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REVIEW ARTICLE

Proton therapy for head and neck cancer: Rationale, potential indications, practical considerations, and current clinical evidence

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Abstract

There is a strong rationale for potential benefits from proton therapy (PT) for selected cancers of the head and neck because of the opportunity to improve the therapeutic ratio by improving radiation dose distributions and because of the significant differences in radiation dose distribution achievable with x-ray-based radiation therapy (RT) and PT. Comparisons of dose distributions between x-ray-based and PT plans in selected cases show specific benefits in dose distribution likely to translate into improved clinical outcomes. However, the use of PT in head and neck cancers requires special considerations in the simulation and treatment planning process, and currently available PT technology may not permit realization of the maximum potential benefits of PT. To date, few clinical data are available, but early clinical experiences in sinonasal tumors in particular suggest significant improvements in both disease control and radiation-related toxicity.

The functional and cosmetic consequences of surgical eradication have led to a reliance on radiation therapy (RT) for the primary management of many head and neck cancers. The most important factor in determining the success or therapeutic ratio from RT is dose distribution; that is, the distribution of the radiation dose in the cancer target relative to the dose distribution in normal non-targeted tissues, which are also subject to radiation injury.

Rationale for proton therapy in head and neck cancers

Most of the radiation energy with x-ray therapy is deposited along the entrance and exit portions of the beam path, outside of the cancer target. Many sophisticated strategies have been developed with x-ray therapy to reduce the risk of complications—three-dimensional conformal RT (3DCRT), stereotactic radiosurgery and RT (SRS and SRT), intensity-modulated RT (IMRT), tomotherapy, intensity-modulated arc therapy (IMAT) and volumetric arc therapy (VMAT). These methods reduce the volume of normal tissue receiving high doses of RT by redistributing the "integral dose" (the radiation dose received by normal non-targeted tissues) over a greater volume of non-targeted tissue. In contrast to x-rays, protons travel in tissue only a finite distance and release most of their energy at the end of their range in a characteristic radiation dose-deposition peak called the Bragg Peak. The depth of the Bragg Peak can be controlled by varying the acceleration of the protons. There is significantly less integral dose to non-targeted tissues with protons than with x-rays, because the entrance dose is greatly reduced relative to the target dose and there is no exit dose. This significant reduction in integral dose with proton therapy (PT) may afford an opportunity to increase the therapeutic ratio of RT in the head and neck [1], both by decreasing toxicity and by increasing the feasibility of dose escalation and/or dose intensification (via hypo-fractionation and a shortened overall treatment time), to increase tumor control.

There are substantial data on head and neck cancer to prove the principles of increased tumor control through radiation dose escalation (in the oropharynx) [2] and dose intensification (in the larynx) [3]. The major limitations to enhanced dose escalation and dose intensification, however, are a

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variety of normal-tissue toxicities observed in tissues receiving integral radiation dose. Tissues at risk for radiation toxicity vary with the cancer site but include the mucosa and those structures critical to visual function (the retinae, optic nerves, optic chiasm, and lacrimal glands), auditory function (the cochlea and eighth nerve), mastication and deglutition (salivary glands, teeth, and constrictor muscles), and endocrine function (pituitary, hypothalamus, and thyroid).

Table I shows typical disease-control outcomes and grade 3 or higher toxicity rates for a variety of head and neck cancers. The therapeutic ratio for radiation therapy in some head and neck cancers, such as early true vocal cord cancer, is quite high; but most head and neck cancers offer some opportunity for improvement in either tumor control and/or toxicity.

