Review Article

Proton therapy for head and neck cancer: current applications and future directions

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Abstract: Radiation therapy is a standard treatment modality for head and neck cancer. However, delivery of radiation therapy to areas of disease in close proximity to critical normal structures, can potentially result in severe toxicity. While advances in conformal radiation techniques, like intensity-modulated radiation therapy (IMRT) have led to improvements in the therapeutic ratio, significant treatment-related morbidity still exists. Proton therapy is an emerging and promising treatment modality for head and neck cancers, because of the potential to improve organ sparing and/or safely escalate doses of radiation delivered. Localized radiation therapy to limited areas of the head and neck, such as for a lateralized salivary gland tumor, can be delivered with proton therapy using current techniques. Proton therapy to the bilateral neck, as required for locally-advanced disease, will require the development of intensity-modulated techniques, intensity-modulated proton therapy (IMPT), using pencil beam scanning. Determining the proper role of proton therapy for head and neck cancer should be done in the setting of clinical studies, with careful attention to quality assurance, and meaningful measures of disease control, toxicity and quality of life.

Key Words: Head and neck cancer; proton therapy; radiation therapy

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Radiation therapy for head and neck cancer: indications and challenges

External beam radiation therapy (EBRT) is a well-established therapeutic modality in the treatment of head and neck cancer, with more than 80% of patients diagnosed with head and neck cancer receiving EBRT as a portion of their therapy. For early-stage cancers, it is often used as the primary treatment, obtaining high local control rates with limited fields (1,2). For locally advanced cancers, it is the standard treatment for cancers not amenable to surgical resection, such as nasopharynx cancer (3), and as an organ-preserving alternative to surgery for cancers such as larynx cancer (4,5). In the post-operative setting for locally-advanced disease with high-risk pathologic features, adjuvant EBRT can improve locoregional control and survival when given alone (6), or in conjunction with chemotherapy (7-9).

EBRT to the head and neck is associated with acute and late toxicity. The need to irradiate areas of disease involvement, which are in close proximity to normal tissues, results in significant radiation exposure to these tissues, with toxicity observed early in the course of treatment. Dose to the oral mucosa results in mucositis, a common side effect which can cause severe pain, difficulty swallowing, and malnutrition due to the inability to eat. Other common acute effects include xerostomia and dysgeusia. These side effects can lead to hospitalization and treatment interruptions (10), which may ultimately adversely affect disease outcomes (11).

Late effects secondary to head and neck radiation are also of concern. Dose to the cochlea can cause hearing loss, particularly in those who have also received platinumbased chemotherapy. Radiation exposure to the salivary glands causes chronic xerostomia, which can affect eating, communication, pain, and emotion (12), as well as increase the risk of developing dental caries. Patients receiving high doses of radiation to the mandible are at risk for mandibular osteoradionecrosis (13), especially if they require post-radiation dental extractions. Exposure of swallowing structures to radiation can lead to long-term dysphagia (14), aspiration, and chronic reliance on nutritional supplementation, such as via gastrostomy tube. Side effects of radiation to the neck include lymphedema, fibrosis, and hypothyroidism (15). Neck radiation can also potentially cause accelerated carotid atherosclerosis, as evidenced by an increased risk of ischemic stroke after RT in younger (16) and older patients (17). Due to the changing epidemiology of head and neck cancer, with an increasing proportion of younger patients developing human-papilloma virus (HPV) positive oropharynx cancer who are treated and cured at high rates (18), minimizing long-term radiation-related morbidity will become increasingly important.

Advances in photon-based external beam radiation therapy: 3-D conformal radiotherapy (3-D CRT) and intensity-modulated radiation therapy (IMRT)

Technical advancements in photon-based radiotherapy, such as with 3-D CRT and IMRT, allow for a more conformal deposition of the high-dose region and therefore, an improved therapeutic ratio. Three-dimensional conformal planning utilizes multiple radiation beams shaped by a static multileaf collimator in an effort to better conform radiation dose to the targets of interest. IMRT further improves this process, through the use of a dynamic multileaf collimator that can modulate both the shape and intensity of individual beams to create an optimal dose distribution to treat disease and further spare normal tissues (*Figure 1*). The addition of daily image guidance (IGRT) has led to a decrease in the planning target volume (PTV) for radiation, which has the potential of decreasing normal tissue exposure to high-dose radiation without compromising locoregional control (19).

