

Reduced acute toxicity and improved efficacy from intensity-modulated proton therapy (IMPT) for the management of head and neck cancer

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Abstract: Cancers in the head and neck area are usually close to several critical organ structures. Traditional external-beam photon radiation therapy unavoidably exposes these structures to significant doses of radiation, which can lead to serious acute and chronic toxicity. Intensity-modulated proton therapy (IMPT), however, has dosimetric advantages that allow it to deposit high doses within the target while largely sparing surrounding structures. Because of this advantage, IMPT has the potential to improve both tumor control and toxicity. To determine the degree to which IMPT can reduce toxicity and improve tumor control, more randomized trials are needed that directly compare IMPT with intensity-modulated photon therapy. Here we examine the existing evidence on the efficacy and toxicity of IMPT for treating cancers at several anatomic subsites of the head and neck. We also report on the ability of IMPT to reduce malnutrition, and gastrostomy tube dependence and improve patient-reported outcomes (PROs).

Keywords: Proton therapy; intensity-modulated proton therapy (IMPT); nasopharynx cancer; oropharynx cancer; malnutrition; gastrostomy tube

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Introduction

Proton radiation therapy has been used for more than 20 years to treat cancer that arises in anatomically challenging head and neck locations. However, most patients with head and neck cancer to date have been treated with photon external-beam radiation therapy (EBRT). Significant improvements have been achieved over time in the planning and delivery of photon therapy, which has evolved from using 2-dimensional plans to 3-dimensional plans and on from there to the highly conformal technique

of intensity-modulated radiation therapy (IMRT). These improvements have led to better radiation dose distribution and improved outcomes. However, proton therapy is becoming increasingly common, largely because of its dosimetric advantages. Protons have a Bragg peak, a unique physical characteristic that allows charged particles to deposit a large fraction of their energy at the end of their path. This largely spares distal structures from being exposed to exit dose beyond the tumor target. The heavier mass of protons also causes smaller scattering angles, which

lead to sharper lateral dose distributions.

At this time, two types of proton therapy are in use: passive scatter or active scanning (also known as pencil beam proton therapy). In passive scatter therapy, the proton beam is spread by using either single- or double-scattering foils. This technique has several drawbacks; patient-specific devices are needed, which can be both expensive and labor-intensive to produce, particularly as tumors change shape over time. Also, the interaction of protons with the scattering material and collimators can lead to increased neutron production, which is associated with a risk of secondary malignancy. Finally, the scattering foils can absorb some of the energy of the protons and reduce the depth of penetration of the Bragg peak. In contrast, in active scanning proton therapy, magnets are used to deflect and steer the beam, which allows the entire treatment volume to be “painted” with the proton beams (1). The depth of the Bragg peak is modified by adjusting the energy of the beam before it enters the nozzle. Intensity-modulated proton therapy (IMPT) plans can be generated either by single-field optimization or by multiple-field optimization (2). Single-field optimization involves individually optimizing the spot intensities for each beam, whereas in multiple-field optimization, all beam intensities are optimized simultaneously to achieve an optimal dose distribution to the target and organs at risk of harboring subclinical disease (3). IMPT further provides greater dose conformity and a smaller integral dose than passive scatter proton therapy does.

The ability of IMPT or pencil beam proton therapy to direct high doses of radiation to tumors while sparing surrounding healthy tissues is particularly important in the treatment of head and neck malignancies. EBRT can allow some degree of organ preservation while avoiding some of the morbidity of surgery. However, traditional EBRT is also associated with significant morbidity because of the close proximity of several critical organ structures, as described further in the next paragraph. IMPT using pencil beam proton therapy has the potential to deliver tumoricidal radiation doses to tumors while sparing surrounding tissues, which would be expected to reduce morbidity and mortality. Notably, the precision of IMPT also has a disadvantage in that its accuracy can be compromised by changes in patient anatomy. Yeh *et al.* (4) showed that adaptive planning (i.e., repeated treatment planning over the course of therapy) is required to maintain initial dose constraints in the treatment of head and neck tumors; Palmer *et al.* (5) found that the fourth week of treatment is the optimal time for off-line adaptive planning.

With regard to side effects, head and neck cancers are of diverse histology and arise at a variety of anatomic subsites, including the paranasal sinuses, salivary glands, oral cavity, pharynx, and larynx. Side effects from EBRT are specific to the anatomic location of the cancer. However, the most common side effects encountered are xerostomia, dysphagia requiring short-term or permanent gastrostomy (feeding tube dependence), necrosis of soft tissue and bone, neck fibrosis, hearing impairment, optic neuropathy, temporal lobe necrosis, and secondary malignancies (6). A systematic review of *in silico* treatment-planning comparison studies demonstrated that protons have a dosimetric advantage over photon EBRT in that they provide lower doses to normal tissues, which raises the possibility of increasing the dose to a tumor without increasing toxicity (7). In this review, we assess the current state of the literature with regard to the effectiveness of IMPT, its acute toxicity, patient-reported outcomes (PROs), and the need for gastrostomy among patients with head and neck cancer.