Potential applications of proton therapy in head and neck cancer

An example of dosimetric evidence for the probable benefit from PT in head and neck cancer is shown in Figure 1 and Table II, which are dosimetry comparisons between PT and IMRT treatment plans for a 46-year-old female with a pT4NO carcinoma of the right maxillary sinus with involvement of the infra-orbital nerve, the orbit, the pterygo-maxillary space, and infra-temporal fossa, status post endoscopic maxillectomy, rhinotomy, and orbital decompression. The prescribed dose to the primary sinonasal lesion is 74.4 CGE, delivered in 1.2 CGE fractions twice daily because of the inclusion of optic structures in the target volume [4], with prophylactic treatment to the low neck with a separate matched 6 MV photon field to 50 Gy in 2 Gy fractions, and concurrent weekly cisplatin. Figure 1A shows color-wash depictions of the dose distributions achieved with the PT plan (left) compared with the alternative IMRT plan (right); both plans were optimized to achieve the same target coverage. IMRT clearly delivers low radiation doses to a larger volume of non-targeted tissue: the left posterior fossa and temporal lobes, as apparent on the axial images; the left orbit, as apparent on the coronal images; and the right orbit and anterior cranial and temporal fossae, as apparent on the sagittal images. It is possible that this additional low dose exposure with IMRT will increase the risks for second malignancy [5]. The dose-volume histograms (DVHs) in Figure 1B shows similar target coverage for the two plans (far right curves), but significant improvements with the PT plan for organs at risk (OARs), including the chiasm, right and left optic nerves, retinae and lacrimal glands. The pertinent differences in exposure to components of the visual apparatus are detailed in Table II. The IMRT plan delivers doses to the ipsilateral (right) optic nerve, retina, and lacrimal gland likely to cause optic neuropathy, retinal damage, and probable dry-eye syndrome; in addition, IMRT doses to the contralateral (left) optic nerve and retina also place these structures at risk. In contrast, the PT plan results in no risk to the contralateral eye and only a small risk for loss of vision or dry-eye syndrome in the ipsilateral eye. In this particular case, PT offers the likelihood of preservation of bilateral vision, while IMRT guarantees unilateral visual loss and risks bilateral visual loss. In actual clinical practice, a radiation oncologist using IMRT might choose to prioritize protection of the left optic nerve and retina to preserve unilateral vision at the risk of decreased probability of tumor control; this compromise in therapeutic ratio is not necessary with PT.

In addition to sinonasal tumors, other sites in the head and neck where PT might be useful include selected oropharyngeal carcinomas (increased sparing of salivary gland and pharyngeal constrictor muscle function and potential dose escalation and/or dose intensification), selected nasopharyngeal carcinomas (increased sparing of the chiasm and nerves, brainstem, and spinal cord to permit dose escala-

Table I. Outcomes and toxicity rates for various head and neck cancers treated with radiation therapy.*

Clinical site	Radiation dose-limiting structure	Typical radiation dose	Grade 3+ toxicity rate	Local-regional tumor control rate	Radiation therapeutic ratio
Early-stage true vocal cord (2)	Thyroid cartilage and arytenoids	63 Gy/28 fx	<1%	~95%	Very high
T3 Base of tongue (3)	Mandible	74.4 Gy/62 fx, BID	8%	82%	High
Nasopharynx (5)	CNS; visual apparatus	74.4 Gy/62 fx, BID	10%	76%	Fair
Paranasal sinus tumor (7)	CNS; visual aparatus	64.8-74.4 Gy at 1.2 Gy/fx, BID	20%	63%	Fair
Skin cancer with clinical perineural invasion (unpublished data)	CNS; visual apparatus	74.4 Gy/62 fx, BID	35%	55%	Fair to poor

*X-ray-based radiation therapy.

Abbreviations: CNS, central nervous system; fx, fractions; BID, twice a day.

