Proton Therapy in the Treatment of Head and Neck Cancer

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ABSTRACT

Aim: To examine the value of proton therapy in relation to other treatment modalities in head and neck cancer.

Review: Proton therapy has evolved into more sophisticated and costly intensity-modulated proton therapy and has resulted in greater dose reduction to normal critical structures at risk as compared with photon therapy. Early clinical studies in head and neck cancers, especially for tumors of the skull base and paranasal sinuses, suggest that proton therapy is excellent in terms of local control and is comparable to intensity-modulated radiation therapy photons but with lower rates of morbidity.

Results: There are many potential advantages to radiation therapy with protons. While there are many single institution studies examining the added value of protons to photon therapy, the value of proton therapy must be examined in prospective randomized clinical studies and across many subsites of head and neck cancer. Additional evidence is necessary to guide efficient clinical practice, patient selection, and tumors that are most likely to benefit from this treatment modality and justify proton therapy use given its significant cost.

Keywords: Head and neck cancer, Proton therapy, Radiation therapy.


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Conflict of interest: None

INTRODUCTION

Background

The Food and Drug Administration approved proton therapy utilization as early as 1988. Over the last decade, there has been a rapid increase in the number of operating proton facilities in the United States, from 2 in 2003 to 22 in 2016. While proton therapy utilization has continued to rise throughout the cancer community, there is an ongoing debate within the cancer community as to whether widespread clinical use is justified given the significant cost. There is a lack of comparative effectiveness data comparing proton to photon therapy and we may be jumping the gun on its use prior to comparative effectiveness data being mature.

Radiation plays a critical role in the treatment of patients with head and neck cancer in the definitive, adjuvant, as well as recurrent salvage settings. Due to the anatomy of the head and neck and the close proximity of the tumor target to normal critical structures at risk, such as optic nerves, orbits, salivary glands, brain, pituitary grand, carotid arteries, reducing radiation toxicity is paramount. The dose distribution with proton therapy limits dose deposition after a finite distance from the Bragg peak and more normal tissue sparing is expected. Therefore, there has been an increased interest in harnessing the unique physical properties of proton therapy in order to dose escalate radiation delivered to the tumor while decreasing dose to normal tissue with the aim of decreasing treatment toxicity. In addition, just as with photon therapy, the development of intensity-modulated proton therapy (IMPT) has enabled enhanced dosimetric optimization.

There are many studies in the development that are assessing the benefit of protons in head and neck cancer. In a study by van der Laan et al, IMPT was superior to intensity-modulated radiation therapy (IMRT) in terms of decreased dose to pharyngeal constrictors, thereby estimating an 8% decrease in grade II to IV dysphagia. Others have proposed that a reduction in dose to the posterior fossa achievable with IMPT may result in decreased treatment-related fatigue. However, these dosimetric-based studies have not yet been analyzed to assess whether they do in fact translate to the proposed clinical benefit.

A larger dosimetric advantage with proton therapy use is appreciable in the setting of ipsilateral treatment targets, such as salivary tumors or early tonsillar tumors. In a study by Romesser et al, 41 patients who underwent ipsilateral RT for major salivary gland cancer or cutaneous squamous cell carcinoma were examined, 56% treated with IMRT and 44% with proton beam RT (PBRT). Proton beam therapy had significantly lower rates of grade II or greater acute dysgeusia (5.6% vs 65.2% p < 0.001), mucositis (16.7% vs 52.2% p = 0.019), and nausea (11.1% vs 56.5% p = 0.003). These results are encouraging and authors...
suggest future studies examining late RT-associated morbidity and quality of life (QoL) measures.

