Published in final edited form as:
Radiother Oncol. 2011 December ; 101(3): 376–382. doi:10.1016/j.radonc.2011.05.028.

Comparison of Intensity-modulated Radiotherapy, Adaptive Radiotherapy, Proton Radiotherapy, and Adaptive Proton Radiotherapy for Treatment of Locally Advanced Head and Neck Cancer

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Abstract

Background and Purpose—Various radiotherapy planning methods for locally advanced squamous cell carcinoma of the head and neck (SCCHN) have been proposed to decrease normal tissue toxicity. We compare IMRT, adaptive IMRT, proton therapy (IMPT), and adaptive IMPT for SCCHN.

Materials and Methods—Initial and re-simulation CT images from 10 consecutive patients with SCCHN were used to quantify dosimetric differences between photon and proton therapy. Contouring was performed on both CTs, and plans (n=40 plans) and dose volume histograms were generated.

Results—The mean GTV volume decreased 53.4% with re-simulation. All plans provided comparable PTV coverage. Compared with IMRT, adaptive IMRT significantly reduced the maximum dose to the mandible ($p=0.020$) and mean doses to the contralateral parotid gland ($p=0.049$) and larynx ($p=0.049$). Compared with IMRT and adaptive IMRT, IMPT significantly lower the maximum doses to the spinal cord ($p<0.002$ for both) and brainstem ($p<0.002$ for both) and mean doses to the larynx ($p<0.002$ for both) and ipsilateral ($p=0.004$ IMRT, $p=0.050$ adaptive) and contralateral ($p<0.002$ IMRT, $p=0.010$ adaptive) parotid glands. Adaptive IMPT significantly reduced doses to all critical structures compared with IMRT and adaptive IMRT and several critical structures compared with non-adaptive IMPT.

Conclusions—Although adaptive IMRT reduced dose to several normal structures compared with standard IMRT, non-adaptive proton therapy had a more favorable dosimetric profile than IMRT or adaptive IMRT and may obviate the need for adaptive planning. Protons allowed significant sparing of the spinal cord, parotid glands, larynx, and brainstem and should be

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Conflict of Interest Statement: none.

considered for SCCHN to decrease normal tissue toxicity while still providing optimal tumor coverage.

Keywords

head and neck cancer; proton therapy; adaptive radiotherapy; IMRT; treatment planning

INTRODUCTION

Radiation therapy with concurrent cisplatin-based chemotherapy is standard treatment for patients with locally advanced SCCHN [1]. Chemoradiation can potentially allow for organ preservation and improve patient quality of life compared with surgery [2]. Concurrent chemoradiation in this region, however, is associated with significant morbidity. The close proximity to vital organs makes it difficult to deliver definitive radiation doses to disease sites without compromising normal tissue function. Xerostomia from salivary gland dysfunction commonly results and is strongly associated with dysphagia, difficulty with social eating, increased oral bacteria colonization, dental caries, and decreased quality of life [3–5]. Radiation to the glottic larynx can result in poor voice function, weight loss, swallowing dysfunction, and decreased quality of life [6]. Mucositis [7], osteoradionecrosis from dose to the mandible [8], and nausea from dose to the brainstem [7] can also occur. Conformal techniques such as intensity-modulated radiotherapy (IMRT) can decrease dose to defined critical normal tissues and achieve dose escalation to SCCHN target volumes [9].

Adaptive radiotherapy for SCCHN is increasingly being employed to account for anatomic changes that can lead to overtreatment of normal tissues or undertreatment of tumors. Since there is a steep dose gradient with conformal techniques between target and normal tissues, interfractional anatomical changes become significant. Interfractional patient weight loss or deformation of tumor or normal tissues are not accounted for with standard radiotherapy but can markedly alter head and neck anatomy and modify treatment parameters [10]. SCCHN often have rapid favorable responses to therapy with significant tumor shrinkage [11–15]. Such response can affect other nearby nontarget structures, particularly the parotid glands. As primary tumors regress, parotid glands in the involved treatment fields often shrink and are displaced medially, potentially increasing radiation exposure [15–18].

Adaptive radiotherapy aims to modify treatment according to changes that occur during therapy. For SCCHN, this involves re-simulating patients during their radiotherapy and modifying target volumes and treatment plans to attempt to minimize effects of anatomic changes in tumors and surrounding structures. Preliminary studies assessing adaptive photon radiotherapy have reported improved sparing of organs at risk (OARs) [12–14].