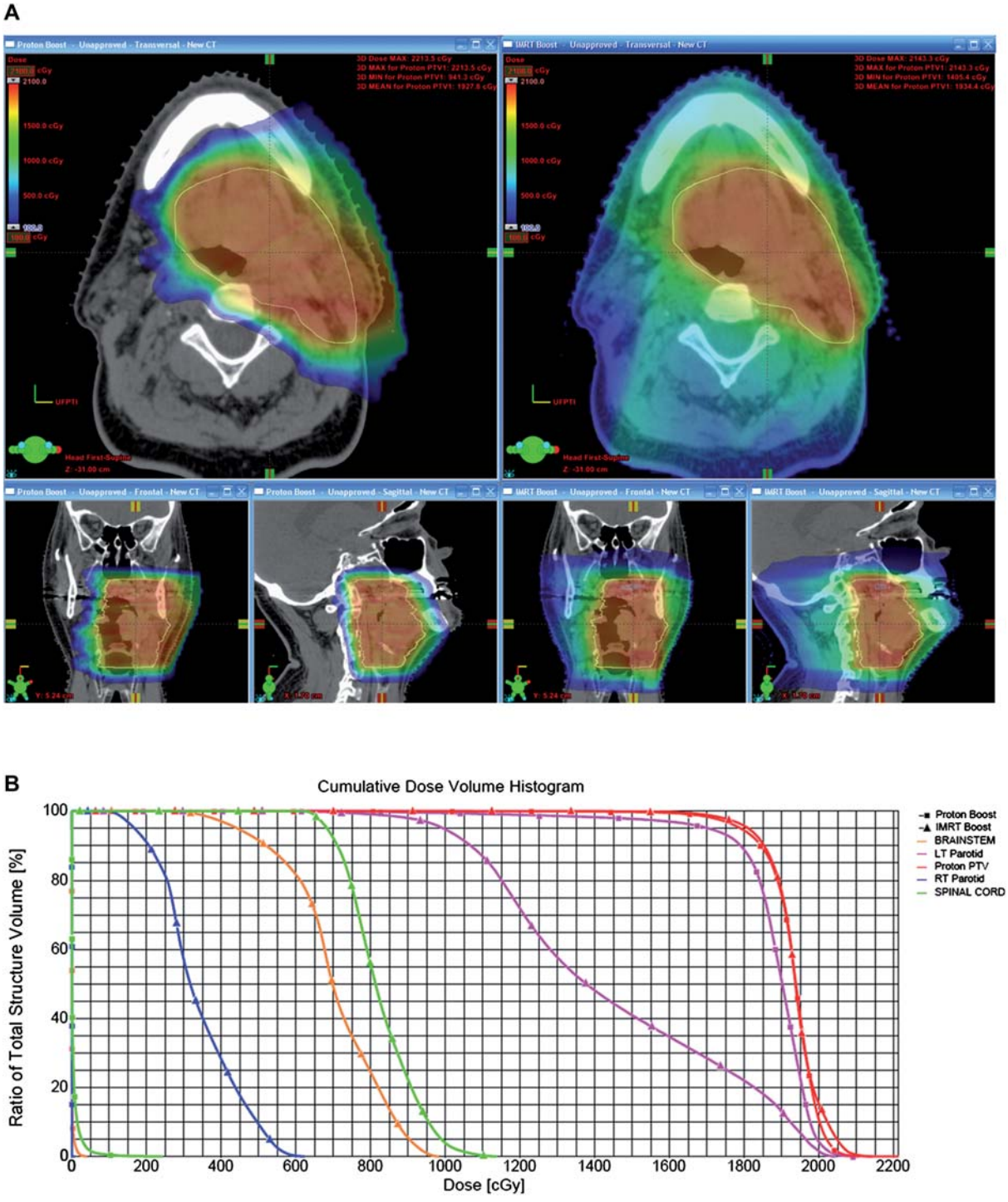

Figure 1. This shows a comparison of an intensity-modulated radiotherapy (IMRT) plan and a proton therapy (PT) plan for a 46-year-old female with a spindle cell carcinoma involving the right maxillary sinus (pT4N0) with involvement of the infraorbital nerve, the orbit, the pterygomaxillary space, and the infratemporal fossa, status post endoscopic maxillectomy, rhinotomy, and orbital decompression. For both plans, the prescribed dose to the primary target was 74.4 Gy/CGE in 1.2 Gy/CGE twice-daily fractions. The low neck was also prescribed 50 Gy in 2 Gy fractions with 6 MV photons with concurrent weekly cisplatin during radiation therapy.

Figure 1A shows color-wash depictions of the dose distributions achieved with the PT plan (left) and the IMRT plan (right). As apparent from the axial, coronal, and sagittal images, there is greater integral dose with the IMRT plan. Figure 1B shows the dose-volume histogram (DVH) comparison between the two plans; as apparent from the curves on the far right, the target coverage was the same for the two plans, but the PT plan delivered a significantly lower dose to the optic structures, including the chiasm, the lacrimal glands, the retinae, and the optic nerves as well as the brainstem and parotids. The differences in dose to these structure are further detailed in Table II.

Table II. Comparison of normal-tissue exposure between IMRT and PT plans* for sinonasal carcinoma.

Radiation dose-limiting structure	Radiation plan (Dose)	Minimum dose	Mean dose	Maximum dose
Chiasm	IMRT (Gy)	21.8 Gy	41.4 Gy	**63.1 Gy**
	PT (CGE)	0.8 CGE	8.6 CGE	**35.2 CGE**
Right optic nerve	IMRT (Gy)	**57.6 Gy**	**65.2 Gy**	70.3 Gy
	PT (CGE)	**12.7 CGE**	**48.7 CGE**	72.5 CGE
Right retina	IMRT (Gy)	37.4 Gy	**59.4 Gy**	72.4 Gy
	PT (CGE)	0.3 CGE	**31.4 CGE**	75.9 CGE
Right lacrimal gland	IMRT (Gy)	23.4 Gy	**37.7 Gy**	**51.9 Gy**
	PT (CGE)	0 CGE	**0.9 CGE**	**5.3 CGE**
Left optic nerve	IMRT (Gy)	41.7 Gy	**57.2 Gy**	**65 Gy**
	PT (CGE)	0 CGE	**6.8 CGE**	**29 CGE**
Left retina	IMRT (Gy)	28.7 Gy	**54.6 Gy**	**59.1 Gy**
	PT (CGE)	0 CGE	**0.8 CGE**	**14.1 CGE**
Left lacrimal gland	IMRT (Gy)	11.6 Gy	30 Gy	47.1 Gy
	PT (CGE)	0 CGE	0.9 CGE	5.3 CGE

*Summary of critical-structure dose data from Figure 1. Doses for IMRT are given in Gy and doses for PT are given in CGE (cobalt gray equivalent); differences in critical-structure dose that are likely to result in differences in preservation of function are shown in bold.
Abbreviations: IMRT, intensity-modulated radiotherapy; PT, proton therapy.

tion), and other less-common situations such as adenoid cystic carcinoma and skin cancers with perineural nerve spread (sparing the optic chiasm and nerves, brainstem, and overall brain to permit dose escalation).

