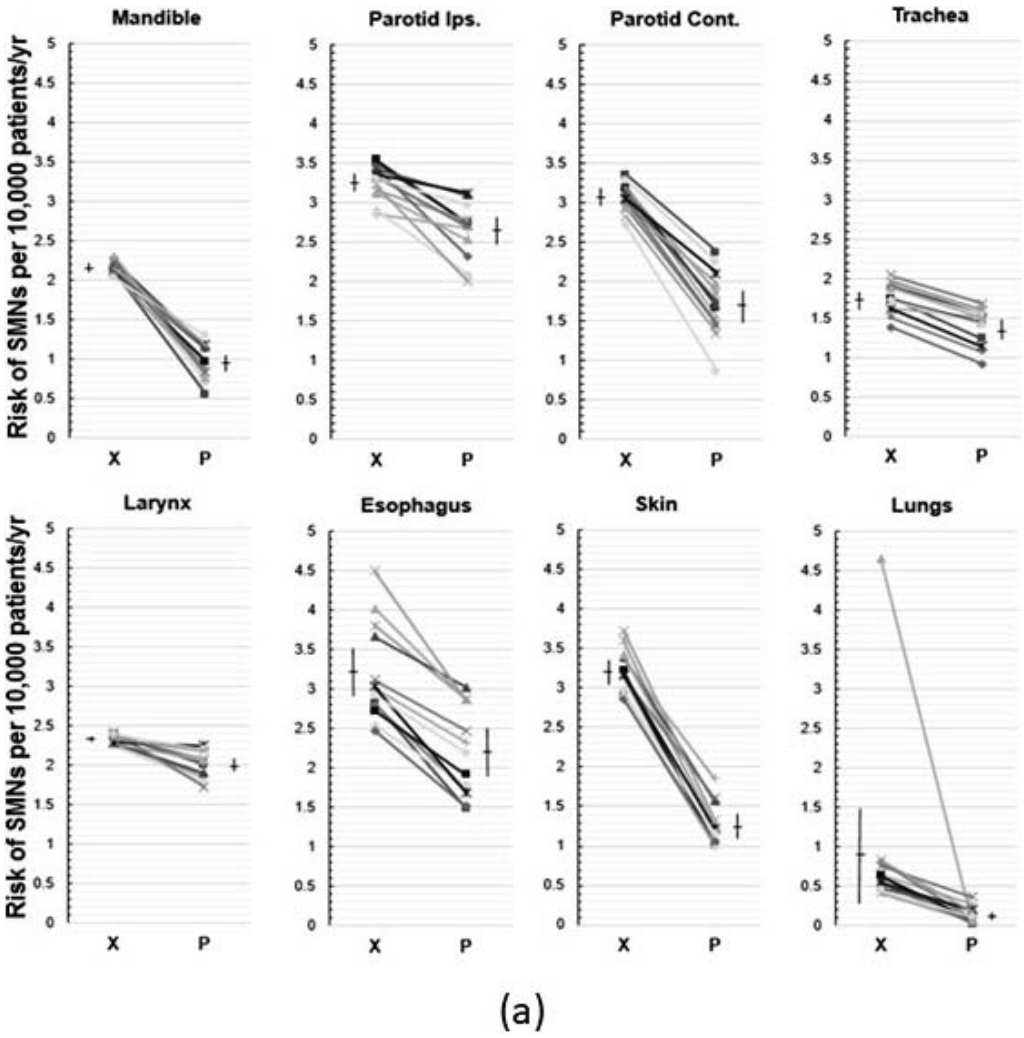


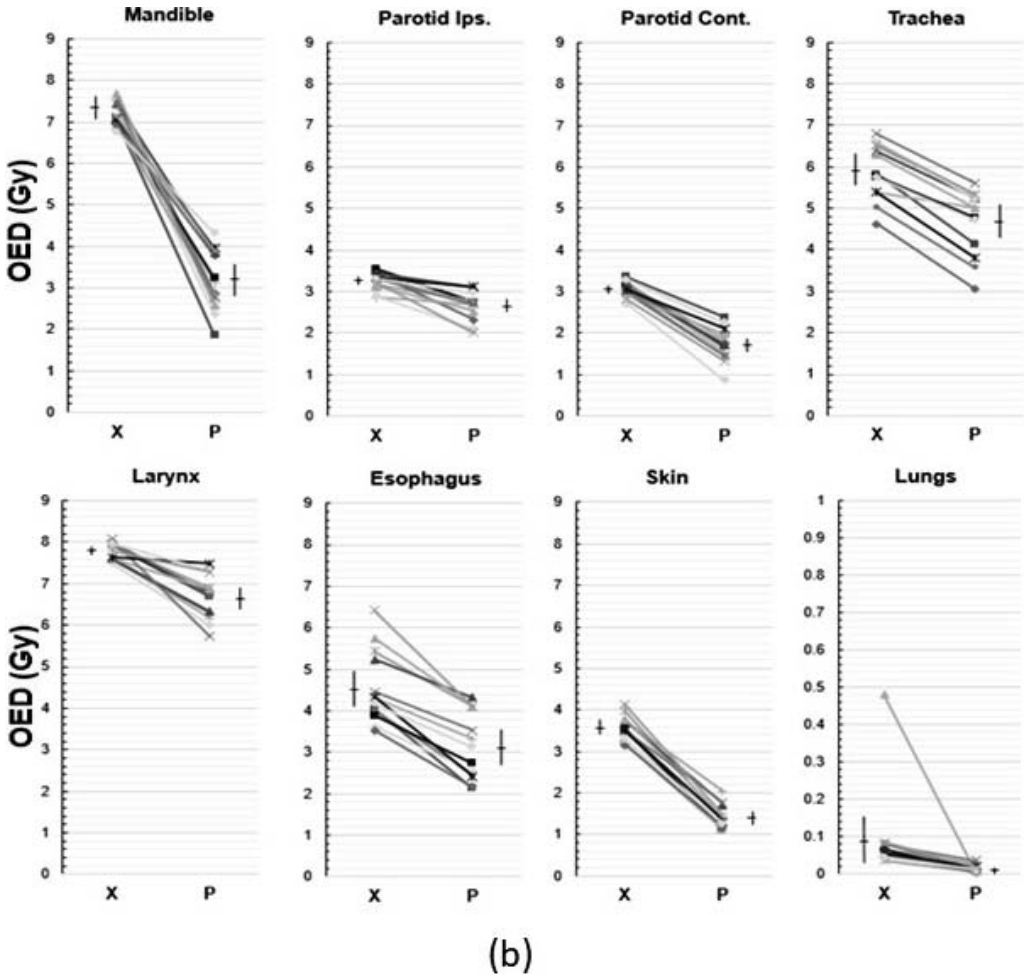
Figure 3. Excess risk of secondary malignant neoplasms per 10 000 patients/y (a) and organ equivalent dose (b) calculated using photon (X) and proton (P) plans for 13 patients with head and neck cancer. Black bars represent mean (horizontal) and 95% CI (vertical).

curve for cancer induction is expected to lie between linear and linear-exponential models. However, previous work by Schneider et al [26] suggests that the difference in OED between linear-exponential and plateau models is $< 10\%$.

Proton relative biological effectiveness (RBE) has been studied extensively in vitro, accompanied by a few in vivo studies, and most of that work was compiled in the American Association of Physicists in Medicine (AAPM) task group 256 recommendations [27]. To date, clinical practice has been to assume a constant RBE of 1.1 across the range of the proton, and all modern clinical treatment planning systems report proton dose as Gy (RBE), accounting for the RBE adjustment. The AAPM recommends that, with the current understanding of proton RBE, that practice should be maintained. Additionally, the proton RBE deviations from 1.1 occur at the end of the proton track where the linear energy transfer is greatest. In appropriately designed and well-optimized plans, any elevated RBE should occur in the target or at the target periphery, and the RBE outside the target should average to 1.1. With the use of Gy (RBE) results in the model here and the lack of literature showing clinical evidence of differences in endpoints between photons and protons for SMNs, we don't expect the proton RBE to add additional uncertainties. We do acknowledge, however, that we are unable to quantify any variations in RBE from 1.1, which may introduce some uncertainty in structures located close to targets. The models we used in this study were derived from studies using the Japanese bomb-survivor data combined with radiotherapy patients (patients with Hodgkin lymphoma) who received doses up to 40 Gy [13, 15]. These were patients who received photon radiotherapy, so there are some uncertainties when applying these models to a proton radiotherapy cohort. However, this has been done in previous studies [14].