Particle therapy may also provide a more favorable toxicity profile than IMRT. Proton therapy allows energy to be deposited at a specific depth known as the Bragg peak, with rapid energy falloff beyond this point [19]. Therefore, normal tissues on the distal side of the target volume can be spared. A single-institution report has documented excellent local control rates and reduced doses to OARs for the treatment of SCCHN with proton therapy [20].

To date, there is limited data directly comparing different radiotherapy modalities and treatment strategies for SCCHN, and to the authors knowledge, no data exists comparing adaptive photon radiotherapy to particle radiotherapy or assessing adaptive particle radiotherapy for SCCHN. This is the first study comparing dose volume histograms (DVHs) of target volumes and normal tissue structures in photon-based versus proton-based plans

using both fixed target volumes and adaptive planning for patients with locally advanced SCCHN.

MATERIALS AND METHODS

Ten consecutive patients with Stage IV locally advanced SCCHN treated at the National Institutes of Health Clinical Research Center (six patients) or Walter Reed Army Medical Center (four patients) from 1/2008 to 9/2009 who required repeat simulation during their course of radiotherapy due to changes in anatomy or difficulties that arose during treatment relating to patient set-up or thermoplastic immobilization devices were included in the present study. Most patients had oropharynx primary malignancies (seven patients), and all patients had N2 nodal disease, with three having bilateral nodal involvement and all but one having multiple positive lymph nodes [AJCC, 6^{th} Ed.] (Table 1). All patients underwent a single repeat simulation planning session that occurred on average 2.9 weeks into treatment with concurrent chemoradiation and were treated to revised target volumes based on the second CT data set following repeat simulation. All patients were treated with IMRT in 2Gy daily fractions to 70Gy over 35 fractions with concurrent cisplatin.

The CT images from these patients were used to quantify dosimetric differences between photon and proton therapy. CT data were acquired with a slice thickness of 3mm. CT images were imported into a photon and proton commercial treatment planning system (Eclipse, Varian Medical Systems, Palo Alto, CA) for defining target and nontarget structures. OARs and planning target volumes (PTVs) were contoured on the initial and re-simulation CT images. Target and nontarget structure sets for a given patient CT image set were held constant for all plans. Assessed OARs included the bilateral parotid glands, glottic larynx, spinal cord, brainstem, and mandible. CT streak artifacts from metal were contoured and assigned a CT value equivalent to tissue prior to calculating all photon and proton plans. Artifacts from teeth were assigned a tissue equivalent value for all proton plans and as necessary for photon plans.

Gross Tumor Volume (GTV) was defined as the maximum extent of all known gross disease determined from clinical examination, endoscopy, or CT, MRI, or PET imaging. In all directions circumferentially, the margin between GTV and Clinical Target Volume 70 (CTV_{70}) was 1cm to include all volumes of known tumor and suspected microscopic spread. This margin was reduced to ≥2mm for tumors in close proximity to bone or air not at risk for subclinical disease. High risk nodal regions, including small volume lymph nodes and all potential routes of spread for primary and nodal disease, were contoured and designated CTV_{64}. Nodal regions at lower risk of disease spread were designated CTV_{50}.

To account for set-up variation and organ and patient motion, a uniform margin of 5mm was added around each corresponding CTV to define PTV_{70}, PTV_{64}, and PTV_{50}, respectively. To account for proton beam properties and range uncertainties, proton beam range compensators were designed to provide proximal and distal margins relative to each PTV, and blocking was designed to create a lateral margin relative to each PTV. These margins were individualized for each patient on the basis of the formulas by Moyers et al. [21]. PTV_{70} was planned to 70Gy for photon plans or 70 cobalt Gray equivalents (CGE) for proton plans, with proton doses corrected with the accepted relative biologic effectiveness value of 1.1 [19]. PTV_{64} was planned to 64Gy or 64CGE, whereas PTV_{50} was planned to 50Gy or 50CGE. Plans were devised to initially target PTV_{50}, followed by a conedown to PTV_{64}, followed by a second conedown to PTV_{70}, with no integrated boost administration planned.

