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Intensity modulated proton therapy (IMPT) – The future of IMRT for head and neck cancer

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ABSTRACT

Radiation therapy plays an integral role in the management of head and neck cancers (HNCs). While most HNC patients have historically been treated with photon-based radiation techniques such as intensity modulated radiation therapy (IMRT), there is a growing awareness of the potential clinical benefits of proton therapy over IMRT in the definitive, postoperative and reirradiation settings given the unique physical properties of protons. Intensity modulated proton therapy (IMPT), also known as "pencil beam proton therapy," is a sophisticated mode of proton therapy that is analogous to IMRT and an active area of investigation in cancer care. Multifield optimization IMPT allows for high quality plans that can target superficially located HNCs as well as large neck volumes while significantly reducing integral doses. Several dosimetric studies have demonstrated the superiority of IMPT over IMRT to improve dose sparing of nearby organs such as the larynx, salivary glands, and esophagus. Evidence of the clinical translation of these dosimetric advantages has been demonstrated with documented toxicity reductions (such as decreased feeding tube dependency) after IMPT for patients with HNCs. While there are relative challenges to IMPT planning that exist today such as particle range uncertainties and high sensitivity to anatomical changes, ongoing investigations in image-guidance techniques and robust optimization methods are promising. A systematic approach towards utilizing IMPT and additional prospective studies are necessary in order to more accurately estimate the clinical benefit of IMPT over IMRT and passive proton therapy on a case-by-case basis for patients with sub-site specific HNCs.

Introduction

Radiation therapy (RT) has been well established as an essential tool to treat head and neck cancers (HNCs) in various clinical settings. While most HNC radiation treatments have been and continue to be photon-based, advancements in diagnostic imaging, RT planning and delivery have largely modernized the field. Intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) plans can yield highly conformal dose distributions resulting in toxicity reduction, faster treatment times, and use of less monitor units [1–3]. However, the physical properties of photons present inherent challenges in our ability to dose escalate safely while respecting normal tissue tolerance constraints.

Particle therapy as a form of cancer treatment was originally proposed by Robert Wilson in 1946 [4]. Compared to photons which continually deposit dose throughout tissue and exhibit an exit dose, the dose distribution of protons forms a Bragg peak, denoting maximal dose deposition at a finite tissue depth followed by a sharp dose falloff with no exit dose. This dosimetric difference, in turn, can theoretically translate into a clinically relevant therapeutic advantage [5]. IMPT is a sophisticated technique of proton delivery that allows for greater degrees of freedom to produce optimized dose distributions which are essential when treating large volumes such as a primary head and neck sites with simultaneous coverage of the (ipsilateral or bilateral) neck.

Herein, we present a critical review of existing literature regarding the evolution and application of proton therapy, specifically IMPT, for the management of HNCs. An assessment of technological limitations and proposal of the future directions for IMPT are also reported. Key proton therapy references cited in this review article were derived from a thorough PubMed query (Fig. 1). Four hundred and forty one references were retrieved using the following formula: "intensity modulated proton therapy" or "impt" or "pencil beam scanning" or "active