Early findings on effectiveness and acute toxicity by organ site

Previous treatment-planning comparisons indicate that IMPT has considerable dosimetric advantages over IMRT and has the potential to reduce treatment-related toxicity, with equivalent or superior effectiveness, compared with IMRT. IMPT, however, is a relatively new technology, and published reports, albeit encouraging, are somewhat sparse. Two examples are studies published by Bhattasali *et al.* and Holliday *et al.*, who used IMPT to treat patients with adenoid cystic carcinoma. At median follow-up times of 24.9 and 27 months, the local control rates in these studies were impressive at 88.9% and 93.8%, and toxicity was considered acceptable (8,9). These findings are a vast improvement over historical local control rates of 0% to 43% for traditional radiation therapy (8), although the possibility of selection bias cannot be ruled out. In the following sections, we discuss the current state of knowledge of the efficacy and toxicity of IMPT for head and neck cancer at different anatomic subsites. A summary of these results can be found in *Table 1*.

Chordomas and chondrosarcoma of the skull base

Both chordomas and chondrosarcomas of the skull base are radioresistant tumors. Early attempts at treatment with photon EBRT led to disappointingly low 5-year

Table 1 Summary of clinical studies of proton beam radiotherapy for head and neck cancers

Subsite	Authors [year]	Patient	Toxicity	Treatment outcome	Patient survival
Chordomas and chondrosarcomas of skull base	Rutz <i>et al.</i> [2008]	10 pts (6 chordomas and 4 chondrosarcomas) treated with spot scanning but 3 pts were treated without IMPT	Acute: grade 1 alopecia was reported. Chronic: one pt had grade 2 insufficiency of the pituitary gland; one pt had grade 1 asymptomatic changes on MRI and grade 1 moderate hearing loss and grade 1 persistent focal alopecia; one pt had grade 1 neurosensory deficit in left arm (pts who received IMPT had no late effects)	Local control and disease free survival 100% at 3 years	OS 100% at 3 years
	Ares <i>et al.</i> [2009]	64 pts (42 chordomas and 22 chondrosarcomas) treated with spot scanning. 20 of these were IMPT	Chronic: five pts developed grade 1 leukoencephalopathy; one pt developed grade 3 unilateral optic neuropathy; one pt had grade 4 toxicity; two pts developed grade 3 symptomatic temporal lobe parenchyma damage	Local control at 5 years for chordomas is 81% local control and 94% for chondrosarcomas	Chordoma: OS 62% at 5 years. Chondrosarcomas: OS 91% at 5 years
	Rombi <i>et al.</i> [2012]	26 pts (19 chordomas and 7 chondrosarcomas) treated with spot scanning and IMPT	Acute: 15 events of grade 2 toxicity; no high grade acute toxicity. Chronic: eight events of late grade 2 toxicity, two pts developed otitis media requiring drainage; one pt developed unilateral hearing impairment; four pts developed partial hypopituitarism, and one pt developed symptomatic nasal mucosal crusting	Local control at 5 years for chordomas is 88% and 86% for chondrosarcomas	Chordoma: OS 89% at 5 years. Chondrosarcomas: OS 75% at 5 years
Nasopharynx	Chan <i>et al.</i> [2012]	23 pts treated with protons to the nasopharynx and upper neck; photons were used for lower neck	Acute: no grade 4 or 5 toxicity. Chronic: 29% of pts had grade 3 hearing loss; 38% of pts had grade 3 weight loss	Local control 100% at 28 months	90% OS at 2 years
	Holliday <i>et al.</i> [2014]	13 pts treated with IMPT	Acute: limited toxicity data reported but three pts needed GT tube placement and median percent body loss was 5.3%. Chronic: one pt developed oropharyngeal dysphagia	Local control 100% at 13.5 months	100% cancer-specific survival at 13.5 months
	Holliday <i>et al.</i> [2015]	10 pts treated with IMPT	Acute: a total of nine grade 3 toxicities four of which were grade 3 dermatitis; four developed grade 2 dermatitis; one developed grade 1 dermatitis. Chronic: five grade 3 toxicities; two developed temporal bone necrosis	Local control 100% at a median follow up of 21.6 months	OS 90% at a median follow up of 21.6 months
	Lewis <i>et al.</i> [2016]	9 pts treated with IMPT	Acute: four pts with grade 3 radiation dermatitis; one pt with grade 3 mucositis; eight pts with grade 2 mucositis; four pts with grade 3 dermatitis; five pts with grade 2 dermatitis. Chronic: two pts with grade 2 xerostomia and six pts with grade 1 xerostomia	Local control 100% at 2 years	88.9% OS at 2 years
Periorbital	Holliday <i>et al.</i> [2015]	20 pts; 14 with passive scatter 9 with IMPT	Acute: seven pts developed acute grade 3 radiation dermatitis. Chronic: three pts developed grade 3 epiphora; three developed grade 3 exposure keratopathy; five pts had decreased visual acuity and four developed asymptomatic retinopathy	Local control 100% at median follow up time of 27.5 months (but one patient had regional recurrence and one had distant metastasis)	Not reported but only one patient had a regional recurrence and only one patient had distant metastasis