Four treatment plans were generated for each patient (n=40 plans): 1) photon IMRT, with treatment planned to the target volumes and normal structures from the initial CT image set, 2) adaptive photon IMRT, with treatment planned to the target volumes and normal structures from the initial CT image set to 36Gy and to the second CT simulation image set to 34Gy, 3) spot scanning proton IMPT, with treatment planned to the target volumes and normal structures from the initial CT image set, and 4) adaptive proton IMPT, with treatment planned to the target volumes and normal structures from the initial CT image set to 36Gy and to the second CT simulation image set to 34Gy. For all adaptive plans, following the first 36 Gy planned to the initial PTV_{50} based on the initial CT data set, the remaining 14Gy planned to a revised PTV_{50} and both conedown doses to PTV_{64} and PTV_{70} were planned to new PTVs devised using the second CT data set. The initial and subsequent CT data sets were fused together to allow for plan sums and composite DVHs to be generated.

IMRT and adaptive IMRT plans were designed with seven equally spaced beams every 50° beginning at 30° (30°, 80°, 130°, 180°, 230°, 280°, 330°) centered on each corresponding PTV (Figure 1A). These beam angles corresponded to the class solution employed by our clinic for treating locally advanced SCCHN. For proton and adaptive proton plans, patients were planned with five beams centered on PTV_{50} and PTV_{64}, with beam angles individualized for each patient. For the final three fractions of proton therapy, patients were planned with an individualized two-field technique, with beams centered on PTV_{70} (Figure 1B–1C). For photon plans, 6 MV photons were used, whereas the maximum clinical beam energy was 235 MeV for proton plans.

For optimization purposes, dose objectives were created for PTVs and OARs. All plans were optimized via Helios Inverse Treatment Planning (Varian Medical Systems) to minimize dose to critical structure by increasing constraints on OARs and OARs with margin (spinal cord, brainstem), while maintaining optimal PTV coverage and dose homogeneity throughout target volumes. Planning was performed to achieve maximum doses to the spinal cord less than 45Gy, brainstem less than 54Gy, and mandible no more than 1cc to exceed 75Gy, as well as mean doses to the parotid glands less than 26Gy (or at least 50% of one gland less than 30Gy) and glottic larynx less than 45Gy. All plans were optimized to ensure 100% of the prescription dose covered ≥97% of each PTV. DVHs of PTVs and OARs were generated for IMRT, adaptive IMRT, IMPT, and adaptive IMPT plans to compare doses to tumor volumes and normal structures.

Various methods were used to minimize bias in the present study. Ten consecutive patients who required re-planning were included in this study to minimize sampling bias. All contours were performed by a single radiation oncologist (CS) and approved by at least one additional radiation oncologist. A standard treatment planning optimization strategy was used for all photon and proton plans. Conformity indexes (see definition in Table 2) and DVHs were assessed to ensure comparable PTV coverage between plans to minimize any bias when comparing normal tissue dosimetry between plans. However, despite these measures, as with any retrospective study [22], it is possible that bias existed in the current study that may have favored a certain type of planning strategy. Furthermore, despite recontouring on and fusing the second CT data sets to the first CT data sets, as deformable registration was not employed and small changes were noted in normal tissue positioning on the second CT data sets following tumor response, a margin of error may exist in the dose accumulate between the initial and subsequent CTs.

Statistical analysis was performed using JMP 7.0 (SAS, Cary, NC). Because the population was not normally distributed, a non-parametric statistical hypothesis was utilized. The Wilcoxon Signed-rank test was used to evaluate the differences between pairwise

comparisons. A two-tailed p-value was utilized, and statistical significance was defined as $p \leq 0.050$.

RESULTS

Patient Statistics

The mean GTV volume from the initial CT image set obtained before concurrent chemoradiation was 76.1cm^3 [range 23.0–173.0cm^3] (Table 1). The mean GTV volume from the second CT image set decreased by 53.4% to 35.5cm^3 [5.1–100.1cm^3]. The corresponding mean PTV_{70} volume decreased 39.7%, from 372.2cm^3 [164.4–878.7cm^3] to 224.4cm^3 [77.8–543.5cm^3]. No appreciable difference in tumor volume reduction was noted by tumor primary location.

Dose Coverage

IMRT, adaptive IMRT, IMPT, and adaptive IMPT plans all provided acceptable target volume coverage, with no significant difference in coverage to PTV_{70}, PTV_{64}, or PTV_{50} among the different plans (Table 2). In all cases, 100% of the prescription dose covered ≥97% of each PTV, and no point dose within or outside PTVs was >114% of the prescribed dose (Figure 1D–1G). Overall, proton plans and adaptive proton plans had superior conformity than either IMRT plans or adaptive IMRT plans, and they delivered less dose outside of target volumes, particularly among low to intermediate dose volumes (Table 2).

