Published in final edited form as:

Radiother Oncol. 2017 June ; 123(3): 401–405. doi:10.1016/j.radonc.2017.05.006.

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

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Conflict of interest: The authors declare no actual or potential financial conflicts of interest.

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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, and 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.

Keywords

oropharyngeal cancer; IMPT; IMRT; osteoradionecrosis; mandibular dose; particle therapy

Introduction

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 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 Table 1), 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.

Results

Patient and treatment characteristics are shown in Table 1; 534 patients had received IMRT and 50 IMPT. Most patients in both groups were men, and most were white. Characteristics were relatively well balanced between groups except that proportionately more patients in the IMPT group had T1-2 disease.

The minimum dose, mean dose, and median dose to the mandible were all lower for patients treated with IMPT (minimum dose: 0.8 Gy IMPT vs. 7.3 Gy IMRT; mean dose: 25.6 Gy IMPT vs. 41.2 Gy IMRT; $P<0.001$). The maximum dose was not different between the two groups (71.3 Gy IMPT vs. 71.7 Gy IMRT, $P=0.503$). Comparisons of the volume of mandible receiving various doses also showed that percent volumes (V5-V70) were all significantly lower in the IMPT group compared to the IMRT group as illustrated in Table 2. Figure 1 also demonstrate that osteoradionecrosis events were significantly associated with higher mandibular percent volumes in the dose volume histogram bins ranging from V35-V70 ($P<0.05$). After Bonferroni correction for multiple comparisons, V45-V70 remained significant ($P<0.003$). These findings are further illustrated on treatment plans for two patients with clinical stage T2N2bM0 left tonsil cancer in Supplementary Figure 1. The patient who received IMPT had less of the mandible exposed to both high and low doses, and the patient treated with IMRT developed osteoradionecrosis in the area exposed to >60 Gy.

Osteoradionecrosis developed in 41 of the 534 patients (7.7%) treated with IMRT therapy. The grades of osteoradionecrosis were: grade 4, 12 patient; grade 3, 5 patients; grade 3,1 patient; and grade 1, 23 patients. In contrast, only one patient in the IMPT group (2%) developed grade 1 osteoradionecrosis.

The median time to osteoradionecrosis was 11.4 months (range 6.7–16.1 months). Scans from the patient who developed osteoradionecrosis at 27.1 months after IMRT are shown in Supplementary Figure 2. By 35.1 months after IMRT, the osteoradionecrosis had resolved after hyperbaric oxygen and antibiotic therapy. In all patients who developed osteoradionecrosis, its location was related to the site of the primary tumor and the highest-dose fields within the mandible; all cases developed on the ipsilateral side of the gross tumor and in regions that received >50 Gy. We compared the mandibular doses for patients who developed osteoradionecrosis and those who did not (Table 3), and we found that that dose was higher among patients with osteoradionecrosis, whatever the high dose area or low dose area (Table 3 and Figure 1).

Discussion

To our knowledge, this is the first report of dosimetric differences between IMRT and IMPT for oropharyngeal cancer as related to risk of osteoradionecrosis. We found that use of IMPT for patients with oropharyngeal cancer led to significantly reduced doses to the mandible compared with IMRT, including mean dose, minimum dose, and V10–V70, but did not affect the maximum dose. This reduction in mandibular dose could have been related to the lower incidence and lesser severity of osteoradionecrosis among the patients treated with IMPT.

Osteoradionecrosis is a relatively uncommon but potentially devastating long-term complication of head and neck radiotherapy. Although it typically appears from 3 to 27 months after radiotherapy, the risk of osteoradionecrosis is thought to extend indefinitely after irradiation [20, 21]. Our findings on time to development (7.7 months, range 3.4–27.1 months) are similar to those of previous reports [4].