Practical considerations in treatment planning and delivery with PT

There are some important considerations in treatment planning and delivery with PT pertinent in the treatment of head and neck cancers.

The proton stopping power must be known for all materials used in positioning and immobilization through which the beam may pass (e.g. head holder, mask, table) and the composition and length of the beam path must be known. Hounsfield units may vary between computed tomography (CT) scanners, so the accuracy for predicting proton stopping power of the specific CT scanner used for simulation must be confirmed in a phantom. Any potential intra-fraction motion (e.g. swallowing) that affects either target position, composition, or length of proton beam path should be assessed and, if necessary, modeled with four-dimensional (4D) CT to determine how best to manage the target motion—e.g. beam gating, treatment of an internal target volume (ITV), or through optimization of beam-path angles. Once the clinical target volume (CTV) and OARs have been defined on the treatment planning CT, specific priorities for PT planning (Table III) must be considered which may differ from x-ray treatment planning priorities. Once beam angles have been selected, proton-range uncertainties are accounted for with proximal and distal margins. In contrast to IMRT, planning target volume (PTV) expansions to account for intra- and inter-fraction setup variations (PTV) are field-specific, thus potentially less than PTV expansions with IMRT. Once proximal and distal margins and PTV have been defined, apertures are designed for placement in the beam path to conform to the beam to the shape of the target in the beam's eye view. Finally, for conformality of the distal edge of the beam, a compensator is designed for placement in the beam path to more finely attenuate the proton range to match the distal target contour. The treatment planning and quality assurance processes are considerably more complex than those for IMRT. Most PT today is delivered with "double scattering" technology to expand the proton beam to a clinically useful field size. Scattering technology requires both apertures and compensators for maximum target conformality. Newer "scanning" technology, which disperses the beam to a clinically useful size with magnets rather than scatters and achieves not only distal but layered target conformality through layer-by-layer dose painting, is available at a few institutions. Scanning does not require compensators or apertures, can deliver intensity-modulated proton therapy (IMPT), and is likely to be capable of much-more conformal dose distributions than scattering technology, further improving the dose distribution over x-ray-based plans. It is likely that more applications for PT in head and neck cancers will be developed when scanning technology is available and treatment planning systems are more mature.

Clinical experience with proton therapy in the head and neck

Thus far, there are few reported clinical experiences with proton or carbon therapy in head and neck

cancer. Those available are often small and/or do not provide information on both disease control and toxicity, so actual clinical benefits in the therapeutic ratio from particle therapy compared with x-ray-based radiation are as yet hard to define. In fact, a systematic review by Ramaekers et al. [6] identified only seven observational PT studies for use in a meta-analysis. In this section, we will review the available particle data that best lends itself to comparison of therapeutic ratio with either contemporary IMRT experiences and/or more mature conventional RT data.

Table III. Guidelines and specific considerations in treatment planning of proton therapy.