IMRT versus Adaptive IMRT

Compared with IMRT plans, adaptive IMRT significantly decreased the maximum point dose to the mandible ($p=0.020$) and mean doses to the left parotid gland ($p<0.002$) and glottic larynx ($p=0.049$) (Table 3, Supplemental Table 1). The maximum dose to the brainstem was somewhat lower with adaptive plans, although this difference was not statistically significant ($p=0.084$). There was no difference in the maximum dose to the spinal cord ($p=0.770$) or mean dose to the right parotid gland ($p=0.846$). When assessing the parotid glands relative to the site of primary disease for each patient, adaptive IMRT decreased the mean dose to the contralateral ($p=0.049$) but not the ipsilateral parotid gland ($p=0.160$) [Supplemental Figure 1].

IMRT versus IMPT

Proton therapy significantly reduced the mean and maximum doses to most OARs examined. Compared with IMRT plans, IMPT reduced the maximum doses to the spinal cord ($p<0.002$) and brainstem ($p<0.002$), as well as the mean doses to the left ($p<0.002$) and right ($p=0.004$) parotid glands and larynx ($p<0.002$). Both the ipsilateral ($p=0.004$) and contralateral ($p<0.002$) parotid glands showed significant sparing with proton therapy. Only the maximum dose to the mandible ($p=0.275$) was not significantly reduced with proton therapy, although the mandible V60 ($p<0.002$) and V70 ($p=0.010$) were lower with IMPT (Figure 1D–1G).

Adaptive IMRT versus IMPT

When compared to adaptive IMRT, IMPT provided a significant dose reduction to all OARs other than the mandible ($p=0.826$). Proton therapy reduced the maximum doses to the spinal cord ($p<0.002$) and brainstem ($p<0.002$), as well as the mean doses to the left ($p=0.010$) and right ($p=0.050$) parotid glands, ipsilateral ($p=0.050$) and contralateral ($p=0.010$) parotid glands, and larynx ($p<0.002$).

IMRT versus Adaptive IMPT

Adaptive IMPT significantly reduced the mean and maximum doses to all OARs examined. Compared with IMRT plans, adaptive IMPT reduced the maximum doses to the spinal cord ($p<0.002$), brainstem ($p<0.002$), and mandible (0.020), as well as the mean doses to the left ($p=0.004$) and right ($p=0.004$) parotid glands, ipsilateral ($p=0.004$) and contralateral ($p=0.004$) parotid glands, and larynx ($p<0.002$).

Adaptive IMRT versus Adaptive IMPT

When compared to adaptive IMRT, adaptive IMPT significantly reduced dose to all OARs examined. Adaptive IMPT reduced the maximum doses to the spinal cord ($p<0.002$), brainstem ($p<0.002$), and mandible ($p=0.049$), as well as the mean doses to the left ($p=0.020$) and right ($p=0.010$) parotid glands, ipsilateral ($p=0.010$) and contralateral ($p=0.020$) parotid glands, and larynx ($p<0.002$).

IMPT versus Adaptive IMPT

When compared to IMPT, adaptive IMPT provided a further reduction in dose to several OARs. Adaptive IMPT reduced the maximum doses to the spinal cord ($p=0.004$) and mandible ($p=0.006$) and mean doses to the larynx ($p=0.010$) and ipsilateral parotid gland ($p=0.020$). Non-significantly lower mean doses to left ($p=0.084$) and right ($p=0.065$) parotid glands and maximum dose to the brainstem ($p=0.106$) were also demonstrated with adaptive IMPT. There was no difference in mean dose to the contralateral parotid gland ($p=0.160$).

DISCUSSION

This study demonstrated that adaptive photon radiotherapy for locally advanced SCCHN can significantly decrease the maximum dose to the mandible and mean doses to the contralateral parotid gland and glottic larynx when compared with IMRT, while still maintaining optimal tumor coverage. Proton radiotherapy, however, allowed further benefits over standard IMRT and adaptive IMRT plans by decreasing the maximum doses to the spinal cord and brainstem and mean doses to the bilateral parotid glands and larynx, while still delivering optimal tumor coverage. Adaptive proton radiotherapy further reduced doses received by the spinal cord, ipsilateral parotid gland, glottic larynx, and mandible compared with non-adaptive proton plans, although this reduction was less clinically significant.