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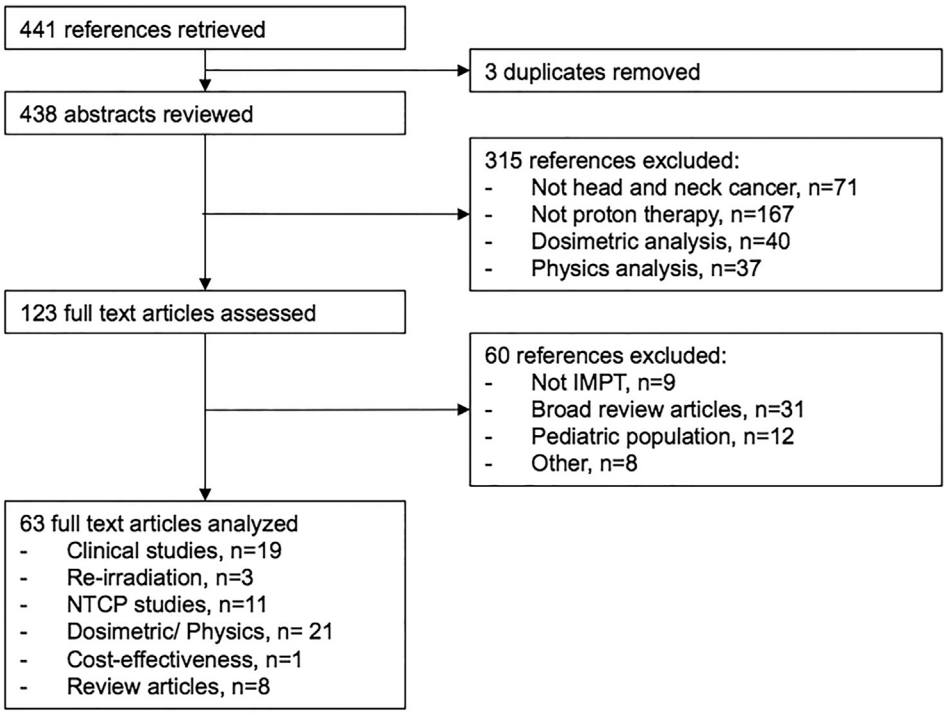

Fig. 1. Critical IMPT reference search algorithm. Abbreviations: IMPT, intensity modulated proton therapy; NTCP, normal tissue complication probability.

scanning" or "scanning beam proton therapy" or "scanned protons" and "head and neck cancer". Out of these, 63 full text articles focusing on dosimetric or clinical studies between IMRT and IMPT, normal tissue complication probability (NTCP) models, re-irradiation studies, and cost-effectiveness analyses were analyzed for content for inclusion in this review.

Dosimetric advantages of proton therapy

The difference in depth dose curves between photons and protons is depicted in Fig. 2. As mentioned earlier, protons exhibit a Bragg peak (or spot) characterized by a sharp increase in dose at the end of the particle range with subsequent absence of dose beyond this range. In comparison, the dose fall off with photons is typically around a few percent per centimeter depending on the medium [6]. Therefore, the rapid fall-off dose of proton beams make them ideal for treating tumors with intracranial extension or those located in critical areas such as the periorbital region, skull base, and/or cavernous sinus. Scattering foils, energy modulation techniques, and brass apertures can be utilized to create spread-out Bragg peak (SOBP) modulated fields conformed to cover a delineated three-dimensional (3D) target volume on CT [7]. This form of RT modality, known as passively scattered proton therapy (PSPT), has been widely studied and used for primary and recurrent HNCs [8–14]. To further corroborate its usage, a recent systematic review and meta-analysis performed by Patel et al. evaluating 43 paranasal sinus and nasal cavity patient cohorts suggested an improvement in 5-year disease free survival (DFS) and locoregional control (LRC) with proton therapy compared to IMRT [15].

IMPT, also commonly referred to as "pencil beam" or "active scanning", is a more sophisticated and complex technical mode of delivering RT. Proton "pencil" beams originating from the accelerator are manipulated to treat tumors in layers of spots at varying depths by