The incidence of osteoradionecrosis varies greatly from study to study, many of which have been retrospective; one estimate of overall incidence is 11.8% before 1968 and 5.4% after that [22]. In a more recent retrospective analysis of 402 patients with T1-T2 oropharyngeal cancer at MD Anderson, the overall rate of osteoradionecrosis was 7.5%, and tended to be less common after IMRT than after 3D conformal radiation therapy (6% vs. 13%) [4]. By comparison, the overall rates in our patient population 7.1% for whole groups and 7.7% for IMRT group, are consistent with previous observation. The risk of osteoradionecrosis also depends on the radiotherapy technique used, being about 5%–15% after 2D radiotherapy techniques but 6% or less after IMRT [7–10]. One comparison of 3D and IMRT approaches showed that IMRT for oral cancer could reduce the volumes of mandible that received >50 Gy, >55 Gy, and >60 Gy, in addition to producing fewer hot spots and a lower maximum dose to the mandible [10]. More recently, numerous reports have been published documenting the theoretical advantages of proton therapy over photon therapy for head and neck cancer [23–25]. The first use of multi-field optimization for IMPT was reported in

2014 for head and neck malignancies [16]; indeed, IMPT (as opposed to passively scattered proton therapy) has been shown in treatment-planning comparisons to be the most effective in reducing the doses to the spinal cord, parotid, and brainstem [13, 26]. Although patients in our retrospective analysis had not been randomized to receive one type of therapy over the other, our results demonstrated a clear reduction in mean mandibular dose with IMPT (25.6 Gy vs. 41.2 Gy for IMRT, $P<0.001$), as well as a reduction of the volume of the mandible exposed to high radiation doses between 60 and 70 Gy, which are known to be related to the occurrence of ORN. We further found that the mandible received lower doses with IMPT regardless of the radiation dose-volume, indicating that dosimetrically, IMPT is clearly superior to IMRT in treating oropharyngeal carcinoma.

The radiation dose to the mandible is the main risk factor for osteoradionecrosis; high total doses, high doses per fraction, large field sizes and technology of radiotherapy are all acknowledged to be linked with increased risk [6]. In 1976, Bedwinek et al. at MD Anderson reported no occurrences of spontaneous osteoradionecrosis when doses were less than 60 Gy given in 6 weeks, uncommon (1.8%) at doses under 70 Gy in 7 weeks, and more common (9%) when doses exceeded 70 Gy [27]. In 2007, Goldwaser and colleagues from Massachusetts General Hospital found that doses greater than 66 Gy were associated with increased risk of osteoradionecrosis [28]. In 2013, Tsai et al. at MD Anderson reported that mandibular V50 and V60 values were higher for patients who developed osteoradionecrosis than for those who did not. Our findings from the current study suggest that using IMPT could reliably reduce the mandibular V50–V70 values and presumably result in lower risk of osteoradionecrosis. Moreover, during our median follow-up time of 35.5 months, only one patient who received IMPT developed osteoradionecrosis, and that incident was mild (grade 1). Among patients who received IMRT, 41 developed osteoradionecrosis. These results suggest that the theoretical advantages of IMPT translated to clinical benefit. Other factors such as tumor location and size, dental status, poor oral hygiene, alcohol consumption, and smoking also contribute to the development and severity of osteoradionecrosis [2, 6, 29, 30]; some those confounding effects are balanced in these two groups (table 1) Finally, osteoradionecrosis is also related to not only the radiation dose but also the primary tumor (and hence high-dose volume) location. Curi and Dib found osteoradionecrosis to be rare among patients who received doses lower than 50 Gy and its frequency to be related to the total radiation dose [8]. In our study, the location of the osteoradionecrosis also reflected both the site of the primary tumor and the high-dose volume; all incidents of osteoradionecrosis were found in areas where the mandible had received more than 50 Gy. Our results suggest that the lower rate of osteoradionecrosis with IMPT resulted from better mandibular sparing, which in turn suggests that stricter constraints for the mandible should be applied in IMRT planning. Better mandibular sparing without compromising target coverage could be done by using better planning techniques for photon therapy[31].

The current study did have some limitations, chief among them its retrospective nature. Because IMPT was implemented in our clinical practice in 2012, our follow-up time (median 35.5 months for all patients) was relatively short. However, one strength of our study is the relatively homogenous procedures for treatment planning and delivery during the study period and systematic pretreatment and follow-up consultations with dental oncologists. The second limitation of this work is relatively fewer proton patients (50)

compared to photon patients (534). However, the dosimetric advantage of the proton therapy is statistically significantly better than IMRT technique. We will perform matched case control study or multi-institution study in the future with more patients being treated by proton therapy. Additionally, this is the first report about evaluation of the risk of osteoradionecrosis from IMPT in head and neck cancer.