Treatment planning	Guidelines and considerations
Simulation setup	1. Verify proton stopping-power algorithm for particular treatment planning CT. 2. Verify proton stopping power of all materials in beam path, including face mask, head holder, and table must be known. 3. Positioning must facilitate as close a placement of beam nozzle to skin as possible to decrease penumbra. 4. Evaluate any anatomical sites in which intrafraction motion may result in variation in target location relative to anatomy used in positioning or variations in composition in length of beam entrance path to target (4D CT and or MR).
Contouring	1. Contour all metals and assign them an appropriate Hounsfield unit. 2. Override any metal artefact with appropriate tissue Hounsfield units. 3. Contour any structures with potentially variable stopping power values through the course of PT treatment (e.g. a sinus cavity which could be filled with air or tissue-equivalent material); assess the potential impact of variations in sopping power; plan rescanning during treatment and adaptive replanning if necessary.
Beam-angle selection	1. Select angles that optimize the target size and volumetric shape in the beam's eye view—either by minimizing the target size or irregularity or thickness. 2. Avoid angles that pass through metal. 3. Avoid angles that stop the beam immediately before a critical structure; in addition to slight uncertainties in the distal range of the beam related to imprecise treatment planning systems, and daily variations in the length and composition of the beam path, there are uncertainties in the RBE at the end of the proton range. 4. Choose angles that provide the shortest beam path to the target as integral dose increases with the proton-path length and penumbra increases with depth in tissue. 5. Choose angles with the most stable path composition and fewest tissue-heterogeneity interfaces. The proton range in tissue varies with the different stopping powers of various tissues; intrafraction and interfraction variations in the composition of the path impact the daily proton range in tissue. 6. Choose beam angles to match the major axes of target motion; beam angles that are perpendicular to major target motion will require much larger PTV expansions.
Uncertainties and expansions	1. Any uncertainties in beam path composition and length must be modeled and accounted for with proximal and distal SOBP margins. 2. PTV expansion is field-specific with PT (IMRT PTV expansion may always be field specific, as daily image guidance may not be performed between segments). 3. If entrance-path composition and length are stable, little or no PTV expansion is necessary beyond the proximal and distal SOBP margins. In the beam's eye view, PTV expansion is dominated by interfraction and intrafraction setup errors and organ motion. The use of daily image-based patient localization allows a significant reduction of PTV margin. Generally, in head and neck tumors, the PTV expansion is 3 mm. 4. Some critical structures may warrant a PTV expansion if they abut the CTV and are at risk for injury with the prescribed PTV dose (e.g. the optic nerve or chiasm with a sinonasal tumor that invades the anterior cranial fossa).
Overall plan evaluation	1. Use the fewest fields necessary to achieve dosimetry goals for target coverage and OARs, and plan robustness. The more fields used, the more tissue exposed to integral dose. The more fields treated each session, the greater the opportunity for intrafraction motion that impacts margins and expansions. However, when complex techniques are required, critical structures are adjacent to the target volume, or there is significant uncertainty in the beam range, the use of more fields may reduce the risk of random and systematic errors and increase the robustness of the daily and overall treatment plan.
Apertures and compensators	1. The distance to the aperture edge must account for penumbra, which will be impacted by distance between nozzle and skin, the field size, and the target depth. 2. Compensators can be used to increase distal beam edge conformality; a "smearing" value of 5 to 7 mm is used within the target volume and "smoothing" value of 8 mm is used outside the target volume I head and neck tumors to account for daily variations related to intrafraction and interfraction motion and set-error.

*These guidelines and considerations are in use at the University of Florida Proton Therapy Institute and pertinent for double scattered proton therapy in head and neck cancer as well as in other sites. With the development of intensity modulated proton therapy (IMPT) using "scanned" proton beams, there will be less indication for apertures and compensators and some of the considerations with beam angle selection may be moot.

Abbreviations: CT, computed tomography; CTV, clinical target volume; IMRT, intensity-modulated radiotherapy; MR, magnetic resonance; OAR, organs at risk; PT, proton therapy; PTV, planning target volume; RBE, relative biological effectiveness; SOBP, spread-out Bragg peak.

Oropharyngeal carcinoma

Mendenhall et al. reported outcomes in 130 patients with de novo oropharyngeal squamous cell carcinomas treated curatively with IMRT at the University of Florida (UF) between 2001 and 2007 and followed for a median of 3.5 years (range, 0.2–7.7 years) [7]. Forty patients (36%) had a T3 or T4 primary lesion and 117 patients (90%) had stage III-IV disease. Altered fractionation, generally the "concomitant boost" technique, was used for 118 patients (91%) to 72 Gy in 42 fractions over six weeks. Sixty-one percent received adjuvant chemotherapy, and 42% underwent a planned neck dissection. The 5-year local control rates were as follows: T1, 93%; T2, 91%; T3, 82%; T4, 67%; and overall, 87%. The five-year overall local-regional control, distant metastasis-free survival, cause-specific survival, and overall survival rates for the group were as follows: 84%., 93%, 85% and 76%, respectively. Severe late complications occurred in 11 patients (8%).

Slater et al. reported on 29 patients with stage II-IV oropharyngeal cancer treated at Loma Linda University Medical Center (LLUMC) with a combination of protons and photons to 75.9 Gy/CGE in 45 fractions over 5.5 weeks. Patients were followed from two to 96 months [8]. The five-year outcomes were as follows: local control, 88%; regional control, 96%; local-regional control, 84%; and disease-free survival, 65%. Late grade 3 toxicity was observed in three patients (10%). The small number of patients and more aggressive radiation fractionation scheme in the LLUMC experience make the outcomes difficult to interpret. It is possible that some of the benefit from PT may have been diluted by the conventional RT used in the regimen; nevertheless, the high disease control rates are promising.