Table 1 (continued)

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Subsite	Authors [year]	Patient	Toxicity	Treatment outcome	Patient survival
Nasal cavity and paranasal sinus	Holliday <i>et al.</i> [2014]	16 pts treated with IMPT	Acute: 1 pt had grade 3 dermatitis; 13 pts had grade 2 dermatitis; 5 pts had grade 2 mucositis; 2 pts had grade 2 dysgeusia	Local control 87.5% at 10.5 months (and two pts have metastatic disease)	Not reported but two patients failed locally and two had metastatic disease
Parotid cancer	Patel <i>et al.</i> [2014]	286 pts treated with charged particles	The toxicity event rate for charged particle therapy for different body systems were 0.19 for eye; 0.54 for head and neck; 0.07 for nasal; 0.20 for ear; 0.20 for neurological; 0.41 for miscellaneous; and 2.31 for hematological (toxicity event rate for proton therapy alone was not reported)	Locoregional control 66% at 5 years for charged particles (n=58) and 43% for proton therapy (n=36)	OS at 5 years 72% for charged particle therapy (n=146) and 66% for proton therapy (n=124)
Parotid cancer	Holliday <i>et al.</i> [2014]	13 pts treated with IMPT	Acute: four pts had grade 3 dermatitis; nine pts grade 2 dermatitis; one patient experience grade 2 mucositis and oral pain. Chronic: no serious long term toxicity	Local control 100% at a median follow up of 13.2 months	OS 100% at a median follow up of 13.2 months
Oropharyngeal	Slater <i>et al.</i> [2005]	29 pts treated with passive scatter proton therapy and photon therapy	Acute: not reported. Chronic: one pt had grade 3 vocal cord paralysis; one pt had grade 3 subcutaneous fibrosis; one pt had grade 3 trismus with secondary tooth decay	Local control 96% at 2 years	OS not reported; disease free survival 88% at 2 years
Oropharyngeal	Gunn <i>et al.</i> [2016]	50 pts treated with IMPT	Acute: 23 pts had grade 3 radiation dermatitis; 29 had grade 3 oral mucositis; 12 had grade 3 dysphagia; 1 had grade 3 weight loss; and 1 had grade 3 dry mouth. Chronic: six pts had dysphagia, one had dry mouth and one had oral mucositis	Local Control 96% at a median follow up of 29 months	OS 94.5% at 2 years
Recurrence	Blanchard <i>et al.</i> [2016]	50 pts treated with IMPT	Acute: 39 pts had grade 2–3 fatigue. Chronic: 21 patients had grade 2–3 xerostomia	Locoregional control 91.0% at 3 years	OS 94.3% at 3 years
Recurrence	Romessor <i>et al.</i> [2016]	18 pts treated with uniform scanning proton therapy	Acute: no grade 4 or higher toxicities. Five cases of acute grade 3 dermatitis, but no other grade 3 acute toxicities. Chronic: not reported	Locoregional control 80% at 1 year	OS 83.3% at 1 year
Recurrence		92 pts treated with uniform scanning proton therapy	Acute: no grade 4 or higher acute toxicities. The grade 3 acute toxicities included nine cases of mucositis, six cases of dysphagia, six cases of esophagitis, and three cases of dermatitis. Chronic: two cases of grade 5 bleeding; five cases of grade 4 skin toxicity; one incident of grade 3 skin toxicity; four incidents of grade 3 dysphagia	Locoregional control 74.9% at 1 year	OS 65.2% at 1 year
Recurrence	Phan <i>et al.</i> [2016]	60 pts treated with passive scatter (n=15) and IMPT (n=45)	Acute: 27 incidents of grade 3 toxicity 8 cases dermatitis; 6 cases of mucositis; 6 cases of odynophagia; 3 cases of dysphagia; 2 cases xerostomia; and 2 cases of weight loss. Chronic: two potential grade 5 toxicities one associated with osteoradionecrosis of the hyoid bone and one associated with mucosal ulceration. 12 incidents of late G3 toxicity. 6 cases of feeding tube placement; 2 cases of neurotoxicity; 2 cases of tracheostomy, 1 case of dysphagia and 1 case of xerostomia	Locoregional control 72.8% at 2 years	OS 69.7% at 2 years