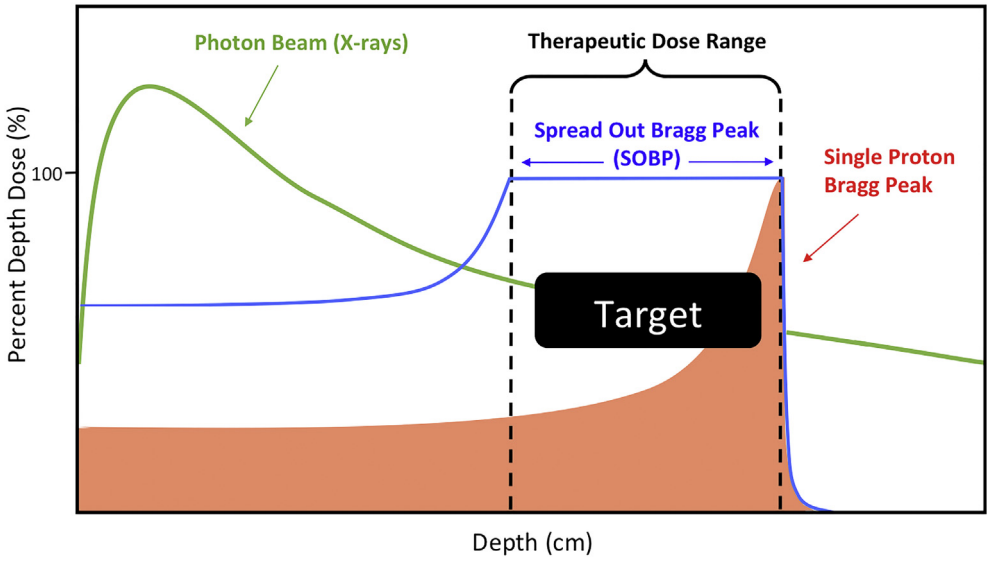

Fig. 2. Dose depth curves for photons and protons. The spread out Bragg peak is the therapeutic radiation distribution created by the sum of multiple individual Bragg peaks (such as the orange single proton Bragg peak) ranging at different depths. Note the rapid falloff of dose after the Bragg peak compared to the photon beam which exhibits an exit dose.