High dose homogeneity and target volume coverage were achieved despite a diverse patient population with varying primary tumor locations and extents of nodal involvement. Importantly, no significant difference in PTV coverage was demonstrated between all plans, thus minimizing bias when comparing normal tissue dosimetry. However, the sensitivity of proton plans to anatomic and target volume changes was generally greater than for photon plans. Plans with fewer beams and with beams in the direction of shrinkage of target volumes were most sensitive. For target volumes in this study that exhibited significant shrinkage following a partial course of chemoradiation prior to repeat CT simulation for adaptive radiotherapy, the actual doses delivered to critical structures just distal to shrinking target volumes varied from the doses expected based on the initial CT data sets more with protons than photons.

Adaptive Radiotherapy

Supporting a potential benefit of adaptive radiotherapy in our study, when contours from the initial CT image sets were compared with those from the re-planning CT image sets, a significant reduction in mean GTV was demonstrated that was similar to tumor reductions reported in previous studies with an average reduction in GTV noted between 69–73% [11–15]. Several patients in this study underwent re-planning early in the course of their

radiotherapy and, therefore, may have had more GTV reduction if re-planning was performed later in therapy.

Preliminary research on adaptive radiotherapy has demonstrated potential improvements in radiation treatment delivery which was also noted in our study. By evaluating serial CT images throughout radiotherapy, Barker et al. reported significant changes in size and positions of target volumes and OARs, suggesting dosimetric underdosing of PTVs or overdosing of parotid glands may occur if such changes are not accounted for with re-planning [13]. Another study demonstrated lack of re-planning decreased dose coverage of originally planned PTVs in 92% of patients and increased the maximum doses delivered to the spinal cord in 100% and brainstem in 85% [14]. Another study showed the dose delivered to parotid glands can be 5–7Gy higher than what was planned at the time of initial simulation in 45% of patients [18]. Although small absolute differences in dose delivered to such organs as the mandible and spinal cord may be less clinically significant, such an increase in dose to parotid glands is not trivial. Parotid glands exhibit a steep dose-response relationship, with functioning impaired after a mean dose as low as 10Gy and grade 4 xerostomia occurring in 70% of patients receiving mean doses greater than 26Gy [4–5].

Although attempt was made to maintain the mean bilateral parotid gland dose under 26Gy, PTVs and ipsilateral parotid glands overlapped in most patients. As the priority of sparing the parotid glands was lower than that for achieving the prescribed PTV coverage, few patients had mean ipsilateral parotid gland doses below 26Gy, and the reduction in ipsilateral parotid gland mean dose from 43.1Gy with IMRT to 39.0Gy with adaptive IMRT in this study was not significant ($p=0.160$). The contralateral parotid gland mean dose was lower with adaptive IMRT (25.3Gy vs. 26.8Gy, $p=0.049$), which is in line with the magnitude of parotid gland dose reduction of up to 10% reported in prior studies assessing adaptive photon radiotherapy [12]. The mean doses to the ipsilateral and contralateral parotid glands with IMPT of 32.9Gy and 19.5Gy, respectively, and adaptive IMPT of 29.8Gy and 18.3Gy, suggest an even larger potential clinical benefit in preservation of parotid gland functioning with protons.

Several concerns exist with adaptive treatment planning. Since adaptive radiotherapy is labor intensive, deformable image registration, automated target delineation, and higher computational power likely will become more important. Additionally, the timing of when to re-plan during chemoradiation is not well-defined. While some practitioners utilize dose thresholds to perform re-simulation, others use anatomical thresholds such as GTV reduction. In this study, patients underwent a single repeat simulation. As has been demonstrated in prior studies [12], a greater benefit with adaptive radiotherapy might have been seen if re-planning occurred more frequently during radiotherapy.

Controversy also exists regarding local control when treating smaller target volumes based on re-planning CT data [23–24]. With tumor responses after both induction chemotherapy and a partial course of concurrent chemoradiation, concern exists that substantial numbers of tumor cells may remain in tissue volumes previously occupied by gross disease that are below the threshold of radiographic detection [23–25]. To evaluate these issues, there are currently three pilot trials lead by U.T.M.D. Anderson Cancer Center, Washington University School of Medicine, and University Hospital Ghent (Belgium) that aim to assess adaptive radiotherapy for the treatment of SCCHN [26]. A recent consensus conference assessing induction chemotherapy recommended treating patients based on prechemotherapy target volumes, regardless of tumor response, to avoid risking marginal recurrences. While no such consensus exists for adaptive radiotherapy, the multidisciplinary team concluded that “many of the same issues and recommendations will apply to adaptive RT…” [27].