Although direct comparisons of IMRT to conventional radiation are limited, the literature supports its use given the promising results obtained with respect to disease control, toxicity, and quality of life. The University of California-San Francisco has reported their experience of treating nasopharynx cancer with IMRT (20). A total of 35 patients were treated, and at a median follow-up of 21.8 months, locoregional control was 100%. An update of their experience, which included 67 patients with a median follow-up of 31 months, continued to show an excellent 4-year locoregional control rate of 98% (21). Compared to conventional radiation, IMRT is superior in its ability to reduce dose to critical normal organs. An example of this is sparing the parotid gland (*Figure 2*) to minimize risk of long-term xerostomia, which can impair quality of life (12). A matched case-control study comparing IMRT to standard radiotherapy for head and neck cancer found that xerostomia and quality of life improved over time (starting at 6 months post-treatment) after IMRT, but not after standard RT (22). A phase III multicenter trial (PARSPORT) randomized 94 patients to receive either IMRT or conventional RT and found that parotid-sparing IMRT significantly reduced the incidence of long-term xerostomia, and improved quality of life (23).

IMRT has also been used in the context of comprehensive nodal radiation of the neck to spare swallowing structures and minimize risk of long-term dysphagia (*Figure 3*). A prospective, clinical study of 73 patients with stage III or IV oropharynx cancer treated with concurrent chemotherapy and IMRT at the University of Michigan found that efforts to spare the pharyngeal constrictors with IMRT could be done safely (3-year locoregional control 96%), and effectively (only 1 patient was feeding tube dependent 12 months after completion of IMRT) (24). They reported that long-term measures of swallowing were only slightly worse than pre-therapy baseline levels, and found a correlation between the mean doses delivered to swallowing organs and long-term dysphagia (25). However, even with IMRT, toxicity remains a pertinent issue, with rates of long-term gastrostomy tube dependence as high as 20% (26), and impaired quality of life secondary to chronic xerostomia and dysphagia (27). Efforts to explore methods to decrease dose to normal tissues, such as with proton therapy, are therefore warranted.

Proton therapy: potential advantages

Unlike photon radiation, proton therapy offers the added advantages of less dose delivered to tissues proximal to the tumor and rapid dose fall off at the distal edge of the tumor (Bragg-Peak effect, *Figure 4*). This allows for potential gains with respect to normal organ sparing and provides opportunities for potential dose escalation. Applied in the treatment of head and neck cancer, proton therapy could be utilized in the following ways:

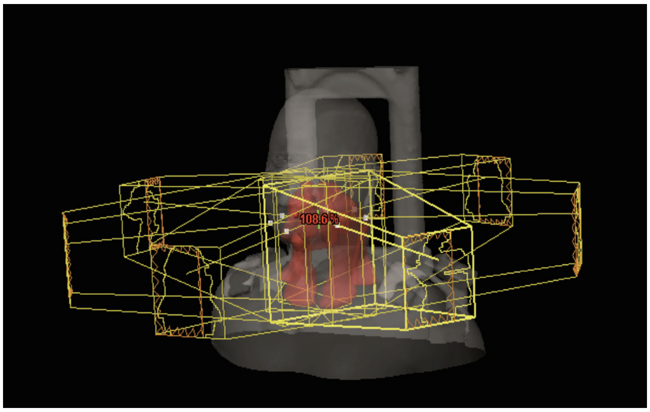

Figure 1 Patient with a stage IVa, base of tongue squamous cell carcinoma. IMRT plan for definitive radiotherapy to primary site and bilateral neck, using seven coplanar, equidistant beams with multileaf collimator