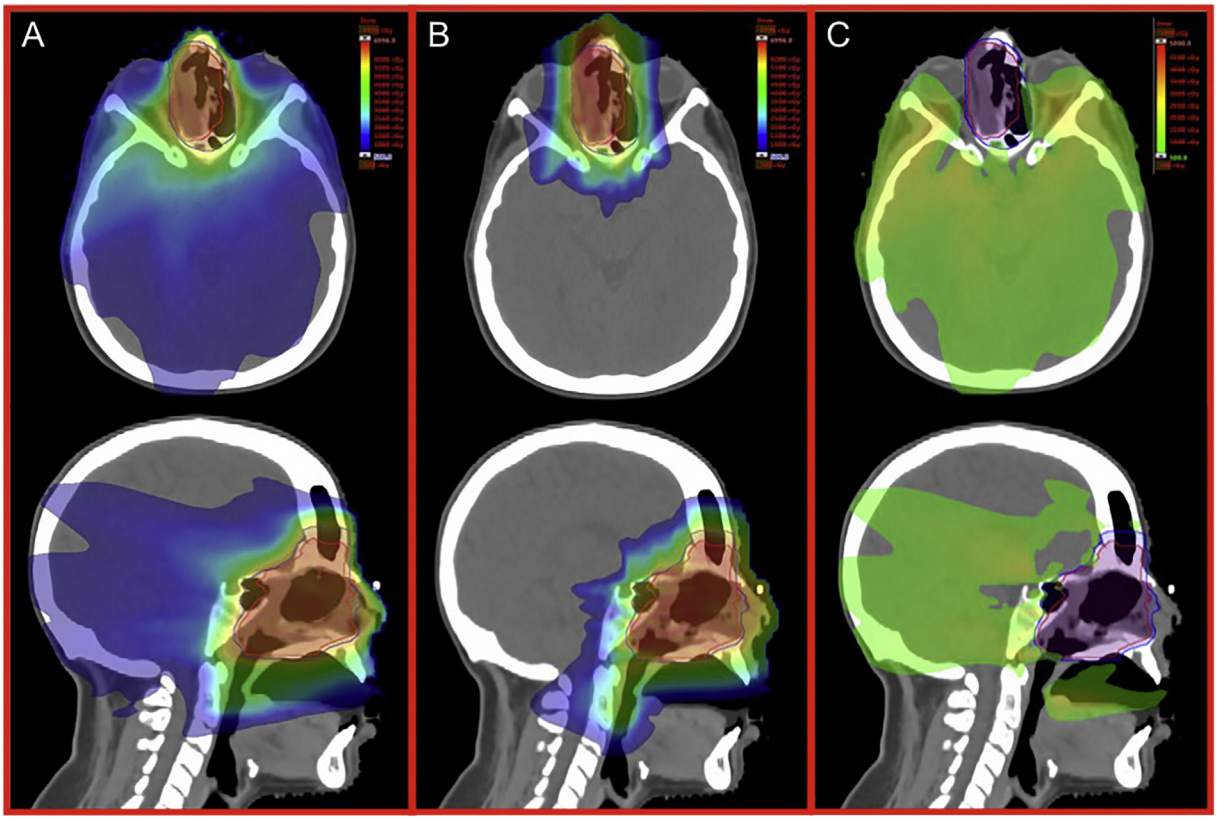

Fig. 3. Comparative VMAT and IMPT treatment plans for a patient with olfactory neuroblastoma. Representative axial and sagittal images for (A) IMRT, (B) IMPT, and (C) subtraction (IMRT minus IMPT) plans are shown.

altering the following: number of protons (local dose deposition), energy (local penetration), and magnetic deflection (off-axis coverage) [16]. Unlike IMRT that achieves a conformal dose distribution through the use of multiple beam arrangements (or arcs) and mechanical multileaf collimators, IMPT relies on electromagnetic control of the pencil beam to achieve comparable target coverage while reducing the integral dose bath. Therefore, IMPT is promising over IMRT for HNC treatments that desire dose escalation while sparing organs-at-risk (OARs). IMPT is also advantageous over PSPT as it eliminates the need for patient-specific devices (i.e. compensators) that can be costly and labor intensive to produce and use during daily treatments. Fig. 3 illustrates comparative VMAT and IMPT treatment plans for a patient with olfactory neuroblastoma.

IMPT planning optimization and limitations

Currently, most commercially available proton beam systems employ therapeutic beam energy ranges from 70 to 250 MeV which translates to water-equivalent thickness depths of over 4 cm [17]. As HNC tumors tend to be more superficially located, range shifters or patient-specific bolus must be utilized with IMPT, or alternatively, high quality plans without range shifters can be achieved through the use of multifield optimization (MFO-IMPT) [18–21]. MFO-IMPT plans are now typically recommended for treating HNCs and can be generated using three to four fields (typically a left and right anterior oblique beams and a single posterior beam ± a vertex beam) subjected to multi-criteria, inverse optimization algorithms that optimize all spots from all fields simultaneously [19,22,23]. Patient-specific apertures can also be implemented with IMPT for a sharper lateral penumbra and further dose reductions to OARs [24].

While IMPT plans have been shown to result in both dosimetric advantages and clinically acceptable treatment-related toxicities compared to IMRT or PSPT, [18,19] there are certain limitations that should be acknowledged with this technology. Firstly, IMPT is highly sensitive to uncertainties in particle range and anatomical changes, the latter of which can be related to interfractional variations in patient positioning, intrafractional organ motion, or target volume changes throughout treatment (i.e. tumor regression or patient weight loss) [25]. With IMRT planning, simple margin expansions to account for anatomical changes and setup errors are quite effective in ensuring adequate target coverage by the prescribed dose. PSPT can account for clinical uncertainties by widening apertures and by compensator smearing [26]. For IMPT, a greater focus is required on improving robust optimization methods and using frequent imaging to verify treatment plans and/or trigger adaptive planning during treatment [27–32]. Using a dataset of 31 locally advanced HNC cases, Stutzer et al. demonstrated the importance of verification CTs with IMPT. In this study where recalculated IMRT or IMPT plans were created on CT scans taken at week 4 of therapy, recalculated IMPT plans showed deterioration of clinical target volume (CTV) coverage and an increase in hotspots within and outside target volumes [33]. Based on reported data, rates of adaptive planning with IMPT can be expected to range from 16% to 38% [34,35].

Limitations in proton beam energy switching time, scanning-spot optimization algorithms, and RBE uncertainties with proton therapy also exist and may affect the accuracy of IMPT planning [16,36–38]. However, these are all areas that are actively being investigated including the development of linear energy transfer-guided optimization and novel methods to seamlessly integrate scanning-spot optimization with beam orientation optimization [39–42]. Establishing and standardizing efficient patient-specific quality assurance protocols are also crucial for successful utilization of IMPT in the clinic [43].