OS, overall survival; pt, patient(s).

progression-free survival rates of <25% (10,11) and significant risks of serious toxicity (6). Combined proton and photon therapy, however, produced more encouraging results. In one such study reported by Munzenrider *et al.* (12), the 5-year local recurrence-free survival rate was 73% for patients with chordoma and 98% for patients with chondrosarcomas; another study from Noël *et al.* (13) revealed a local control rate of 54% at 4 years. Unfortunately, the toxicity of these treatments was unacceptably high: in the Munzenrider study, three patients died from brain stem injuries, eight had temporal lobe injuries, and other patients had hearing loss, cranial neuropathy and endocrinopathy (12). Another group used uniform scanning proton therapy for recurrent chordoma (14) and achieved much higher local control and overall survival (OS) rates (85% and 80% at 2 years). Unfortunately, re-irradiation was associated with high-grade acute and chronic toxicity, with one patient experiencing grade 3 laryngeal edema that necessitated a permanent tracheostomy and another grade 4 acute fourth ventricular obstruction that required placement of a shunt. Another patient experienced grade 3 chronic toxicity (radiation necrosis) and two others had grade 4 chronic toxicity (ischemic brainstem stroke and cerebrospinal fluid leak with meningitis).

The next generation of radiation therapy, IMPT, has had excellent efficacy with less toxicity relative to combined proton and photon EBRT. Rutz was the first to report the use of IMPT for skull-base chordoma and chondrosarcomas (15). In that small study, 10 patients were treated with spot scanning proton therapy (3 with IMPT) to a total dose of 66–74 Gy(RBE) without chemotherapy. The local control rate, disease-free survival rate, and OS rate were all 100% at 3 years, and no patient experienced acute toxicity that was worse than grade 1. However, 30% of these patients had some form of late toxicity. These early results were subsequently confirmed by Ares *et al.* (16) and Rombi *et al.* (17). Ares and colleagues reported results from 64 patients with skull-base chordoma or chondrosarcoma who had been treated to a mean dose of 68.4 Gy(RBE) with spot scanning proton beam radiation therapy. Twenty of these patients were treated with IMPT. At a mean follow-up time of 38 months, the estimated 5-year local control rate was 81% for chordomas and 94% for chondrosarcomas, and the estimated 5-year disease-specific survival rate was 81% for chordomas and 100% for chondrosarcomas. Toxicity results were also encouraging: at 5 years, 94% of patients were free from high-grade toxicity (two patients had grade

3–4 optic neuropathy and two had grade 3 symptomatic temporal lobe damage). The study reported by Rombi *et al.* involved 26 patients with chordoma or chondrosarcoma who were treated with spot scanning proton therapy; again, a subset of those patients received IMPT. Local control rates at 5 years were encouraging at 88% for chordomas and 86% for chondrosarcomas, as were 5-year survival rates (89% for chordomas and 75% for chondrosarcomas). No patient experienced acute or chronic toxicity that was worse than grade 2. These results demonstrate the potential of IMPT to improve local control and reduce toxicity relative to photon external-beam or combined proton and photon therapy.

Nasopharyngeal cancer

Nasopharyngeal carcinoma is common in Asia, and radiation therapy can lead to significant toxicity. The four most common types of severe (grade ≥ 3) toxicity after 2D radiotherapy as reported by Sanguineti *et al.* (18) are pituitary dysfunction, cranial nerve dysfunction, fibrosis and trismus. Late toxicity associated with 2D and conformal radiotherapy has also been reported in larger studies by Tuan *et al.* and Lee *et al.* (19,20), who highlighted the extremely narrow therapeutic margin for this type of cancer. IMRT with chemotherapy is often used for nasopharyngeal cancer, but combined proton and photon therapy has had promising results as well (21). Chan *et al.* published preliminary results of a phase II trial of 23 patients with stage III/IVb nasopharyngeal cancer. At a follow-up interval of 28 months, 2-year rates of local control, disease-free survival, and OS were 100%, 90%, and 100%. Side effects, however, were significant. Although no patient had grade 3 or higher xerostomia, 48% had a gastrostomy tube placed during treatment, 38% had grade 3 weight loss, and 29% had hearing loss (22).