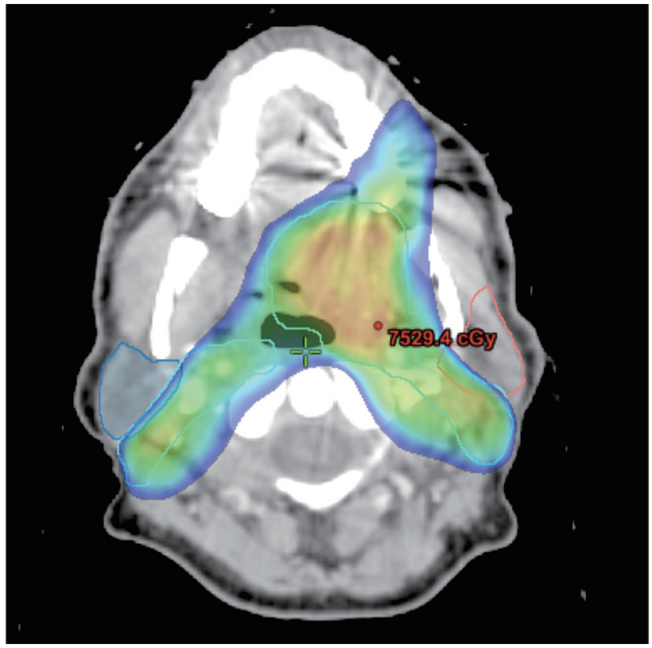

Figure 2 Stage IVa T4aN2aM0 squamous cell carcinoma of the left base of tongue, treated with definitive chemoradiation, using an IMRT technique (dose color wash set to lower limit of 57 Gy). The planning target volume (PTV, in light blue) is being covered with high dose, while the contralateral parotid gland (blue) is being spared to a mean dose of 25 Gy

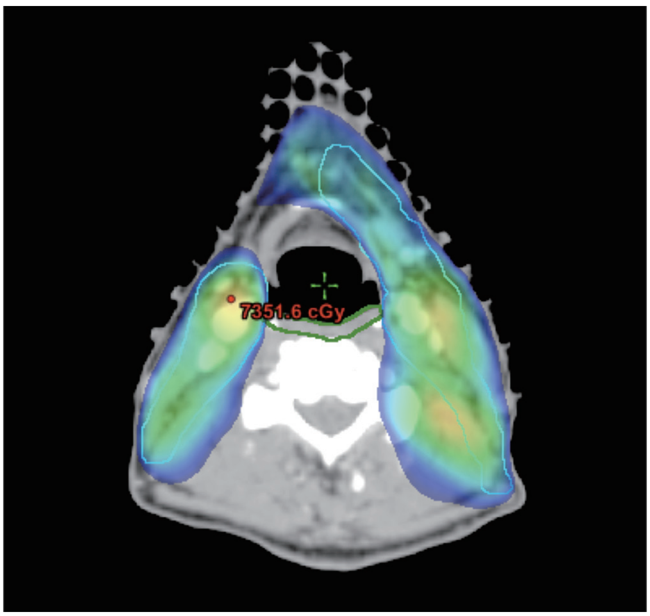

Figure 3 Sparing of swallowing structures. IMRT plan for the patient described in Figure 2 (dose color wash set to lower limit of 57 Gy). Even with elective nodal radiation of the bilateral necks (PTV in light blue), the midline, pharyngeal constrictors (green) are being spared to a mean dose of 48 Gy

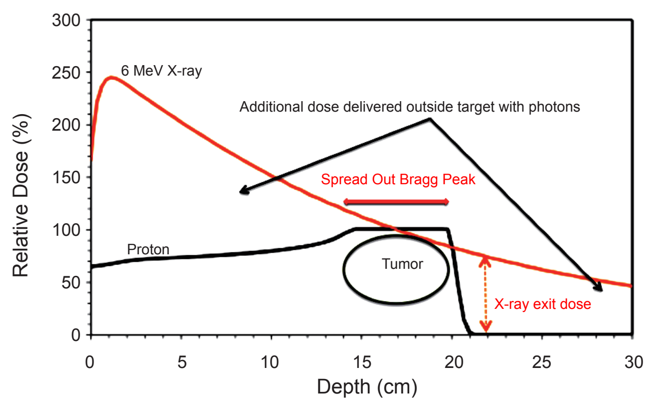

Figure 4 The physics of proton therapy. X-rays deliver a greater dose outside the target for the same dose within the target as protons

(I) Dose escalation for cancers where locoregional control is currently limited by an inability to adequately deliver therapeutic doses without excessive risk of toxicity.

(II) Minimizing exposure of normal tissues and decreasing toxicity in patients for whom long-term control is obtained with currently-prescribed doses, but at the cost of potential significant toxicity.