Another limitation of this study is the neglect of the effect of the secondary neutron dose received by the patients. Effective dose from neutrons is not accounted for in any commercial treatment-planning system and is not accounted for in the data used for the secondary malignancy calculation here. The estimation of the secondary neutron effective dose present for proton

Figure 3. Continued.



therapy treatments has been attempted via Monte Carlo simulations, with a few validation measurements, by other groups [25, 28–34]. Furthermore, only a few studies specifically evaluated the neutron effective dose from PBS systems [33, 34]. These simulations and measurements carry a large uncertainty, with Schneider et al [34] estimating a 50% uncertainty in both measurements and simulations. That uncertainty, in addition to the different characteristics of the 85-145 MeV PBS system in Tessa et al [33] and the 177-MeV PBS system in Schneider et al [34], lead to more than an order of magnitude difference in the effective neutron dose at a distance from the field edge reported between the 2 groups. Zacharatou Jarlskog and Paganetti [35] compiled a review of the literature comparing out-of-field neutron dose between IMRT photon, passive-scattering, and PBS treatments showing a difference of about 2 orders of magnitude across all studies. In the context of the patients examined in this study, each was treated with a 230-MeV PBS system, making an accurate comparison to the neutron effective dose in other studies challenging without a full characterization of the ambient neutron dose for the specific system in question.

In summary, we demonstrate that treatment with IMPT can achieve comparable target dose coverage and significantly reduce the dose to healthy organs, which can lead to fewer predicted SMNs compared with IMRT.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts of interest to disclose.
Ethical Approval: All patient data were collected under internal review board–approved protocol.

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