Clinical experience with IMPT by head and neck sub-sites

While definitive concurrent chemoradiation is standard of care for the majority of nonsurgical, locally advanced head and neck cases, [44]

Table 1
Studies evaluating IMPT for Head and Neck Cancers.

Study	HN Site	Study Type	Accrual Period	No. of Patients	Median follow up	Outcomes$_{(years)}$	Toxicities (n, %) and interventions
Gunn [35] (2016)	OPC	PS	2011–2014	50 IMPT	29 mo	$LRC_{2.4}$: 92% OS_2: 94.5% PFS_2: 88.6%	Acute: G3 mucositis (29, 58%), G3 dermatitis (23, 46%). Acute vs. late G3 dysphagea (12, 24% vs. 6,12%). G-tube placed in 11 (22%) patients.
Blanchard [54] (2016)	OPC	RS	2010–2014	A) 50 IMPT B) 100 IMRT	32 mo	A) OS_3: 94.3% B) OS_3: 89.3%	G-tube or weight loss > 20% (A vs. B) after 3-mo: (9, 18%) vs. 34 (34%) and after 12-mo: 4 (8%) vs. 22 (25%).
Lewis[63] (2016)	NPC	PS	2011–2013	10 IMPT	24.5 mo	LRC_2: 100% OS_2: 88.9%	Acute: G3 dermatitis (4, 44%), G3 mucositis (1, 11%). Chronic: G2 xerostomia (2, 22%). No chronic G3-G5 toxicities.
Holliday [64] (2015)	NPC	RS	2011–2013	A) 10 IMPT B) 20 IMRT	21.6 mo	A) LC_2: 100% B) LC_2: 95%	G-tube insertion (A vs. B): 2 (20%) vs. 13 (65%). Swallowing dysfunction (A vs. B): 0 vs 3 (15%).
Holliday [68] (2014)	Sinonasal	PS	2011–2013	16 IMPT	10.5 mo	LC: 87.5%	Acute: G2 dermatitis (13, 81%), G3 dermatitis (1, 6%), G2 mucositis (5, 31%), G2 dysgeusia (2, 13%).
Holliday [68] (2014)	Parotid	PS	2011–2013	13 IMPT	13.2 mo	LC: 100% OS: 100%	Acute: G2 dermatitis (9, 69%), G3 dermatitis (4, 31%).
Holliday [68] (2014)	Periorbital	PS	2011–2013	21 proton (9 IMPT)	27.5 mo	LC: 100%	Acute: G3 dermatitis (7, 33%). Chronic: Visual changes (5, 24%), G3 keratopathy (3, 14%).
Holliday [71] (2016)	Periorbital	PS	2008–2014	6 IMPT, 14 PSPT	27.1 mo	LC: 100%	Chronic: G3 epiphora (3, 15%), G3 exposure keratopathy (3, 15%). Decreased visual acuity (4, 20%)
Ares [74] (2009)	BOS	RS	1998–2005	20 IMPT, 44 scanning[ψ]	38 mo	LC_5: 81%[a] and 94%[b] OS 100%[a] and 91%[b]	Chronic: G3 optic neuropathy (1, 2%), G4 optic neuropathy (1, 2%), G3 brain necrosis (2, 3%).
Phan [11] (2016)	Recurrence	RS	2011–2015	15 PSPT, 45 (75%) IMPT	13.6 mo	OS_1: 83.8% PFS_1: 60.1%	Acute G3 toxicities in 18 (30%). G-tube insertion: 13 (22%).

Abbreviations: BOS, base of skull tumors; G-tube, gastrostomy tube; Mo, months; NPC, nasopharyngeal carcinoma; OPC, oropharyngeal cancer; OS, overall survival; PFS, progression free survival; PS, prospective study; PSPT, passive scatter proton therapy; RS, retrospective study; SCC, squamous cell carcinoma.

[ψ] In this study, 44 patients received proton therapy using a spot-scanning technique.

[a] Five-year LC and OS rates for chordomas.