Multiple comparative planning studies have shown that the dose distribution attainable with proton therapy appear superior to those possible with photon radiation. Two separate studies from the Paul Scherrer Institute, each derived from the CT scans of 5 patients treated for head and neck cancer, explored the potential benefits of proton radiotherapy compared to conventional treatment. The first study, in which 3-D conformal radiation was compared to IMRT and proton therapy (passively scattered and spot scanned), demonstrated that proton therapy provided the best dose homogeneity with respect to PTV coverage, as well as spinal cord and parotid gland sparing (28). The second study, a comparison of IMRT versus intensity-modulated proton therapy (IMPT) showed that critical organs were optimally spared with IMPT, with lower estimated secondary cancer risks as a result of lower integral dose received by normal tissue (29). Reduced second-malignancy risk also appears to be an advantage for non-IMPT, double-scatter proton therapy (30), even despite concerns about secondary neutrons from protons causing second malignancies. This risk should be significantly lower with the implementation of IMPT, given the reduced secondary neutron scatter associated with this technique.

For treatment of sinonasal tumors (for which adequate dose delivery is often limited due to the proximity of normal organs), proton-based planning was superior to conventional, conformal, as well as IMRT for normal organ sparing (31), while IMPT was superior to IMRT in sparing normal organs at both low- and high-dose levels (32). To study the potential gains with respect to long-term dysphagia, van der Laan *et al.* (33) conducted a comparative study in which IMPT plans were generated for 25 patients who were treated with IMRT to the bilateral neck for oropharynx or hypopharynx cancer. In an adaptive planning study, initial and re-simulation CT images from 10 patients with head and neck cancer were used to compare differences in doses to normal structures with non-adaptive and adaptive IMRT and IMPT replanning (34). Adaptive IMPT significantly reduced doses to multiple critical structures when compared against non-adaptive IMPT, and reduced doses to all critical structures when compared to non-adaptive and adaptive photon planning.

While planning studies clearly show the dosimetric advantages of proton therapy over photon radiation, clinical implementation and correlation to outcomes have been largely limited to small, single-institution series. Early results of local control appear promising, especially in anatomic sites in which organs at risk currently limit delivery of adequate photon doses. The Massachusetts General Hospital reported a 2-year locoregional control rate of 86% in their series of 20 patients with locally advanced sphenoid sinus malignancies treated with proton beam to a median dose of 76 Gy (35). Treatment appears well-tolerated, as evidenced by the published acute and late-toxicity rates. Tokuuye *et al.* reported toxicity results on 33 patients who received definitive proton therapy to a median dose of 76 Gy, at 2.8 Gy per fraction, with one (3%) and six (18%) patients experiencing > grade 3 acute and late toxicity, respectively (36). The Heidelberg ion therapy center published one of the largest series, in which 118 patients with skull base tumors were treated with proton and carbon ion radiotherapy (37). Few side effects were observed, which were mainly grade 1. The administration of large doses per fraction with protons also appears safe. In a pilot study of 14 patients with mucosal melanoma of the head and neck treated with proton therapy three times per week for 15 fractions to a total dose of 60 Gy, all patients were able to receive the full dose of therapy (38). Initial local control was 85.7%, and at a median follow-up of 3 years, there were no treatment-related deaths. Twenty-one percent of patients experienced grade 3 mucositis, 2 patients had unilateral decrease in visual acuity.

Although these data are encouraging, there are several factors which limit the ability to draw definitive conclusions regarding proton therapy. First, proton therapy is associated with uncertainties in dose delivery typically related to uncertainty regarding the precise location of the distal edge of the Bragg peak (39-42). Second, many of the dosimetric advantages of proton radiotherapy seen in planning studies were achieved with pencil-beam scanning and IMPT, a modality which still requires further technical development and ideally, means for *in vivo* range verification prior to clinical implementation. Third, worldwide, there are still relatively few proton therapy centers, which has limited the ability to treat and analyze a large number of patients and determine the most appropriate indications for proton therapy. Additional comparative effectiveness research is needed to best understand the benefit of proton therapy for specific patient populations and clinical conditions (43).

Current indications and future applications: the University of Pennsylvania experience

At our institution, there are several indications for delivering proton therapy for head and neck cancer. One indication is for treating patients with salivary gland cancers.

