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Osteradionecrosis

Intensity-modulated proton therapy and osteoradionecrosis in oropharyngeal cancer

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ABSTRACT

Purpose: We compared mandibular doses and osteoradionecrosis in patients with oropharyngeal cancer after intensity-modulated radiation therapy (IMRT) or intensity-modulated proton therapy (IMPT).
Methods and materials: We identified 584 patients who received definitive radiotherapy for oropharyngeal cancer from January 2011 through June 2014 at MD Anderson Cancer Center (534 IMRT and 50 IMPT). The dosimetric variables and osteoradionecrosis were compared with Chi-square test or Fisher's exact test.
Results: Median follow-up time for all patients (534 IMRT and IMPT) was 33.8 months (33.8 months IMRT vs. 34.6 months IMPT, $P = 0.854$), and median time to osteoradionecrosis was 11.4 months (range 6.74–16.1 months). Mandibular doses were lower for patients treated with IMPT (minimum 0.8 vs. 7.3 Gy; mean 25.6 vs. 41.2 Gy; $P < 0.001$), and osteoradionecrosis rates were lower as well: 2% IMPT (1 grade 1), 7.7% IMRT (12 grade 4, 5 grade 3, 1 grade 2 and 23 grade 1). Osteoradionecrosis location depended on the primary tumor site and high-dose field in the mandible.
Conclusions: Osteoradionecrosis events were significantly associated with higher dose irradiation to mandibular. Use of IMPT minimized excess irradiation of the mandible and consequently reduced the risk of osteoradionecrosis for oropharyngeal cancer.
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Radiotherapy combined with chemotherapy is the mainstay of treatment for head and neck cancer. Although radiotherapy can increase cure rates, it does carry the risk of secondary effects and potential orofacial complications. Osteoradionecrosis is one of the most feared complications of head and neck radiotherapy, as it can significantly affect quality of life [1]. Preventing or reducing the risk of osteoradionecrosis resulting from definitive radiotherapy for head and neck cancer can be a considerable challenge, especially for tumors such as oral or oropharyngeal carcinoma that are close to the mandible. Risk factors for osteoradionecrosis include radiation dose and mandibular volume exposed, dental extraction after radiation, radiotherapy technique, and chemotherapy [2,3], The risk of osteoradionecrosis increases with radiation dose [4], and higher total doses, short regimens using high doses per fraction, large field sizes, and the delivery of radiotherapy through a single field are all associated with increased risk of osteoradionecrosis [4–6]. In the era of 2-dimensional (2D) radiotherapy, osteoradionecrosis rates ranged from 5% to 20% [7,8]. Recent advances in the delivery of photon radiotherapy such as 3D conformal radiotherapy (3D CRT) or intensity-modulated radiotherapy (IMRT) have reduced the risk of osteoradionecrosis [9,10].

In contrast to photon therapy, proton therapy allows energy to be deposited at a specific depth within tissues (the Bragg peak), with rapid energy falloff beyond that point. Use of intensity-modulated proton therapy (IMPT) theoretically allows delivery of highly conformal and homogeneous dose distributions to the target while simultaneously sparing adjacent organs at risk to a greater degree than is possible with IMRT [11–14], suggesting that IMPT may have a more favorable toxicity profile. Although some evidence exists to suggest that IMPT can reduce the rates and severity of acute mucositis, dysphagia, and xerostomia in head and neck cancer [15,16], to date no direct comparisons have been made of the dosimetric characteristics of IMRT and IMPT in terms

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of mandibular irradiation and subsequent osteoradionecrosis. To our knowledge, this is the first report of such a comparison of the late complication between proton and photon.

Methods and materials

Patient selection

This retrospective analysis was approved by the appropriate institutional review board. We respectively identified patients who had received radiotherapy as part of definitive therapy for oropharyngeal cancer between January 2011 and June 2014 at The University of Texas MD Anderson Cancer Center. Exclusion criteria included a history of radiotherapy to the head and neck region, or (cured) primary tumor at any other site. We identified 534 patients who had received definitive IMRT and 50 patients who had received definitive IMPT, and extracted information on their demographics, disease stage, and treatment modality from the medical records.

Radiation treatment dental evaluation

All patients underwent computed tomography (CT) for treatment planning and simulation purposes, with customized thermoplastic masks and bite blocks used for immobilization. Treatments to be delivered as IMRT were planned with a Pinnacle system (version 6.2b or later, Philips Medical Systems), and radiation was delivered as 6-MV photons generated by a linear accelerator (Varian Medical Systems, Palo Alto, CA) with a multileaf collimator in a step-and-shoot, multiple static beam arrangement [17]. Treatments for IMPT were planned with an Eclipse system (also from Varian Medical Systems) and involved multifield optimization. The relative biological effectiveness (RBE) value for protons was assumed to be 1.1.