[b] Five-year LC and OS rates for chondrosarcomas.

RT techniques are constantly evolving and now include proton therapy as an alternative to IMRT. Multiple studies published in the past few years have demonstrated the ability of proton therapy, mainly PSPT, to significantly reduce toxicities such as acute dysgeusia and mucositis compared to photon-based therapies, regardless of primary sub-site or whether only unilateral neck radiation was delivered [45]. The cumulative clinical experience with IMPT for HNCs, however, is still relatively new and therefore the primary focus of this review article. Table 1 summarizes several retrospective and prospective studies investigating clinical and toxicity outcomes after IMPT for the treatment of head and neck cancers of various sub-sites [46–48]. Of note, several units to describe proton dose have been used throughout the literature but for the purposes of this review, all will be reported as the relative biological effectiveness (RBE)-weighted absorbed dose, Gy_{RBE}, which is the latest International Commission on Radiation Units and Measurements (ICRU) recommendation [49]. Gy_{RBE}, defined as the product of absorbed proton dose and the constant relative biological effectiveness (RBE) value of 1.1, is a concept that estimates the photon dose that would produce the same therapeutic effect as the proton dose under identical conditions.

Oropharyngeal cancers (OPC)

With over 51,500 new cases diagnosed in the United States in 2018 alone, cancers of the oropharynx collectively exhibit an average 5-year OS of 65% despite aggressive medical interventions with traditional RT techniques [50,51]. Early efforts to improve locoregional control of OPCs by using proton therapy as a boost with photons were first reported by Slater et al. in 2005 [52]. In this prospective study from 1991 to 2002, a total of 29 patients with localized Stage II-IV OPC received accelerated photon and proton therapy to a total dose of 75.9 Gy_{RBE} in 45 fractions over 5.5 weeks (50.4 Gy_{RBE} in 28 fractions of photon-based RT followed by a PSPT concomitant boost of 25.5 Gy_{RBE} in 17 fractions delivered to the primary tumor and involved neck nodes). The 2- and 5-year locoregional control (LRC) rates were 93% and 84% respectively, while the corresponding disease-free survival rates were 81% and 65%, respectively. Of equal importance with improved outcomes, this treatment was well tolerated with late grade 3 toxicities reported in 3 (11%) patients.

Over time, the focus has shifted from treating large volume OPCs with a combined RT modality approach to IMPT only. In 2016, Gunn et al. reported favorable disease control and toxicity profiles when using IMPT to treat 50 patients with OPC, 98% of whom had clinical stage III/IV disease and 64% of whom were treated with concurrent systemic therapy. After a median follow up of 29 months, LRC was 92%, and 2-year OS and progression-free survival (PFS) rates were high at 95% and 89%, respectively [35]. The same institution published on patient reported outcomes after concurrent chemoradiation using IMPT (n = 35) or IMRT (n = 46) techniques. No differences in acute and chronic phase symptom burden were detected between both groups. However, during the subacute recovery phase (3 months after treatment completion), patient reported symptom burden was significantly lower with IMPT [53]. Moreover, after a 2:1 case matched analysis of 50 IMPT and 100 IMRT patients, IMPT was associated with significantly reduced rates of feeding tube dependency and severe weight loss at 3 months (hazard ratio, HR 0.44 [95% confidence intervals, CI: 0.19–1]; p = 0.05) and at 12 months (HR 0.23 [0.07–0.73]; p = 0.01) post RT [54]. These observed toxicity reductions with IMPT are likely reflective of a clinical translation of dose reduction to several OPC substructures including the oral cavity, larynx, salivary glands, and esophagus [55–58]. Such favorable findings with IMPT have triggered an ongoing clinical trial (NCT01893307) evaluating IMPT versus IMRT for the management of OPC. Lastly, additional studies investigating IMPT use in the postoperative setting for OPC patients is warranted, although there is evidence to suggest potential maintenance of the dosimetric superiority of IMPT compared to IMRT or VMAT [59].