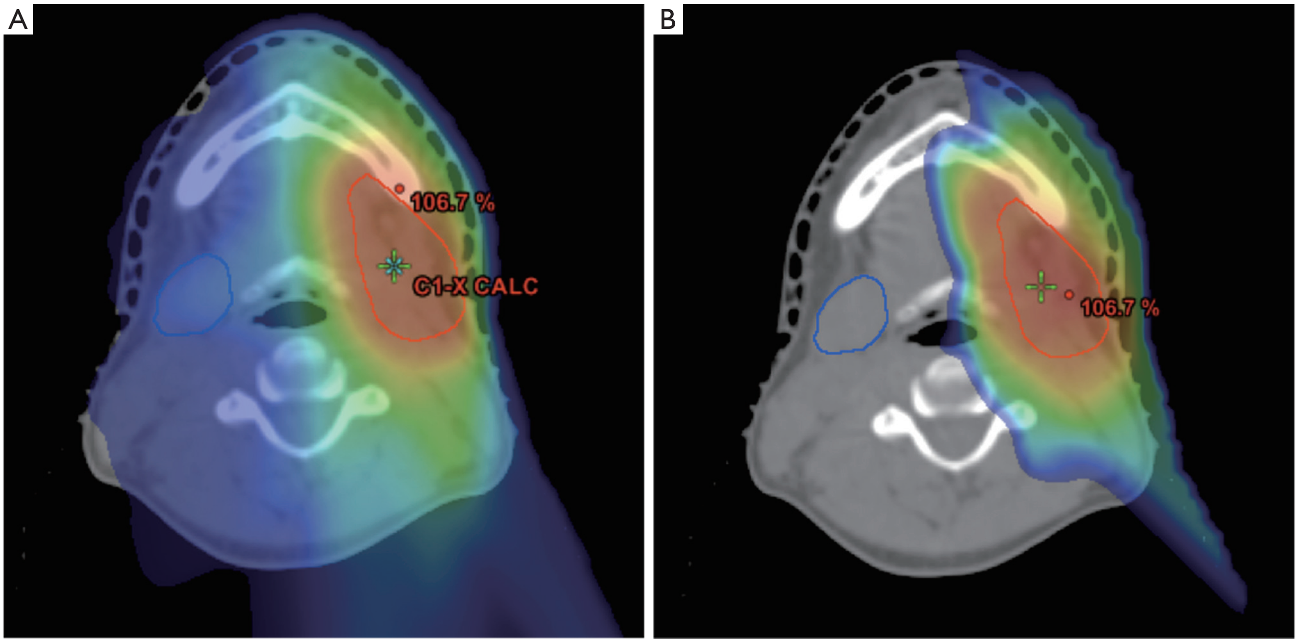

Figure 5 Patient with left submandibular gland adenoid cystic carcinoma. Tumor volume outlined in red, right submandibular gland in blue (dose color wash set at lower limit of 7 Gy). A. IMRT plan, with low dose delivered to the contralateral submandibular gland; B. Double scattering proton plan, with low dose limited to the ipsilateral neck

Previously, these patients were treated with IMRT, but are now currently treated with double scattering or uniform scanning proton therapy, as shown in *Figure 5*. When compared to IMRT, proton therapy can decrease dose to adjacent normal organs such as the brainstem, cochlea, temporal lobe, and the contralateral salivary glands. Other dosimetric advantages include limiting the area of low dose radiation delivered to normal tissues. These dosimetric gains could potentially translate to improved long-term results such as decreasing rates of chronic xerostomia and radiation-induced secondary malignancies. The potential decrease in radiation-induced malignancy with proton therapy is of particular importance, given the increasing incidence of oropharynx cancer (44), which is typically diagnosed in younger patients, and for whom long-term disease control is likely (18).

Pencil beam scanning is being used for the treatment of base of skull malignancies. Treatment of tumors at this particular site with conventional radiation has traditionally been limited by an inability to deliver adequate doses of radiation without exceeding constraints on critical structures in the brain and optic apparatus. Unlike double scattering or uniform scanning proton therapy, pencil beam scanning allows for enhanced conformal dose around critical structures through modulation of dose in depth, while retaining the rapid dose fall-off from the Bragg-Peak effect (*Figure 6*). For both of these indications, it is critical to enroll patients on clinical trials or registries to collect outcome data, thereby assessing the effectiveness and role of proton therapy.