Our findings indicate that use of IMPT minimized excess irradiation of the mandible and consequently reduced the risk of osteoradionecrosis as compared with IMRT for oropharyngeal cancer. Further prospective studies with larger number of patients incorporating mandibular dose-volume histogram analysis should be undertaken to clarify the influence of radiation technique (IMRT or IMPT) on the prevalence of and severity of osteoradionecrosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Wencheng Zhang and Xiaodong Zhang receive fund by the sister institution network fund of MDACC. Drs. Lai, Mohamed and Fuller receive funding support from the National Institutes of Health (NIH)/National Institute for Dental and Craniofacial Research (1R01DE025248-01/R56DE025248-01).

Dr. Fuller received/receives grant and/or salary support from: the NIH/National Cancer Institute Head and Neck Specialized Programs of Research Excellence Developmental Research Program Award (P50CA097007-10) and Paul Calabresi Clinical Oncology Program Award (K12 CA088084-06); a National Science Foundation (NSF), Division of Mathematical Sciences, Joint NIH/NSF Initiative on Quantitative Approaches to Biomedical Big Data (QuBBD) Grant (NSF 1557679); a General Electric Healthcare/MD Anderson Center for Advanced Biomedical Imaging In-Kind Award; an Elekta AB/MD Anderson Department of Radiation Oncology Seed Grant; the Center for Radiation Oncology Research (CROR) at MD Anderson Cancer Center; and the MD Anderson Institutional Research Grant (IRG) Program. Dr. Fuller has received speaker travel funding from Elekta AB. These listed funders/supporters played no role in the study design, collection, analysis, interpretation of data, manuscript writing, or decision to submit the report for publication.

Funding sources: Dr. Wencheng Zhang and Xiaodong Zhang receive fund by the sister institution network fund of MDACC. Drs. Lai, Mohamed and Fuller receive funding support from the National Institutes of Health (NIH)/National Institute for Dental and Craniofacial Research (1R01DE025248-01/R56DE025248-01). Dr. Fuller received/receives grant and/or salary support from: the NIH/National Cancer Institute Head and Neck Specialized Programs of Research Excellence Developmental Research Program Award (P50CA097007-10) and Paul Calabresi Clinical Oncology Program Award (K12 CA088084-06); a National Science Foundation (NSF), Division of Mathematical Sciences, Joint NIH/NSF Initiative on Quantitative Approaches to Biomedical Big Data (QuBBD) Grant (NSF 1557679); a General Electric Healthcare/MD Anderson Center for Advanced Biomedical Imaging In-Kind Award; an Elekta AB/MD Anderson Department of Radiation Oncology Seed Grant; the Center for Radiation Oncology Research (CROR) at MD Anderson Cancer Center; and the MD Anderson Institutional Research Grant (IRG) Program. Dr. Fuller has received speaker travel funding from Elekta AB. These listed funders/supporters played no role in the study design, collection, analysis, interpretation of data, manuscript writing, or decision to submit the report for publication.

References

1. Wang L, Su YX, Liao GQ. Quality of life in osteoradionecrosis patients after mandible primary reconstruction with free fibula flap. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*. 2009; 108:162–8.
2. Niewald M, Fleckenstein J, Mang K, Holtmann H, Spitzer WJ, Rube C. Dental status, dental rehabilitation procedures, demographic and oncological data as potential risk factors for infected osteoradionecrosis of the lower jaw after radiotherapy for oral neoplasms: a retrospective evaluation. *Radiation oncology*. 2013; 8:227. [PubMed: 24088270]