Nasopharynx

Nasopharyngeal carcinoma (NPC) is thought to be chemoradiosensitive; therefore, RT plays a crucial role in both the definitive and postoperative settings. This particular region of the head and neck presents unique challenges for treatment as surrounding neurological structures can be affected by high doses of radiation and result in hearing impairment, optic neuropathy, or temporal lobe necrosis [60]. Given these dose-limiting structures, several studies have demonstrated the feasibility of improving tumor coverage and reducing integral dose to OARs with MFO-IMPT relative to IMRT and helical tomotherapy [61,62].

The University of Texas MD Anderson Cancer Center (Houston, TX) has published most of the existing clinical data on IMPT use for NPC. LRC and OS at 2 years was excellent at 100% and 89%, respectively, for a cohort of 10 NPC patients treated with platinum-based concurrent chemoradiation using IMPT (prescribed dose of 70 Gy_{RBE} in 33 fractions) [63]. The most common acute grade 3 toxicity was dermatitis (n = 4) and only one patient suffered from acute grade 3 mucositis. No chronic grade 3 or higher toxicities were seen. Furthermore, a dosimetric comparison between treatment IMPT plans and theoretical IMRT plans in this study suggest potential dosimetric benefits with IMPT as significant differences in OAR doses favored IMPT in 13 out of 15 cases. Furthermore, a 2:1 case-matched analysis comparing this prospective data with 20 IMRT NPC cases found significantly lower rates of gastrostomy tube insertion with IMPT (20% vs. 65%; p = 0.02), [64] a noteworthy finding that supports the preferential usage of IMPT for management of these anatomically challenging cancers.

Nasal cavity and paranasal sinuses

Tumors of the nasal cavity and paranasal sinuses are primarily managed with surgery followed by postoperative RT (PORT) with or without systemic therapy based on high-risk pathologic features such as nodal involvement or close/positive margins. Local control and OS are highly correlated with the extent of surgical resection; however as demonstrated by Resto et al., [65] PORT delivered with proton therapy can allow for safer dose escalation and improved survival rates compared to historical photon-based outcomes. Using a retrospective cohort of 102 patients with locally advanced sinonasal malignancies that were treated with a combination of proton and photon beam RT, Resto et al. reported 5-year LC rates of 95%, 82%, and 87% as well as 5-year OS rates of 90%, 53%, and 49% in patients who underwent a complete resection, partial resection, or biopsy only, respectively. Similarly for nonsurgical patients, definitive PSPT has been shown to provide adequate 2- to 3-year OS rates over 60% and LC rates of 70–95% for various histological subtypes and extent of disease [66,67]. In order to compare charged particle therapy (protons or carbon ions) to photon therapy for treatment of sinonasal tumors, Patel and colleagues performed a meta-analysis using data collected from 43 cohorts from 41 non-comparative observational studies [15]. The authors found a significantly improved OS at 5 years with charged particle therapy (relative risk, RR 1.51, 95% CI 1.14–1.99; p = 0.0038) as well as improved LRC at longest follow up. Moreover, a subanalysis of proton therapy to IMRT showed significantly higher 5-year DFS (RR, 1.44; 95% CI 1.01–2.05; p = 0.045) and LRC at longest follow up (RR 1.26, 95% CI 1.05–1.51; p = 0.011) with proton therapy. While these findings are supportive of proton therapy use for tumors of the nasal cavity and paranasal sinuses, additional prospective investigations are necessary as most of the studies included in this analysis are retrospective and potentially biased. Besides, caution must be taken during the RT planning phase since proton therapy as with IMRT can also result in significant toxicities such as osteonecrosis, brain necrosis, cataracts and retinopathy [67].

Long term outcomes associated with IMPT use for treatment of sinonasal tumors is still in its infancy with limited data available in the

current literature. One notable prospective study by Holliday et al. included 16 patients with sinonasal tumors out of which 13 (81%) of patients received IMPT in the postoperative setting [68]. The median radiation dose delivered was 62 Gy_{RBE} and treatment was well tolerated with no reported grade 4 or 5 toxicities. In the acute setting, the most common treatment-related toxicity was grade 2 dermatitis (13 patients, 81%) followed by grade 2 mucositis (5 patients, 31%), and grade 2 dysgeusia (2 patients, 13%).