Proton Radiotherapy

Particle radiotherapy has also been shown in preliminary reports and modeling studies to improve tumor dose distribution and decrease normal tissue toxicity in the treatment of many cancers [28–30] SCCHN compared with photon therapy [31–36]. Cozzi et al. performed a treatment planning comparison of mixed photon-electron, 3D conformal photon, IMRT, and proton therapy (passively scattered and spot scanned) for patients with advanced SCCHN. Proton plans provided improved dose homogeneity and delivered the least dose to the spinal cord and parotid glands [31]. Investigators from Loma Linda University Medical Center treated 29 patients with stage II-IV oropharyngeal cancers using an accelerated fractionation schedule with a combination of photons and protons to 75.9CGE in 45 fractions. Their reported 84% locoregional control and 65% disease-free survival rates at five years compare very favorably to historical controls without increasing treatment toxicity [20]. Another dosimetric study of hypopharyngeal patients similarly demonstrated lower doses to non-target tissues with protons than photon IMRT [32].

The dosimetric advantages of proton radiotherapy demonstrated in this study might improve the therapeutic ratio for patients with locally advanced SCCHN. Based on historical dose-response relationships, with significantly lower radiation doses to several OARs demonstrated in this study, patients treated with protons may have improved quality of life and reduced rates of xerostomia, dental problems, voice changes, weight loss, swallowing dysfunction, mucositis, nausea, and other radiation-induced toxicities. Longitudinal studies examining normal tissue toxicities from photon and proton radiotherapy are needed to confirm the clinical significance of our findings.

In this study, although adaptive photon radiotherapy reduced dose to several OARs compared with standard IMRT, non-adaptive proton plans were dosimetrically superior to all photon plans despite planning to treat larger target volumes than were planned with adaptive photon radiotherapy. To date, no previous data exist assessing adaptive proton therapy for SCCHN, and adaptive proton therapy has only previously been evaluated in a single dosimetric analysis of patients with non-small cell lung cancer [37]. Although adaptive proton plans in this study, compared with IMPT, significantly lowered the radiation doses to the spinal cord, ipsilateral parotid gland, glottic larynx, and mandible, this dose reduction was less clinically significant and the magnitude of this reduction compared with IMPT plans was much less than the reduction in dose achieved by non-adaptive proton plans over IMRT and adaptive IMRT photon plans. With concerns regarding adaptive treatment strategies and the limited resources of the few proton therapy centers worldwide at this time, it is unlikely that adaptive proton therapy will become a clinically utilized modality for treating patients with SCCHN solely in an attempt to minimize the volumes of targets treated, particularly in light of the significant benefit demonstrated in this study with standard proton therapy over all photons plans. However, as proton plans are more sensitive than photon plans to interfractional changes in tumor volumes and patient anatomy, care must be taken to account for these changes or otherwise ensure accuracy of the beam range when using protons to treat SCCHN. The role of adaptive proton radiotherapy may best be answered in the context of a clinical trial with serially planning repeat CT simulations.

The possible advantages to proton therapy are being assessed in three phase II trials for SCCHN. Researchers at University of Florida and Massachusetts General Hospital are investigating proton therapy for the treatment of nasopharygeal carcinomas, and investigators at University of Florida are assessing proton therapy to treat oropharynx cancers. Each of these trials is enrolling patients with considerably less advanced disease than was included in the present study [26].

Standard vs. Adaptive Radiotherapy

This study assessed a population of SCCHN patients with a high disease burden, all of whom had stage IV non-metastatic disease. The advanced nature of their diseases may have allowed for a greater advantage for adaptive plans over non-adaptive plans following an initial tumor response to chemoradiation. However, an even greater benefit to adaptive radiotherapy may have been demonstrated if the study population had been limited only to patients with clinically significant responses to initial partial courses of chemoradiation. Additionally, neither photon technique could maintain optimal PTV coverage while sparing OARs to the same extent as either proton technique. It is possible that the dosimetric advantage to OARs with protons demonstrated in this study would be even greater in patients with less advanced disease. As such, the study results may not be applicable to patients with early-stage SCCHN and may underestimate the potential benefit of proton therapy over photon therapy. However, it is also possible that the spot scanning proton techniques utilized in this study allowed for a greater benefit with proton therapy than would be seen in centers treating SCCHN patients with scattered beam delivery.