3. Nabil S, Samman N. Risk factors for osteoradionecrosis after head and neck radiation: a systematic review. *Oral surgery, oral medicine, oral pathology and oral radiology*. 2012; 113:54–69.
4. Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *International journal of radiation oncology, biology, physics*. 2013; 85:415–20.
5. Glanzmann C, Gratz KW. Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*. 1995; 36:94–100. [PubMed: 7501817]
6. Chrcanovic BR, Reher P, Sousa AA, Harris M. Osteoradionecrosis of the jaws--a current overview--part 1: Physiopathology and risk and predisposing factors. *Oral and maxillofacial surgery*. 2010; 14:3–16. [PubMed: 20119841]
7. Kluth EV, Jain PR, Stuchell RN, Frich JC Jr. A study of factors contributing to the development of osteoradionecrosis of the jaws. *The Journal of prosthetic dentistry*. 1988; 59:194–201. [PubMed: 2963910]
8. Curi MM, Dib LL. Osteoradionecrosis of the jaws: a retrospective study of the background factors and treatment in 104 cases. *Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons*. 1997; 55:540–4. discussion 5–6.
9. Ben-David MA, Diamante M, Radawski JD, Vineberg KA, Stroup C, Murdoch-Kinch CA, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. *International journal of radiation oncology, biology, physics*. 2007; 68:396–402.
10. Ahmed M, Hansen VN, Harrington KJ, Nutting CM. Reducing the risk of xerostomia and mandibular osteoradionecrosis: the potential benefits of intensity modulated radiotherapy in advanced oral cavity carcinoma. *Medical dosimetry: official journal of the American Association of Medical Dosimetrists*. 2009; 34:217–24. [PubMed: 19647632]
11. Zhang X, Li Y, Pan X, Xiaoqiang L, Mohan R, Komaki R, et al. Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. *International journal of radiation oncology, biology, physics*. 2010; 77:357–66.
12. Simone CB 2nd, Ly D, Dan TD, Ondos J, Ning H, Belard A, et al. Comparison of intensity-modulated radiotherapy, adaptive radiotherapy, proton radiotherapy, and adaptive proton radiotherapy for treatment of locally advanced head and neck cancer. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*. 2011; 101:376–82. [PubMed: 21663988]
13. Kandula S, Zhu X, Garden AS, Gillin M, Rosenthal DI, Ang KK, et al. Spot-scanning beam proton therapy vs intensity-modulated radiation therapy for ipsilateral head and neck malignancies: a treatment planning comparison. *Medical dosimetry: official journal of the American Association of Medical Dosimetrists*. 2013; 38:390–4. [PubMed: 23916884]
14. De Ruyscher D, Mark Lodge M, Jones B, Brada M, Munro A, Jefferson T, et al. Charged particles in radiotherapy: a 5-year update of a systematic review. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*. 2012; 103:5–7. [PubMed: 22326572]
15. Jakobi A, Bandurska-Luque A, Stutzer K, Haase R, Lock S, Wack LJ, et al. Identification of Patient Benefit From Proton Therapy for Advanced Head and Neck Cancer Patients Based on Individual and Subgroup Normal Tissue Complication Probability Analysis. *International journal of radiation oncology, biology, physics*. 2015; 92:1165–74.
16. Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, et al. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice. *International journal of radiation oncology, biology, physics*. 2014; 89:846–53.
17. Garden AS, Morrison WH, Wong PF, Tung SS, Rosenthal DI, Dong L, et al. Disease-control rates following intensity-modulated radiation therapy for small primary oropharyngeal carcinoma. *International journal of radiation oncology, biology, physics*. 2007; 67:438–44.
18. Jacobson AS, Buchbinder D, Hu K, Urken ML. Paradigm shifts in the management of osteoradionecrosis of the mandible. *Oral oncology*. 2010; 46:795–801. [PubMed: 20843728]

19. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Statistics in medicine*. 2014; 33:1242–58. [PubMed: 24122911]
20. Chaux-Bodard AG, Gourmet R, Montbarbon X, Bodard S, Breton P. Postradiation dental extractions. *Revue de stomatologie et de chirurgie maxillo-faciale*. 2004; 105:269–73. [PubMed: 15602426]
21. Sulaiman F, Huryn JM, Zlotolow IM. Dental extractions in the irradiated head and neck patient: a retrospective analysis of Memorial Sloan-Kettering Cancer Center protocols, criteria, and end results. *Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons*. 2003; 61:1123–31.
22. Wahl MJ. Osteoradionecrosis prevention myths. *International journal of radiation oncology, biology, physics*. 2006; 64:661–9.
23. van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. *The oncologist*. 2011; 16:366–77. [PubMed: 21349950]
24. Steneker M, Lomax A, Schneider U. Intensity modulated photon and proton therapy for the treatment of head and neck tumors. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*. 2006; 80:263–7. [PubMed: 16916557]
25. McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. *Radiation oncology*. 2016; 11:32. [PubMed: 26922239]
26. Grant SR, Grosshans DR, Bilton SD, Garcia JA, Amin M, Chambers MS, et al. Proton versus conventional radiotherapy for pediatric salivary gland tumors: Acute toxicity and dosimetric characteristics. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*. 2015; 116:309–15. [PubMed: 26232128]
27. Bedwinek JM, Shukovsky LJ, Fletcher GH, Daley TE. Osteonecrosis in patients treated with definitive radiotherapy for squamous cell carcinomas of the oral cavity and naso-and oropharynx. *Radiology*. 1976; 119:665–7. [PubMed: 935406]
28. Goldwasser BR, Chuang SK, Kaban LB, August M. Risk factor assessment for the development of osteoradionecrosis. *Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons*. 2007; 65:2311–6.
29. Reuther T, Schuster T, Mende U, Kubler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review. *International journal of oral and maxillofacial surgery*. 2003; 32:289–95. [PubMed: 12767877]
30. Dhanda J, Pasquier D, Newman L, Shaw R. Current Concepts in Osteoradionecrosis after Head and Neck Radiotherapy. *Clinical oncology*. 2016
31. Zhang X, Li X, Quan EM, Pan X, Li Y. A methodology for automatic intensity-modulated radiation treatment planning for lung cancer. *Physics in medicine and biology*. 2011; 56:3873–93. [PubMed: 21654043]

Fig. 1.

Comparison of the Dose volume histograms (DVHs) between the IMRT and IMPT plans of the patients; Each error bar is constructed using a 95% confidence interval of the mean.

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)	

Characteristic	IMRT No. (%)	IMPT No. (%)	P Value
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.

Table 2Mean mandibular dosimetric variables for 584 patients

	IMRT	IMPT	P Value
Min dose, cGy	734.28	84.03	<0.001
Max dose, cGy	7173.18	7132.26	0.503
Mean dose, cGy	4120.42	2559.33	<0.001
V5, %	99.5	77.74	<0.001
V10, %	98.65	69.14	<0.001
V15, %	92.51	60.99	<0.001
V20, %	87.88	52.36	<0.001
V25, %	81.52	44.71	<0.001
V30, %	72.70	37.64	<0.001
V35, %	62.36	31.79	<0.001
V40, %	52.01	26.78	<0.001
V45, %	42.46	22.05	<0.001
V50, %	34.17	17.35	<0.001
V55, %	26.41	12.61	<0.001
V60, %	18.59	7.86	<0.001
V65, %	10.88	4.08	<0.001
V70, %	4.35	1.70	<0.001

Abbreviations: IMRT, intensity-modulated (photon) radiation therapy; IMPT, intensity-modulated proton therapy; Vx, percentage volume of the mandible that received x dose of radiation.

Table 3

Mandibular mean dosimetric values for 584 patients without mandibular osteoradionecrosis and 41 patients (40 IMRT patients and 1 IMPT patient) with mandibular osteoradionecrosis.

	No Mandibular Osteoradionecrosis <u>537</u> patients	With Mandibular Osteoradionecrosis <u>41</u> patients	<i>P</i> Value
Min dose, cGy	661.25	897.73	<0.001
Max dose, cGy	7151.20	7411.19	<0.001
Mean dose, cGy	3932.26	4676.50	<0.001
V5, %	97.54	98.84	0.360
V10, %	95.95	98.06	0.740
V15, %	89.33	95.75	<0.001
V20, %	84.20	92.75	<0.001
V25, %	77.66	87.27	<0.001
V30, %	69.00	78.40	<0.001
V35, %	58.95	69.74	<0.001
V40, %	48.90	61.98	<0.001
V45, %	39.70	53.74	<0.001
V50, %	31.70	45.96	<0.001
V55, %	24.24	37.91	<0.001
V60, %	16.72	29.97	<0.001
V65, %	9.43	21.54	<0.001
V70, %	3.63	10.66	<0.001

Abbreviations: IMRT, intensity-modulated (photon) radiation therapy; IMPT, intensity-modulated proton therapy; Vx, percentage volume of the mandible that received x dose of radiation.