To date, most of the published reports on IMPT for nasopharyngeal cancer have come from The University of Texas MD Anderson Cancer Center; initial results have been promising. In one of those studies, Lewis *et al.* compared the dose to 29 organs at risk on treatment plans for IMPT versus IMRT; mean doses to 15 of those organs were significantly different for the two modalities, with doses to 13 of those organs being lower on the IMPT plans (23). Another study (24) reported early outcomes for 13 patients given IMPT for nasopharyngeal cancer from 2011 to 2013; 2 of those patients had recurrent disease and had previously received photon RT, and the

other 11 had newly diagnosed disease (five T1, two T2, two T3, and two T4; one N0, three N1, seven N2). Nine patients received induction chemotherapy and all patients received concurrent chemotherapy. During the median follow-up interval of 4.6 months (range, 1.8–9 months), side effects were mild, with a median percent body weight loss of 5.3% (range, 1.1% to 14%), with only one patient experiencing swallowing dysfunction. In another study from MD Anderson, 10 patients who received IMPT for nasopharyngeal cancer were case-matched with another 20 patients who received IMRT for nasopharyngeal cancer, with match criteria being T status, N status, radiation dose, chemotherapy type, WHO classification, sex, and age. Toxicity associated with IMPT, quantified in terms of gastrostomy tube placement, was significantly lower among patients treated with IMPT (20% *vs.* 65% for IMRT, $P=0.02$). Notably, no patient who received a mean oral cavity dose of <26 Gy required a gastrostomy tube (25). Future prospective clinical trials are planned with the goals of reducing the toxicity associated with treatment of nasopharyngeal cancer as well as improving disease outcomes for patients with T4 disease.

Periorbital tumors

Periorbital tumors are quite rare, with an estimated incidence of only 0.072 per 100,000 people (24). This low prevalence precludes using randomized controlled trials to determine the optimal treatment for periorbital tumors. To date, most cases have been managed with orbital exenteration, with adjuvant radiation therapy or chemoradiation depending on the pathologic findings. Some evidence exists to suggest that postoperative radiation can improve clinical outcomes; photon EBRT has been shown in retrospective analyses to improve local control rates by up to 50% (24). However, radiation is also associated with acute toxicity, most often conjunctivitis, loss of eyelashes, xerophthalmia, and punctate erosion of the cornea (26). Proton therapy may be able to reduce the toxicity burden to ocular structures after orbit-sparing surgery, which would complete the “trifecta” of cure, cosmesis, and function. In a landmark study by Holliday *et al.* (27), 20 patients who had had orbit-sparing surgery for a new diagnosis of periorbital cancer received postoperative IMPT ($n=6$) or passive scatter proton therapy ($n=14$). The median radiation dose to the tumor was 60 Gy(RBE) [range, 50–70 Gy(RBE)]; 11 patients had concurrent chemotherapy; and the median follow-up time was

27.1 months (range, 2.6–77.2 months). No patient experienced grade 4 or grade 5 toxicity; three patients developed chronic grade 3 epiphora and three developed grade 3 exposure keratopathy. Visual acuity dropped below baseline levels in four patients, but all four maintained vision sufficient to perform all activities of daily living without difficulty. The maximum dose to the ipsilateral cornea was related to grade 3 chronic ocular toxicity: no patient whose maximum dose to the ipsilateral cornea of <36 Gy(RBE) developed grade 3 chronic toxicity, but 46% of those who received >36 Gy(RBE) developed grade 3 chronic toxicity. Also notable was the finding that grade 3 acute toxicity seemed to depend on treatment modality, with 67% of the IMPT group having grade 3 acute toxicity versus 21% of the passive scatter group ($P=0.052$). At this time, a multidisciplinary approach to periorbital tumors that includes proton therapy seems essential for ensuring the highest cure rates with excellent cosmesis and preservation of vision.

Nasal cavity and paranasal sinus cancers

Nasal cavity and paranasal sinus tumors are typically treated with surgery followed by postoperative EBRT. This therapy can produce good 5-year local control rates (82% for T1–3 tumors and 50% for T4 tumors) (28), but it can also cause blindness in up to 38% of patients owing to retinopathy and optic neuropathy (29–31). Combined proton and photon therapy and passive scatter proton therapy seem to have better toxicity and tumor control. Fitzek *et al.* (32) and Resto *et al.* (33) both described their experience with combined proton and photon therapy. In Fitzek's study of 19 patients with olfactory neuroblastoma, the 5-year local control rate was 88% and no patients experienced radiation-induced vision loss, although four patients had evidence of radiation-induced damage on magnetic resonance imaging. The larger study reported by Resto *et al.* included 102 patients with locally advanced sinonasal cancer; 5-year local control rates were 95% for patients who had complete resection, 82% for those with a partial resection, and 87% for those who had biopsy only. A prospective non-randomized trial reported by Okano *et al.* (34) involved using passive scatter proton therapy to treat 13 patients with T4b nasal and sinonasal cancers; results of that study were excellent, with 85% of patients achieving complete response and no patients experiencing blindness or acute brain damage. These positive results were corroborated by a meta-analysis by Patel *et al.* (35) comparing outcomes

after charged particle therapy versus photon therapy. In that study, charged particle therapy led to superior 5-year rates of OS, disease-free survival and local-regional control over IMRT.