CONCLUSION

For patients with locally advanced SCCHN, adaptive photon radiotherapy offers some benefit over standard IMRT in reducing dose to several regional OARs. Proton therapy has a more favorable dosimetric profile than either standard IMRT or adaptive IMRT and significantly lower radiation doses to the spinal cord, bilateral parotid glands, glottic larynx, and brainstem. As such, the dosimetric advantage demonstrated with non-adaptive proton therapy in this study may obviate the need for adaptive treatment planning for patients with SCCHN. With decreased doses delivered to OARs, patients treated with proton therapy may benefit from fewer radiation-induced side effects. Proton therapy should be considered for patients with locally advanced SCCHN to decrease normal tissue toxicity while still providing optimal tumor coverage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported in part by U.S. Army Medical Research and Materiel Command under Contract Agreement No.DAMD17-W81XWH-04-2-0022, in conjunction with the Roberts Proton Therapy Center at University of Pennsylvania Health System. Research support was also through the Intramural Research Program of the NIH. D.L. was supported by the Clinical Research Training Program, a public-private partnership supported jointly by NIH and Pfizer, Inc. Opinions, interpretations, conclusions, and recommendations are those of the authors and not necessarily endorsed by the U.S. Army.

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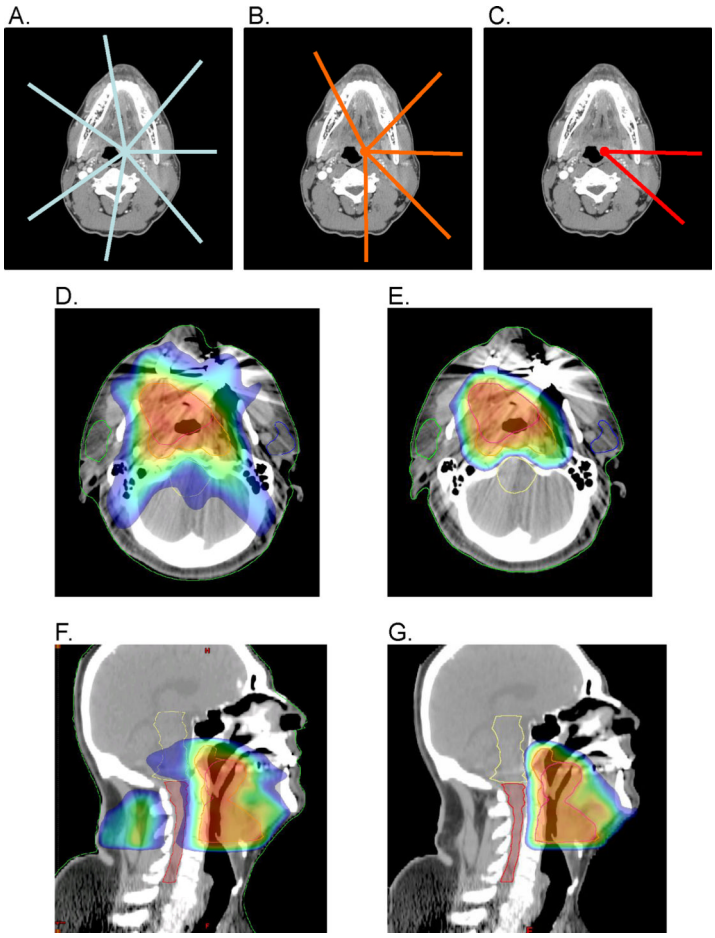

Figure 1.

Beam arrangements and treatment planning images. Representative beam arrangements used for A) photon plans to treat PTV_{70} with a seven-field technique, B) proton plans to treat PTV_{50} and PTV_{60} with a five-field technique, and C) proton plans to treat PTV_{70} with a two-field technique. Beam angles for photon plans were equally spaced and centered on each corresponding PTV. Beam angles for proton plans were individualized for each patient to minimize dose to critical structure and maintain optimal PTV coverage and dose homogeneity throughout the target volumes. Representative treatment planning images for a patient with cT4N2cM0 stage IVA squamous cell carcinoma of the oropharynx (base of tongue) in axial planes for D) IMRT and E) proton therapy, and in sagittal planes for F) IMRT and G) proton therapy. Images depict treatment to PTV_{70}, the final treatment conedown targeting gross disease with margin. The same slices from the same initial CT data set were employed for Figures 1D and 1E and Figures 1F and 1G. Color coding: red = 100% to blue = 50% of 6Gy in 2Gy fractions.