In a study by Gunn et al., 50 patients with oropharyngeal cancer treated with IMPT were evaluated and 2-year overall and progression-free survival was 94.5 and 88.6% respectively. While there were no patients with grade IV or V toxicity, grade III acute toxicity occurred in 23 patients. In another study by Blanchard et al., patients with oropharyngeal cancer were case matched: 50 patients IMPT vs 100 patients IMRT, with lower rates of severe weight loss and feeding tube placement in the IMPT group and on multivariate analysis, insertion of a G tube during the acute phase was associated with decreased progression-free survival [hazard ratio (HR) = 3.09; 95% confidence interval (CI): 1.19–8.00; p = 0.02] and overall survival (OS) (HR = 4.96; 95% CI: 1.1–23.0; p = 0.04). These findings are compelling and suggest a possible role of protons in decreasing morbidity and associated health care costs and have spurred interest in oropharyngeal cancer and proton therapy.

The majority of the literature in head and neck cancer and proton therapy are single institution studies and include base of skull chordomas or paranasal sinus tumors. In a meta-analysis examining outcomes with protons vs photons in over 43 cohorts of paranasal sinus and nasal cavity carcinoma, at 5 years both OS and disease-free survival (DFS) were significantly higher with protons vs photons in over 43 cohorts of paranasal sinus and nasal cavity carcinoma. In another study by Blanchard et al., 92 patients with recurrent head and neck cancer previously treated with radiation were examined. In the largest multi-institutional series on proton reirradiation therapy, 92 patients with recurrent head and neck cancer previously treated with radiation were examined. The cumulative index of 1 year locoregional failure was 25.1%, while OS was 65.2%. Acute grade ≥3 toxicity rates were very low and included mucositis (9.9%), dysphagia (9.1%), esophagitis (9.1%), and dermatitis (3.3%). Late grade ≥3 toxicity rates were also low, with dermatitis occurring in 8.7% and dysphagia in 71%. These reported toxicities favorably compare with photon reirradiation in which dermatitis is in the range of 13 to 32% and mucositis 13 to 43%. Unfortunately, two patients without evidence of disease developed grade V bleeding, likely due to blood vessel injury. In this study, locoregional control and survival outcomes were substantial, while toxicity was limited as compared with historical studies using photon therapy. The authors emphasize that additional prospective studies are warranted and they plan to prospectively validate the study and include cost-effectiveness data.

Notwithstanding all possible therapeutic gains associated with proton therapy dose distribution, its use in head and neck has been challenged by heterogeneity of volume density, especially sinuses (air gaps, bone) and tumor volume changes and anatomic shifts over the course of treatment. Changes in density and volumes of the course of treatment may adversely impact dose delivery. In a study on prostate cancer, at 1 year posttreatment, there was no difference in genitourinary toxicity (18.8 vs 17.5%; OR = 1.08, 95% CI = 0.76–1.54, p = 0.66). Moreover, there was no statistically significant difference in gastrointestinal toxicity at 6 or 12 months posttreatment. The lack of clear benefit thus far does not justify the higher cost associated with protons in this patient context. Many agencies have called for evidence-based guidelines to guide clinical practice. The Agency for Health Care Research and Quality,21 Institute of Medicine,2 and the Patient-Centered Outcomes Research Institute have all called for well-designed, hopefully, randomized studies examining the added value of proton therapy.

In terms of head and neck cancer, the currently open studies are shown in Table 1. A direct comparison of treatment modalities, proton vs photon radiation therapy in head and neck cancer, is NCT01893307. This is a phase II/III randomized trial of IMPT vs IMRT for the treatment of oropharyngeal cancer of the head and neck. The primary outcome of the study assesses the rate and severity of late grade III to V toxicity between IMRT and IMPT with an expected accrual of 360 patients and completion date of 2023.