Given the relative rarity of nasal cavity and paranasal sinus cancers, little is known of the potential advantage of IMPT for these tumors, and randomized controlled trials are unlikely. At MD Anderson, Holliday and Frank described initial results for 16 patients with nasal or paranasal sinus tumors treated with IMPT (24), 6 with adenoid cystic carcinoma, 6 neuroblastoma, 3 squamous cell carcinoma, and 1 with an undifferentiated carcinoma. The median follow-up time was 10.2 months (range, 1.33–20.3 months). Thirteen patients had received IMPT after resection and 3 received IMPT as definitive treatment; disease was newly diagnosed in 12 patients and recurrent in the other 4. The median radiation dose received was 62 Gy(RBE) [range, 60–70 Gy(RBE)]; 11 patients received concurrent chemotherapy and 2 received induction chemotherapy. Treatment was well tolerated, with no grade 4 or 5 toxicity. One patient had grade 3 dermatitis; 13 had grade 2 dermatitis; 5 had grade 2 mucositis; and 2 had grade 2 dysgeusia. Eight patients required opioids for pain management during treatment, and 2 patients required a gastrostomy tube for nutritional support. At last follow-up, no patient had grade 3–5 late effects. Of the 13 patients who had surgery before IMPT, 10 had no evidence of disease, 2 had metastatic disease, and 1 had locally recurrent disease. Of the three patients who received IMPT with definitive intent, two had stable disease and one had progressive disease.

Parotid tumors

Salivary tumors are also fairly uncommon, contributing less than 5% of all head and neck tumors (36). Surgery is the main form of treatment for parotid tumors, but certain subtypes of tumors and tumors with certain high-risk features are treated with postoperative radiation. Local control and OS rates for patients given postoperative radiation therapy are 73–94% and 69–78% (37,38). Little has been published on proton therapy for parotid tumors. One dosimetric study comparing proton therapy with IMRT showed that proton therapy was associated with significantly lower doses to the contralateral parotid gland and submandibular gland, spinal cord, brainstem, and oral cavity (39). Another study reported by Romesser *et al.* (40) compared acute toxicity between uniform scanning

proton therapy and IMRT for patients with recurrence or metastatic disease to the major salivary glands. That study showed that grade ≥ 2 acute effects such as dysgeusia, mucositis, and nausea were less common among patients treated with protons. The only other published study to date has been from MD Anderson (24), reporting 13 patients with parotid tumors (4 with metastatic disease and 9 with newly diagnosed disease) who received IMPT from 2011 to 2013. Twelve of these patients had received surgery before radiation; 1 patient had had induction chemotherapy (for borderline resectable disease) followed by chemoradiation and surgery. Radiation doses ranged from 50 to 70 Gy(RBE) [median 60 Gy(RBE)]. At a median follow-up time of 13.2 months (range, 3.2–15.9 months), all patients had completed radiation as planned; treatment was well tolerated, with no grade 4 or grade 5 toxicity. Four patients had grade 3 dermatitis, nine patients had grade 2 dermatitis, and one patient had grade 2 mucositis and oral pain. Two patients required opioids for pain management. The median change in body weight was -1.3% and ranged from -3.7% to $+3.1\%$. No patient required a gastrostomy tube, and no patient had any serious late toxicity by the time of last follow-up. When that review was published, none of the patients had any evidence of recurrent or metastatic disease.

Oropharyngeal cancer

Radiation therapy, with or without chemotherapy, is typically used to treat oropharyngeal cancer, but local failure and acute toxicity are common with this treatment. Common acute effects include mucositis, dermatitis, dysphagia, sore throat, odynophagia, thickened secretions, in-field alopecia, xerostomia, and taste disturbance (41). Historically, local control rates have been suboptimal, being only 55% in the concomitant boost arm of the RTOG 9003 trial (42). Slater *et al.* (43) described 29 patients with stage II–IV oropharyngeal cancer treated with a combination of passive scatter proton therapy and photon therapy to a total dose of 75.9 Gy(RBE), with promising results. Although the follow-up period varied from 2 to 96 months, the actuarial 2-year local control rate was 96%. Only three incidents of grade 3 late toxicity were reported, namely a vocal cord paralysis, subcutaneous fibrosis, and trismus with secondary tooth decay. Acute toxicity rates were not reported, but all patients were said to have been able to complete treatment as planned, with the aid of nutritional and anesthetic support.