Another indication is for reirradiation for recurrent head and neck cancer. Patients who require head and neck reirradiation generally have poor outcomes, with median survival typically less than 12 months, and reirradiation limited by treatment-related morbidity (45-48). Proton therapy, by potentially allowing for high-dose reirradiation while decreasing normal tissue exposure, may lead to improved outcomes. Lin *et al*. reported results on 16 patients reirradiated with protons for recurrent nasopharyngeal carcinoma (49), for which 2-year local control and overall survival were approximately 50%. Priority was given to minimizing toxicity (no patients experienced CNS toxicity) over tumor coverage. The 2-year survival was significantly higher in those with "optimal" dose-volume histogram coverage versus those with "suboptimal" coverage (83% and 17%, respectively, P=0.006). Patients who require head and neck reirradiation with proton therapy at the University of Pennsylvania are

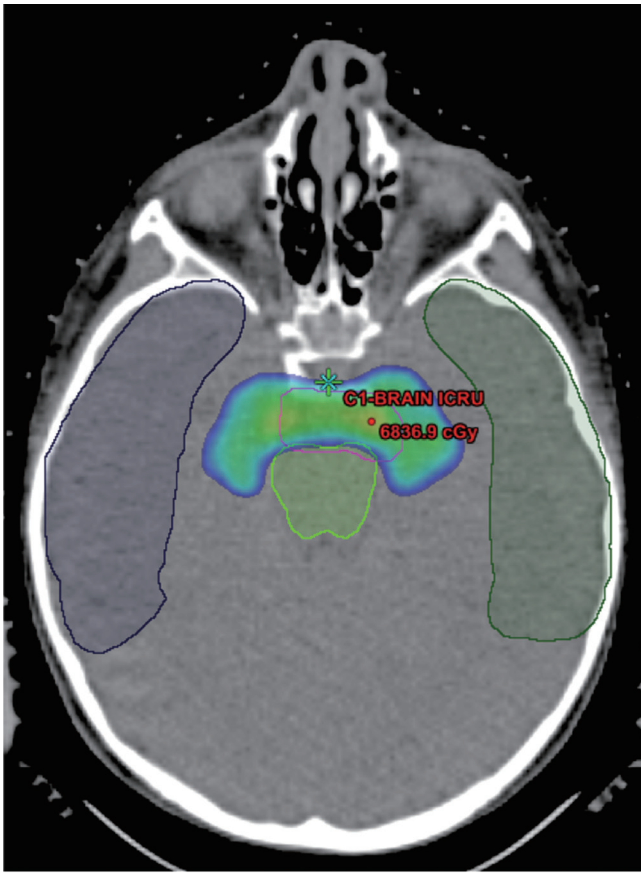

Figure 6 Pencil beam scanning proton plan for treatment to a skull base chordoma. The high-dose region is limited to the area of disease (red), sparing adjacent brainstem (green), as well as the bilateral temporal lobes (dark blue and dark green)

currently enrolled on clinical study, with the hopes that improving coverage of affected areas while minimizing normal tissue toxicity can improve clinical outcomes in a population that otherwise has limited options.

Current efforts include the development of pencil beam scanning proton therapy for treatment of the comprehensive, bilateral neck, which is required in the majority of patients with locally advanced mucosal squamous cell carcinoma of the head and neck. In order to take full dosimetric advantage of proton therapy, treatment requires a small beam spot size, which can be difficult to achieve when treating a superficial target, such as the neck. Presently at our institution, the minimum deliverable energy for pencil beam scanning is 100 MeV, requiring the use of a range shifter for treatment of targets that extend within 7.5 cm water-equivalent depth of the skin surface. There is a large air gap, typically greater than 30 cm, between the range shifter and patient surface through which spots scattered in the range shifter increase in size before reaching the target. The incorporation of a tissue-equivalent bolus that conforms and can be placed over the skin of the neck decreases the spot size of the beam at the depth of the neck lymphatics by eliminating the large air gap between the bolus and the patient. Dosimetric plans utilizing such a system show quite promising potential gains compared to IMRT, with possible further sparing of the swallowing structures (*Figure* 7), as well as the ability to protect structures not currently spared via IMRT, such as the submandibular glands (*Figure* 7). We plan to begin treatment of the comprehensive, bilateral neck within the next year by using such an approach. Other technical challenges specific to proton therapy include uncertainties in estimating proton stopping power from the planning CT image especially in cases with substantial CT image artifacts and sensitivity to anatomical changes such as patient setup or weight loss that may impact the dose distribution. Further research to quantify and minimize the impact of image artifacts is necessary to ensure robust proton therapy. Adaptive therapy and replanning during the course of therapy may be a clinical necessity in proton therapy given the dosimetric sensitivity to anatomical changes.