Delineation of target volumes and treatment doses were as described previously [16]. Briefly, organs at risk, including brain, brainstem, spinal cord, cochleas, salivary glands, oral cavity, larynx, mandible, had specified dose constraints and were contoured for treatment planning. The delineation of planning target volumes (PTVs) for patients who received IMPT was similar to that for IMRT-treated patients. For patients receiving concurrent chemoradiation, the prescribed dose to the tumor (clinical target volume, CTV1) was 70 Gy in 33 fractions of 2.12 Gy per fraction; dose to the CTV2 was 63 Gy in 1.9-Gy fractions; and the dose to the CTV3 was 57 Gy in 1.7-Gy fractions. For patients who received only radiotherapy, the prescribed dose to the CTV1 was 66 Gy in 30 fractions of 2.2 Gy each; to the CTV2, 60 Gy in 2.0-Gy fractions; and to the CTV3, 54 Gy in 1.8-Gy fractions.

All patients underwent a comprehensive dental evaluation by a dental oncologist before radiation therapy was begun [4]. Patients with poor dentition underwent preradiation dental extraction, with close attention paid to the posterior mandible. Dental records were reviewed, and patients grouped in one of two categories: normal dentition without treatment at baseline, or dental extraction or edentulous at baseline.

Definition of osteoradionecrosis

Osteoradionecrosis was defined as slow-healing radiation-induced ischemic necrosis of bone with associated soft tissue necrosis, in the absence of local primary tumor necrosis, recurrence, or metastatic disease [6], with bone exposed through the skin or mucosa persisting for more than 3 months [18]. The Common Terminology Criteria for Adverse Events v4.0 and Tsai et al. [4] grade the severity of osteoradionecrosis as follows: grade 1, minimal bone exposure with conservative management only, or diagnostic abnormality without medical intervention; grade 2, minor debridement received; grade 3, hyperbaric oxygen needed; grade 4, major surgery required.

Follow-up

Follow-up visits were to take place at 1 month after completing radiotherapy, then every 3 months during the first year, every 4–6 months during the following 2 years, and then annually thereafter. Follow-up visits included dental clinic visits as needed for assessment of dentition and signs of osteoradionecrosis; at those visits, the presence or absence of bony exposure, trismus, and fistula was recorded. Positron emission tomography (PET)/CT or CT scans were obtained every 3–6 months and evaluated for evidence of osteonecrosis or recurrence of primary tumor.

Statistical analysis

Basic demographic variables, clinical disease stage, human papillomavirus status, and general treatment-related information were compared according to treatment received for all 584 patients. Categorical variables were compared with Chi-square test or Fisher's exact test (Fisher's exact test was used for Tumor location comparison in Table1), and differences in radiation dose were compared with independent sample t tests. Statistical analyses were done with Statistical Product and Service Solutions version 23 (SPSS Inc., Chicago, IL). *P* values < 0.05 were considered statistically significant.

Table 1
Patient characteristics.

Characteristic	IMRT No. (%)	IMPT No. (%)	*P* Value
Age, years			0.093
≤60	301 (56.4)	22 (44.0)	
>60	233 (43.6)	28 (56.0)	
Sex			0.621
Female	72 (13.5)	8 (16.0)	
Male	462 (86.5)	42 (84.0)	
Race			0.272
White	476 (89.1)	42 (84.0)	
Other	58 (10.9)	8 (16.0)	
Disease site			0.365
Base of tongue	260 (48.7)	21 (42.0)	
Tonsil/other	274 (51.3)	29 (58.0)	
Tumor location			0.256
Left	238 (44.6)	26 (52.0)	
Right	288 (53.9)	22 (44.0)	
Midline	2 (0.4)	1 (2.0)	
Bilateral	6 (1.1)	1 (2.0)	
T category			0.032
T1-2	347 (65.0)	40 (80.0)	
T3-4	187 (35.0)	10 (20.0)	
N category			0.622
N0-1	92 (17.2)	10 (20.0)	
N2-3	442 (82.8)	40 (80.0)	
HPV status			0.635
Positive	364 (68.2)	35 (70.0)	
Negative	75 (14.0)	4 (8.0)	
Equivocal	18 (3.4)	2 (4.0)	
Not detected	77 (14.4)	9 (18.0)	
Induction CT			0.930
Yes	217 (40.6)	20 (40.0)	
No	317 (59.4)	30 (60.0)	
Concurrent CT			0.623
Yes	360 (67.4)	32 (64.0)	
No	174 (32.6)	18 (36.0)	

Abbreviations: IMRT, intensity-modulated (photon) radiotherapy; IMPT, intensity-modulated proton therapy; HPV, human papillomavirus; CT, chemotherapy.