Indeed, additional randomized studies are required to ascertain the comparative effectiveness of different
radiation types. Moreover, compounding these challenges, the definitions of comparative effectiveness, incremental effectiveness, and cost vary among stakeholders and countries.\textsuperscript{23} Medicare reimbursements for proton beam therapy is estimated two to three times that of IMRT. One proposed suggestion to curb costs until evidence accrues is suggested by Bekelman and Hahn,\textsuperscript{24} wherein payers will reimburse proton therapy at the photon therapy rate provided patients participate in trials that are expected to generate high-quality evidence. This reference pricing model maintains access to proton therapy with the aim of expanding the necessary research needed. The Centers for Medicare and Medicaid Services does not use cost-effectiveness data to make coverage decisions, which contrasts the views of the UK National Institute for Health and Care Excellence, which considers cost per quality-adjusted life-year when making coverage recommendations.\textsuperscript{23} The American Society for Radiation Oncology has addressed proton coverage for head and neck cancer as suitable for coverage with evidence development, if the patient is enrolled in an institutional review board-approved clinical trial or multi-institutional patient registry.\textsuperscript{25}

**CONCLUSION**

There are many potential advantages to radiation therapy with protons. While there are many single institution studies examining the added value of protons to photon therapy, the value of proton therapy must be examined in prospective randomized clinical studies and across many subsites of head and neck cancer. Additional evidence is necessary to guide efficient clinical practice, patient selection, and tumors that are most likely to benefit from this treatment modality and justify proton therapy use given its significant cost.

**REFERENCES**


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Table 1: Proton therapy studies of head and neck cancer

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Study Description</th>
<th>Outcome</th>
<th>Enrollment</th>
<th>Start date</th>
<th>Expected completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02923570</td>
<td>Phase II study of proton vs photon beam radiotherapy in the treatment of head and neck cancer</td>
<td>Grade ≥ 2 acute mucositis</td>
<td>Unilateral head and neck cancer 132 patients</td>
<td>10/2016</td>
<td>10/2021</td>
</tr>
<tr>
<td>NCT01893307</td>
<td>Phase II/Ill randomized trial of IMPT vs IMRT for the treatment of oropharyngeal cancer of the head and neck</td>
<td>Late grade III–V toxicity between the two groups cumulative late grade III+ toxicity anytime 2 years postcompletion of RT</td>
<td>360 patients</td>
<td>8/2013</td>
<td>8/2023</td>
</tr>
<tr>
<td>NCT01627093</td>
<td>Observational study prospective data collection: Proton therapy for head and neck malignancies</td>
<td>Overall survival analysis of proton therapy</td>
<td>375 patients</td>
<td>1/2012</td>
<td>1/2018</td>
</tr>
<tr>
<td>NCT01973179</td>
<td>Reirradiation of recurrent head and neck cancer</td>
<td>Primary: Late toxicity (2 years) Secondary: Acute toxicity; 2 years local recurrence-free survival; 2 years OS; QoL</td>
<td>50 patients</td>
<td>7/2015</td>
<td>8/2023</td>
</tr>
<tr>
<td>NCT02663583</td>
<td>IMPT or trans oral robotic surgery (TORS) for the treatment of low-risk oropharyngeal squamous cell</td>
<td>Primary: Functional outcome using longitudinal wristband activity monitoring; functional outcome using patient-reported outcome measures</td>
<td>44 patients</td>
<td>1/2016</td>
<td>1/2018</td>
</tr>
<tr>
<td>NCT02736786</td>
<td>A study of mucosal-sparing proton beam therapy in resected oropharyngeal tumors</td>
<td>Primary: Local control rate with protons after resection with TORS</td>
<td>67 patients</td>
<td>3/2016</td>
<td>3/2020</td>
</tr>
<tr>
<td>NCT01586767</td>
<td>Phase II: Intensity-modulated or proton radiation therapy for locally advanced sinonasal malignancy</td>
<td>Primary: 2 years local control rates Secondary: 5 years vision preservation rates; 2 years regional control; 5 years OS; 5 years QoL; 5 years tumor relapse; 5 years local control; 5 years neurocognitive function</td>
<td>90 patients</td>
<td>7/2011</td>
<td>7/2016</td>
</tr>
</tbody>
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T: Tumor; N: Node; M: Metastasis