While from a dosimetric perspective, proton therapy appears superior to IMRT, it is still unclear whether these physical advantages translate to improved clinical outcomes. Therefore, the importance of enrolling patients who are to receive proton therapy on clinical studies cannot be overstated. These studies should have carefully described clinical endpoints, such as disease control, toxicity, and quality of life, and patients receiving proton therapy should ideally be compared to a control cohort receiving IMRT. At our institution, the goal is for all patients receiving proton therapy to be enrolled on a clinical study and/or registry. In patients receiving CNS or base of skull proton therapy, neuropsychiatric testing is performed routinely before, during and after treatment to assess the neurocognitive changes secondary to RT. In our pending implementation of bilateral neck proton therapy, we plan to assess patients with objective, functional swallow testing as well as with general, head and neck, and xerostomia-specific quality of life inventories prior, during, and after treatment. Results will then be compared to a matched cohort of patients receiving IMRT, in order to correlate dosimetric with clinical advantages.

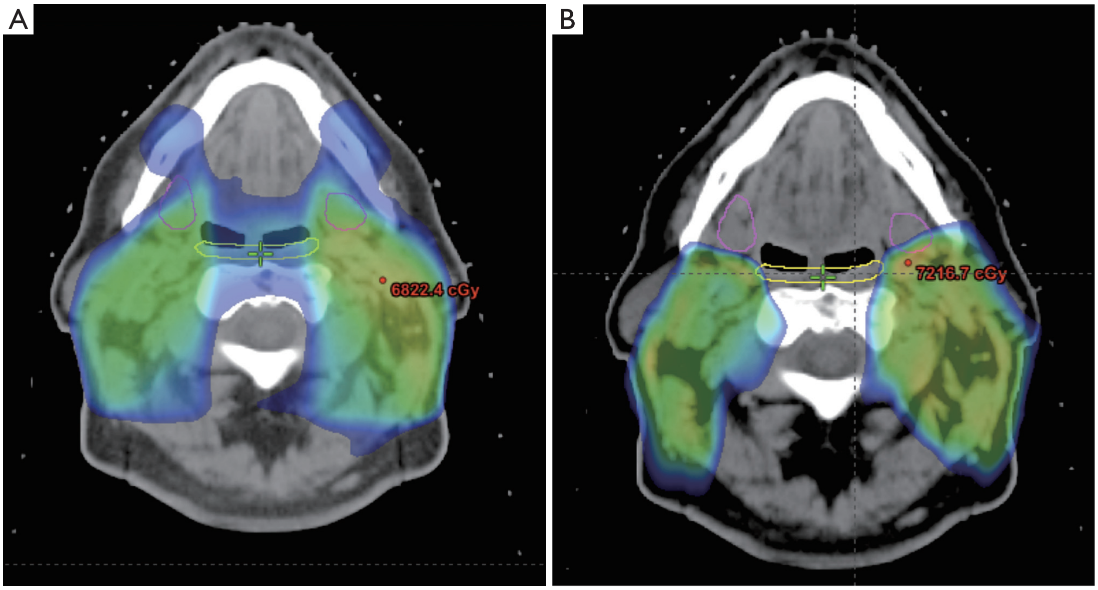

Figure 7 Patient with locally advanced larynx cancer treated with definitive chemoradiation (dose color wash set to lower limit of 45 Gy). A. Delivered IMRT plan, with areas of high dose exposure to the bilateral submandibular glands (pink) and pharyngeal constrictors (yellow); B. Pencil beam proton plan, with significant sparing of both submandibular glands (right submandibular gland mean dose 59 Gy with IMRT *vs.* 32 Gy with IMPT) and pharyngeal constrictors (mean dose 52 Gy with IMRT *vs.* 39 Gy with IMPT)

Conclusions

Proton therapy is a promising and emerging modality of radiation therapy for patients with head and neck cancers. The physical advantages inherent to protons, with rapid dose fall off, can yield improvements in the ability to escalate radiation dose, or to better spare organs at risk. Although emerging clinical data are promising, new techniques, such as pencil beam scanning and IMPT need to be developed further in order to overcome current limitations, and to potentially expand the indications under which proton therapy should be considered. Patients should ideally be treated on clinical study and compared, when possible, to a similar cohort of patients treated with IMRT.

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Footnote

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