Nasopharyngeal carcinoma

Mendenhall and colleagues reported on 82 patients treated with definitive RT for nasopharyngeal carcinoma at UF between 1983 and 2003 and followed for a median of five years (range, 0.2–22 years) [9]. The median follow-up on living patients was 10.8 years (range, 2.8–22 years). Thirty-one patients (38%) received induction (n = 17) or concomitant (n = 14) chemotherapy; 14 patients (17%) underwent a planned neck dissection after RT. The five-year outcomes were as follows: local control, 78%; regional control, 90%; local-regional control, 76%; distant metastasis-free survival, 80%; cause-specific survival, 66%; and overall survival, 57%. Moderately severe late complications were observed in six patients (7%) and included bilateral 11th and 12th nerve palsies (one patient), decreased short-term memory (one patient), hypopituitarism (three patients), and decreased unilateral vision (one patient). In addition, five patients (6%) experienced severe late complications including bilateral blindness (one patient), permanent gastrostomy (one patient), unilateral optic neuropathy and/or temporal lobe necrosis (two patients), and mandibular osteoradionecrosis (one patient).

Chan and Liebsch reported on 17 patients treated at MGH between 1990 and 2002 with a combination of protons and x-rays for previously untreated T4N0-N3 nasopharyngeal carcinoma and followed for a median of 43 months [10]. The median dose to the gross target volume was 73.6 Gy. The three-year outcomes were as follows: local-regional control, 92%; relapse-free survival, 79%; and overall survival, 74%. Toxicity was not described, so it is difficult to assess the therapeutic ratio, but the high disease control rates are very promising.

Nasal cavity and paranasal sinuses

Mendenhall and colleagues reported on 109 patients with carcinoma of the nasal cavity and paranasal sinuses treated with conventional RT at the UF between 1964 and 2005 [11]. Fifty-six patients were treated with definitive RT and 53 patients received surgery and adjuvant RT. Median follow-up on living patients was 9.4 years (range, 0.2–35.9 years). The five-year local control rates were as follows: T1-T3, 82%; T4, 50%; and overall, 63%. Local control at five years was 43% after RT and 84% after surgery and RT. Multivariate analysis of local control revealed that advanced overall stage and treatment with RT alone adversely impacted this endpoint. The five-year cause-specific survival rates were as follows: stage I-III, 81%; stage IV, 54%; and overall, 62%. Thirty one (20%) patients sustained severe complications; 17 of 56 patients (16%) after definitive RT and 14 of 53 patients (25%) after surgery and adjuvant RT.

Hoppe and coworkers reported on 39 patients with stage IVB paranasal sinus carcinomas treated with definitive RT alone (n = 4) or combined with chemotherapy (n = 35) between 1990 and 2006 at the Memorial Sloan-Kettering Cancer Center (New York, NY; MSKCC) [12]. The median dose was 70 Gy. The median follow-up was 90 months. Severe late complications were observed in only two patients (5%). However, the five-year outcomes were poor compared with the UF experience: local control, 21%; neck control, 61%; distant metastasis-free survival, 51%; disease-free survival, 14%; and overall survival, 15%. Hoppe et al. also reported on 37 patients with carcinomas of the nasal cavity, paranasal sinuses, and lacrimal glands treated with surgery and postoperative IMRT at the MSKCC

between 2000 and 2006 and followed for a median of 28 months [13]. The median doses were as follows: tumor, 60 Gy; optic nerve maximum dose, 53 Gy; and optic chiasm maximum dose, 51 Gy. Although there were no late grade 3 or 4 optic toxicities, the local control rate at two years was only 75%, in comparison with 84% at five years at UF, where higher radiation doses were used.

Dirix et al. reported on 40 patients treated with surgery and postoperative IMRT to a dose of 60 to 66 Gy between 2003 and 2008 for sinonasal cancers and followed for a median of 30 months [14]. The two-year outcomes were as follows: local control, 76%; overall survival, 89%; and disease-free survival, 72%. No severe acute or late toxicity was observed, although loss of vision through exenteration was not considered a toxicity. These three experiences with conventional RT in sinonasal tumors suggest that when faced with the dose distributions possible with x-rays, some clinicians prioritize maximum tumor control and others prioritize minimum toxicity.

Chan and Liebsch reported on 102 patients with paranasal sinus cancers treated between 1991 and 2002 with PT to a median dose of 71.6 Gy at the Massachusetts General Hospital (Boston, Massachusetts; MGH) and followed for a median of 6.6 years [10]. Only 20% of patients had a complete resection prior to RT. The five-year local control rate was 86%; no toxicity information was offered in this report. In a separate publication of a subset of the MGH experience, Weber et al. reported on 36 patients treated with proton/photon accelerated fractionated RT between 1991 and 2001 at MGH for paranasal sinus cancers to a median dose of 69.6 Gy [15]; the median follow-up was 52 months. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (CTC) and late effects normal tissue (LENT) scoring systems. Thirteen patients developed late visual toxicity including cataracts in three patients (LENT grade 1, two patients; LENT grade 3, one patient), LENT grade 1 vascular retinopathy in one patient, LENT grade 1 optic neuropathy in one patient, lacrimal duct stenosis in three patients (CTC grade 2, two patients; CTC grade 3, one patient), and dry-eye syndrome in five patients (CTC grade 1, one patient; CTC grade 2, four patients). No patients were reported to have lost vision. These excellent outcomes suggest the possibility of achieving both high rates of tumor control and low rates of severe toxicity with PT in sinonasal tumors.