In a recent case-matched control analysis of IMRT and

IMPT plans, the IMPT plans delivered significantly lower doses to the anterior and posterior oral cavity, hard palate, larynx, mandible, esophagus, and several central nervous system structures involved in the nausea and vomiting response (44). This improved dose distribution may lead to a decrease in treatment-related toxicity. Gunn and colleagues from MD Anderson recently published results from 50 patients with oropharyngeal cancer treated with IMPT (45). In that study, overall and progression-free survival rates at 2 years were 94.5% and 88.6%. Toxicity was considered encouraging, with no patients having grade 4 or 5 acute or late toxicity. Grade 3 acute toxicity was relatively common and included 23 incidents of radiation dermatitis, 29 oral mucositis, 12 dysphagia, 1 weight loss, and 1 dry mouth; grade 3 late toxicity consisted of 6 incidents of dysphagia, 1 dry mouth, and 1 oral mucositis. The median body weight loss was 7.4%, and 12 patients required gastrostomy tube placement. Blanchard and colleagues used a case-matched design to compare 50 patients with oropharyngeal cancer who received IMPT with 100 patients with the same type of cancer treated with IMRT (46). Rates of severe weight loss and feeding tube placement were both lower for patients who received IMPT, and OS and progression-free survival rates at 3 years for the IMPT group were 94.3% and 85.8%. In terms of toxicity, 12 patients in the IMPT group had gastrostomy tubes placed, and 39 had grade 2–3 fatigue during treatment. At 3 months after treatment, 4 patients had lost more than 20% of their baseline body weight and 21 had grade 2–3 xerostomia. Currently, a multi-institutional randomized controlled phase II/III trial is underway to compare the incidence and severity of chronic grade 3–5 toxicity for patients with advanced oropharyngeal cancer treated with IMPT or IMRT [NCT01893307, “Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck”]. The results of this trial are expected to help clarify the extent to which IMPT can reduce toxicity for patients with oropharyngeal cancer.

Recurrent head and neck cancer

A significant proportion of patients with head and neck cancer will need repeated radiation therapy for disease that recurs after definitive treatment; indeed, local-regional recurrence is the leading cause of death for such patients (47). Re-irradiation can be curative but also has

significant toxic side effects, with rates of grade ≥ 3 toxicity ranging from 34% to 65% (48). These forms of toxicity can include trismus, osteoradionecrosis, subcutaneous fibrosis, late mucosal side effects, pharyngeal, laryngeal, esophageal dysfunction, or carotid ruptures (48). Survival rates after conventional re-irradiation are less than optimal, ranging from 26% to 57% at 2 years (49). Some preliminary evidence exists to suggest that proton therapy may reduce toxicity and improve survival among patients needing re-irradiation. For instance, Stuschke *et al.* found that IMPT was better able to spare normal tissues than was helical tomotherapy (48). Romesser *et al.* (40) analyzed patients with recurrent head and neck cancer, comparing 18 patients who received uniform scanning proton therapy with 23 patients who received IMRT. That study showed that patients treated with protons had significantly lower rates of grade ≥ 2 acute dysgeusia, mucositis, and nausea. Actuarial rates of local-regional control and OS for the proton group at 1 year were 80% and 83.3%. No patient in the proton group had grade ≥ 4 toxicity; five had acute grade 3 dermatitis, but no other forms of grade 3 acute toxicity were experienced. A more recent multi-institutional study by the same group (50) analyzed 92 patients treated with uniform scanning proton therapy for recurrent head and neck cancer; rates of local-regional control and OS at 1 year were 74.9% and 65.2%. No patients experienced grade ≥ 4 acute toxicity; as for grade 3 acute toxicity, nine patients had mucositis, six had dysphagia, six had esophagitis, and three had dermatitis. Late effects included two cases of grade 5 bleeding and five of grade 4 skin toxicity; one patient had late grade 3 skin toxicity and four had late grade 3 dysphagia. Finally, 32 patients (35%) received a gastrostomy tube during this study. These encouraging results were recently confirmed by Phan *et al.* (49), who examined 60 patients treated with either passive scatter proton therapy ($n=15$) or IMPT ($n=45$); rates of local-regional control and OS at 2 years were 72.8% and 69.7%. The 27 incidents of grade 3 toxicity consisted of 8 cases of dermatitis, 6 mucositis, 6 odynophagia, 3 dysphagia, 2 xerostomia, and 2 weight loss. Thirteen of the patients in that study (22%) required placement of a gastrostomy tube. As for late effects, two patients developed possibly treatment-related late grade 5 toxicity, one with osteoradionecrosis of the hyoid bone and another with mucosal ulceration. The 12 incidents of late grade 3 toxicity consisted of 6 patients requiring feeding tubes, 2 with neurotoxicity, 2 with tracheostomy, 1 with dysphagia, and 1 with xerostomia. In summary, these early results suggest that re-irradiation with protons seems to

offer favorable survival, tumor control, and toxicity relative to conventional radiation therapy. However, more patients, and large prospective trials, are needed to confirm these results.