Table 1

Patient Characteristics

Patient Number	Primary Disease	T Stage*	N Stage*	GTV Initial Volume (cm^3)	GTV Rescan Volume (cm^3)	PTV_{70} Initial Volume (cm^3)	PTV_{70} Rescan Volume (cm^3)
1	Supraglottic Larynx	T2	N2c	41.2	30.6	164.4	124.6
2	Oropharynx: Tonsil	T3	N2b	57.4	5.1	214.0	77.8
3	Oroharynx: Base of Tongue	T4	N2c	89.7	54.8	490.2	370.0
4	Supraglottic Larynx	T2	N2b	40.4	6.6	193.8	120.3
5	Oropharynx: Tonsil	T1	N2a	36.7	17.7	282.3	144.7
6	Oropharynx: Tonsil	T2	N2b	173.0	62.2	514.0	268.1
7	Oropharynx: Tonsil	T2	N2b	71.1	33.4	386.2	175.8
8	Oropharynx: Tonsil	T4	N2b	23.0	11.7	194.9	131.0
9	Nasopharynx	T2	N2 (bilateral)	160.5	100.1	878.7	543.5
10	Oropharynx: Tonsil	T1	N2b	67.6	32.4	403.5	288.0

*AJCC, 6^{th} Ed.

Table 2

Comparison[†] of the Mean Dose to Target Volumes and Conformity Index[*] for IMRT, Adaptive IMRT, IMPT, and Adaptive IMPT

	Volume of PTV Receiving 100% of the Prescribed Dose			Conformity Index		
	PTV_{50}	PTV_{64}	PTV_{70}	PTV_{50}	PTV_{64}	PTV_{70}
IMRT	99.9% (±0.2%)	99.1% (±0.3%)	98.6% (±0.7%)	1.97 (±0.48)	1.59 (±0.28)	1.49 (±0.26)
Adaptive IMRT	99.8% (±0.4%)	99.0% (±0.5%)	99.0% (±0.8%)	2.06 (±0.56)	1.53 (±0.39)	1.75 (±0.69)
IMPT	99.9% (±0.1%)	99.5% (±0.5%)	99.0% (±0.7%)	1.52 (±0.31)	1.30 (±0.18)	1.23 (±0.11)
Adaptive IMPT	99.9% (±0.1%)	99.5% (±0.5%)	99.4% (±0.7%)	1.64 (±0.38)	1.40 (±0.19)	1.54 (±0.46)

[†]Values listed for PTV volumes and conformity indexes are the mean values for the study population. The standard deviations for each comparison are listed in brackets.

[*]Conformity index was calculated as the ratio of the reference isodose volume to the volume of each planning target volume being assessed, with the 95% isodose line of each PTV selected as the reference isodose volume in accordance with ICRU 50 guidelines.

Table 3

Comparison of the Average Maximum or Mean Doses to Normal Tissues Between IMRT, Adaptive IMRT, IMPT, and Adaptive IMPT

	Spinal Cord	Left Parotid		Right Parotid		Ipsilateral Parotid		Contralateral Parotid		Glottic Larynx	Brain stem	Mandible		
	Max† (Gy)	Mean (Gy)	V20*	Mean (Gy)	V20*	Mean (Gy)	V20*	Mean (Gy)	V20*	Mean (Gy)	Max† (Gy)	Max† (Gy)	V60*	V70*
IMRT	42.1	37.8	60.4%	32.0	55.5%	43.1	68.4%	26.8	47.5%	45.4	44.8	75.1	34.2%	15.0%
Adaptive IMRT	41.7	32.8	54.0%	31.6	54.8%	39.0	63.6%	25.3	45.2%	41.8	42.2	73.0	25.3%	6.7%
IMPT	30.5	27.2	47.9%	25.3	45.8%	32.9	54.5%	19.5	39.2%	35.3	31.3	73.8	22.8%	8.9%
Adaptive IMPT	28.4	25.0	43.3%	23.1	43.5%	29.8	51.3%	18.3	35.7%	31.0	29.0	71.1	19.5%	5.2%

†Max = average maximum point dose

*V20/60/70 = volume receiving 20/60/70 Gy