Demizu et al. reported on 75 patients treated between 2001 and 2006 with protons or carbon ions for head and neck/skull base malignancies adjacent to the optic nerve(s) at the Hyogo Ion Beam Medical Center (Hyogo, Japan) and followed for at least 12 months [16]. Eight patients (11%) developed visual loss due to optic neuropathy; no disease control information was provided. Insufficient information is available to know whether tumor location, dose prescription, carbon relative biological effectiveness, or treatment technique may have contributed to the high rate of visual loss in this series.

Adenoid cystic carcinoma

Mendenhall et al. reported on 101 previously untreated patients who were treated curatively between 1966 and 2001 at UF with RT alone (n = 42) or combined with surgery (n = 59) for adenoid cystic carcinoma (ACC) of the head and neck. Those treated with RT alone generally had more-advanced incompletely resectable disease [17]. The median follow-up was 6.6 years (range, 0.4 –30.6 years); all living patients were followed for at least one year. The local control rates after RT alone or combined with surgery at five years were 56% and 94%, and at 10 years were 43% and 91%. Multivariate analysis revealed that advanced T-stage ($p = 0.0101$) and treatment with RT alone ($p = 0.0008$) adversely impacted the likelihood of local control. The cause-specific survival rates after RT alone or combined with surgery were 65% and 81% at five years and 48% and 71% at 10 years. Multivariate analysis of cause-specific survival revealed that advanced T-stage ($p = 0.0008$) and clinical nerve invasion ($p = 0.0005$) significantly impacted this endpoint. Six patients experienced severe late complications including bone necrosis requiring surgical intervention (three patients), permanent jejunostomy due to aspiration (one patient), fistula necessitating flap reconstruction (one patient), and fatal hemorrhage after a reconstructive procedure to correct tracheal stenosis (one patient). One patient experienced fatal meningitis after a salvage operation for a locally recurrent nasal cavity cancer treated with RT alone 49 months earlier. In addition, six patients received high-dose RT to an ipsilateral eye and experienced anticipated loss of vision in that eye. Although loss of vision has not necessarily been considered a complication with either RT or surgery in these tumors, vision might have been spared with proton RT.

Pommier and coworkers reported on 23 patients treated for de novo ACC with skull base extension with photon/proton RT at MGH between 1991 and 2002; the median follow-up on surviving patients was 64 months [18]. Twenty patients (87%) had gross disease at the time of RT. The median dose to the primary lesion was 75.9 Gy. The five-year outcomes were as follows: local control, 93%; distant metastasis-free survival, 62%; disease-free survival, 56%; and overall survival, 77%. One patient developed grade 4 retinopathy. Three patients developed

grade 3 complications requiring surgery including dacrocystorhinostomy in one patient, surgery for ectropion in one patient, and lens replacement for a cataract in one patient. These results suggest the possibility of both high rates of disease control and low rates of severe toxicity with PT alone in ACC.

Discussion

While opportunities exist in several head and neck tumor sites to improve the therapeutic ratio of RT with the dose distributions achievable with particle therapy, there is minimal clinical experience currently available. Reasons likely include the paucity of treatment centers until recently, relative rarity of head and neck cancers, complacency about the current results with RT, and, importantly, the commonly acknowledged complexity of head and neck tumors requiring subspecialty imaging and clinical experience for treatment planning. Dosimetric advantages in oropharynx, nasopharynx, sinonasal tumors, adenoid cystic carcinomas known for their propensity for perineural spread and skin cancers with perineural invasion are likely to translate into clinical benefits and, thus, these tumors are the subjects of ongoing trials in several proton and carbon facilities. To date, however, clinical data are lacking in all sites except sinonasal tumors; the early reports in sinonasal tumors suggest possible substantial benefit in both avoidance of toxicity and improvement in disease control related to improved radiation dose distributions of PT. In some clinical circumstances, the potential advantages of PT may not be fully achieved with current proton delivery technology, such as with bilateral neck node involvement, tumor near critical structures, situations requiring entrance-beam paths that contain tissues with significantly different proton stopping powers (as with tumors in the base of skull when beams must pass through air in the sinus cavities, bone, and soft tissue).