PROs associated with IMPT

PRO surveys are increasingly being used to assess symptom burden and quality of life from the patient's perspective, without the need to rely on a third party (51). PROs may also reflect symptom burden more accurately, as patient-reported symptoms are often more severe than those assessed by physicians (52). Investigators at MD Anderson recently completed the first study of PROs among patients given IMPT for oropharyngeal tumors (53). That study involved giving 35 patients who had received IMPT and 46 patients who had received IMRT the MD Anderson Symptom Inventory-Head and Neck Module (MDASI-HN), a validated tool that has been shown to correlate well with some physician-assessed outcomes such as mucositis (54). Patients were given questionnaires to document their symptoms at baseline, during treatment, during the subacute recovery phase (from the end of treatment to 3 months after treatment), and >3 months after treatment. No statistically significant differences were found between groups in symptom burdens at baseline, during treatment, or >3 months after treatment; however, the patients who received IMPT had a lower symptom burden during the subacute recovery phase than did the IMRT patients. This suggests that symptoms for patients given IMPT may return to baseline more quickly than for patients who received IMRT. The apparent improvements in dose distribution for IMPT relative to photon therapy might be expected to decrease the symptom burden for patients with head and neck cancer. Trial NCT01893307, the comparison of IMPT and IMRT for oropharyngeal cancer, also includes several PRO instruments that will provide additional prospective data on IMPT and symptom burden among patients receiving concurrent chemoradiation for advanced oropharyngeal tumors.

Gastrostomy tube and nutritional requirements during and after IMPT

A gastrostomy tube is often necessary to maintain appropriate hydration and nutrition status during radiation treatment for head and neck cancer; however, tube placement is an invasive procedure with reported minor

complication rates of 19.5%, major complication rates of 7.45%, and mortality rates of 2.2% (55). Tube placement is also expensive, with one estimate indicating \$31,832 for placement and use of a gastrostomy tube for 1 year (56). Many symptoms can prompt placement of a gastrostomy tube, including mucositis, xerostomia, dysphagia, dysgeusia, and nausea (25). The dosimetric advantages of IMPT have the potential to reduce the dose to organs at risk and thereby decrease the related symptoms and possibly reduce the number of tubes needed. A case-matched control study reported by Holliday and others (25) of patients with nasopharyngeal carcinoma who received IMRT or IMPT showed that IMPT outperformed IMRT with respect to the need for gastrostomy tubes (20% in IMPT *vs.* 65% in IMRT, $P=0.02$) and dose to several organs at risk. On multivariate analysis, higher mean dose to the oral cavity was significantly associated with higher tube-placement rates, and IMPT was associated with a lower oral cavity dose than IMRT. Specifically, no patient who received <26 Gy(RBE) to the oral cavity dose had a gastrostomy tube placed, but all patients who received >41.8 Gy required a tube. IMPT was also associated with significantly lower mean doses to the brain stem, whole brain, and mandible. Also, as noted previously, Blanchard and colleagues compared feeding-tube placement rates and body weight loss among 50 patients with oropharyngeal cancer treated with IMPT and 100 patients with oropharyngeal cancer treated with IMRT (46). IMPT was associated with reduced rates of feeding tube placement and severe weight loss both during and after treatment. During treatment, only 24% of IMPT patients had a gastrostomy tube placed compared with 38% of IMRT patients. By 3 months after treatment, 18% of IMPT patients had lost >20% of their baseline body weight or had a gastrostomy tube, versus 34% of IMRT patients ($P=0.05$). At 1 year after treatment, these percentages had dropped to 8% for the IMPT group and 27% for the IMRT group ($P=0.008$). As noted previously, the ongoing clinical trial NCT01893307 is underway to compare the incidence and severity of toxicity associated with IMRT and IMPT. Enrollment in this study, and others like it, is necessary to establish whether IMPT can consistently reduce toxicity and reduce the need for gastrostomy tubes.

Conclusions

Early trials of IMPT have shown promising results, suggesting that proton therapy is safe and effective for the management of head and neck tumors. IMPT eliminates

the unnecessary radiation delivered to proximal organs and structures associated with IMRT and seems to be associated with improved PROs during the first 3 months after treatment, decreased gastrostomy tube dependence, and lower rates of grade ≥ 3 toxicity while resulting in equivalent or improved effectiveness for tumors at a variety of anatomical subsites of the head and neck. Ongoing and future prospective clinical trials will further establish the degree to which IMPT can enhance tumor control and reduce symptom burden.

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Footnote

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