Although particle therapy facilities are substantially more expensive than photon facilities and operational expenses somewhat higher, it is possible that overall health-care costs in head and neck cancer patients could ultimately be reduced with particle therapy. Because the dose-distribution patterns between x-ray therapy and PT are so different, a paradigm shift may be required for radiation treatment planning and combined-modality strategies. Reduced doses to normal tissues may permit much higher or intense radiation regimens than previously considered safe. Reduced doses to normal tissues may also permit the use of more-intense chemotherapy regimens or combined surgical and radiation strategies previously considered too toxic. These strategies may reduce costs through shortened radiation treatment regimens as well as by reducing the costs of treatment complications and uncontrolled cancer.

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References

[1] Nystrom H. The role of protons in modern and biologically-guided radiotherapy. Acta Oncol 2010;49:1124–31.

[2] Mendenhall WM, Riggs CE, Vaysberg M, Amdur RJ, Werning JW. Altered fractionation and adjuvant chemotherapy for head and neck squamous cell carcinoma. Head Neck 2010; 32:939–45.

[3] Mendenhall WM, Amdur RJ, Morris CG, Hinerman RW. T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. J Clin Oncol 2001;19: 4029–36.

[4] Bhandare N, Monroe AT, Morris CG, Bhatti MT, Mendenhall WM. Does altered fractionation influence risk of radiation-induced optic neuropathy? Int J Radiat Oncol Biol Phys 2005;62:1070–7.

[5] Yoon M, Ahn SH, Kim J, Shin DH, Park SY, Lee SB, et al. Radiation-induced cancers from modern radiotherapy techniques: Intensity-modulated radiotherapy versus proton therapy. Int J Radiat Oncol Biol Phys 2010;77: 1477–85.

[6] Ramaekers BL, Pijls-Johannesma M, Joore MA, van den Ende P, Langendijk JA, Lambin P, et al. Systematic review and meta-analysis of radiotherapy in various head and neck cancers: Comparing photons, carbon-ions and protons. Cancer Treat Rev 2011;37:185–201.

[7] Mendenhall WM, Amdur RJ, Morris CG, Kirwan JM, Li JG. Intensity-modulated radiotherapy for oropharyngeal squamous cell carcinoma. Laryngoscope 2010;120: 2218–22.

[8] Slater JD, Yonemoto LT, Mantik DW, Bush DA, Preston W, Grove RI, et al. Proton radiation for treatment of cancer of the oropharynx: Early experience at Loma Linda University Medical Center using a concomitant boost technique. Int J Radiat Oncol Biol Phys 2005;62:494–500.

[9] Mendenhall WM, Morris CG, Hinerman RW, Malyapa RS, Amdur RJ. Definitive radiotherapy for nasopharyngeal carcinoma. Am J Clin Oncol 2006;29:622–7.

[10] Chan AW, Liebsch NJ. Proton radiation therapy for head and neck cancer. J Surg Oncol 2008;97:697–700.

[11] Mendenhall WM, Amdur RJ, Morris CG, Kirwan J, Malyapa RS, Vaysberg M, et al. Carcinoma of the nasal cavity and paranasal sinuses. Laryngoscope 2009;119:899–906.

[12] Hoppe BS, Nelson CJ, Gomez DR, Stegman LD, Wu AJ, Wolden SL, et al. Unresectable carcinoma of the paranasal sinuses: Outcomes and toxicities. Int J Radiat Oncol Biol Phys 2008;72:763–9.

[13] Hoppe BS, Wolden SL, Zelefsky MJ, Mechalakos JG, Shah JP, Kraus DH, et al. Postoperative intensity-modulated radiation therapy for cancers of the paranasal sinuses, nasal cavity, and lacrimal glands: Technique, early outcomes, and toxicity. Head Neck 2008;30:925–32.

[14] Dirix P, Vanstraelen B, Jorissen M, Vander Poorten V, Nuyts S. Intensity-modulated radiotherapy for sinonasal cancer: Improved outcome compared to conventional radiotherapy. Int J Radiat Oncol Biol Phys 2010;78:998–1004.

[15] Weber DC, Chan AW, Lessell S, McIntyre JF, Goldberg SI, Bussiere MR, et al. Visual outcome of accelerated

fractionated radiation for advanced sinonasal malignancies employing photons/protons. Radiother Oncol 2006;81: 243–9.

[16] Demizu Y, Murakami M, Miyawaki D, Niwa Y, Akagi T, Sasaki R, et al. Analysis of vision loss caused by radiation-induced optic neuropathy after particle therapy for head-and-neck and skull-base tumors adjacent to optic nerves. Int J Radiat Oncol Biol Phys 2009;75:1487–92.

[17] Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Hinerman RW, Villaret DB. Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. Head Neck 2004;26:154–62.

[18] Pommier P, Liebsch NJ, Deschler DG, Lin DT, McIntyre JF, Barker FG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. Arch Otolaryngol – Head Neck Surg 2006;132:1242–9.