Salivary gland tumors

Major and minor salivary gland tumors are a relatively rare diagnosis with only 2000–2500 cases diagnosed in the United States per year and represent approximately 5–8% of all head and neck cancers [69]. While the parotid is the most common site to harbor disease, the main therapeutic approach remains the same for all salivary gland tumors, which is surgical intervention followed by PORT for adverse features. With regards to the efficacy of proton therapy in general, the Patel meta-analysis which showed improved OS and DFS with particle therapy over photon therapy was based on multiple studies that included patients with minor salivary gland tumors [15]. Due to the rarity of this diagnosis, however, there is a low volume of published evidence demonstrating the potential benefit of IMPT over PSPT or IMRT to treat these cancers. A small study that investigated 13 patients with parotid cancers demonstrated excellent 1-year LC and OS rates with IMPT [68]. In this study, acute grade 2 and grade 3 dermatitis was reported in 9 and 4 patients, respectively. Furthermore, no significant chronic toxicities were reported which is promising when considering RT options for treating the unilateral head and neck.

Periorbital tumors

Due to the complexity of the surrounding anatomy, tumors of the orbit and periorbital regions have been traditionally managed with orbit exenteration in order to ensure widely negative surgical margins. However, a multidisciplinary orbit-sparing treatment approach is now generally recommended when feasible in order to preserve some visual function while maintaining high rates of local control [70–72]. El-Sawy and colleagues have published their institution's experience with globe-sparing treatment for patients with primary lacrimal sac or nasolacrimal duct carcinoma. In this retrospective study of 14 surgical patients (9 limited surgery, 1 biopsy only, and 4 orbital exenteration due to extensive orbital tissue involvement), 13 patients underwent PORT with protons or IMRT (median dose, 60 Gy) and 8 patients received chemotherapy. The globe was spared in all 10 patients after a median follow up of 27 months, and 9 (90%) patients either maintained or saw an improvement in their baseline visual acuity [70].

In a slightly larger cohort of 20 patients with epithelial tumors of the orbit/ocular adnexa, Holliday et al. demonstrated the feasibility of achieving disease control after orbit-sparing surgery followed by proton therapy [71]. The median radiation dose was 60 Gy_{RBE}, and 6 (30%) patients received IMPT using an eye-deviation technique for patients with lateralized tumors. After a median follow-up of 27.1 months, no patient experienced a local recurrence (1 regional, 1 distant), and the treatment was overall well tolerated with the exception of some cases of grade 3 epiphora (3 patients, 15%) and grade 3 exposure keratopathy (3 patients, 15%). All patients maintained vision in the ipsilateral eye with only four (20%) patients experiencing a decrease in visual acuity. One interesting finding the authors noted was an association of grade 3 or higher chronic ocular toxicities with a higher max dose to the ipsilateral cornea (median 46.3 Gy_{RBE} vs. median 37.4 Gy_{RBE}, P = 0.017). Additional investigations are warranted to identify the most optimal patient setup, IMPT planning specifications, and sub-ocular structure radiation dose tolerance limits in order to provide the most favorable outcomes with IMPT for this patient population.

Base of skull tumors

Tumors located at the base of skull (BOS) are challenging to manage as surgical interventions are often not possible for patients with locally advanced disease, and efforts to deliver ablative doses to the tumor can be hindered by the need to respect the tolerance limits of nearby structures such as the brain and brainstem. From a dosimetric standpoint, IMPT may again offer a benefit over IMRT. Leeman et al. recently reported dose-volume characteristics for IMRT and IMPT plans in the preoperative and postoperative settings for two patients with BOS disease. In one particular case, an 80-year old male with adenocarcinoma of the ethmoid sinus with extensive involvement of the anterior BOS and paranasal sinuses, IMPT resulted in either comparable or significantly improved dose sparing of several OARs in the preoperative setting compared to IMRT (brainstem max dose, 35.8 Gy_{RBE} vs. 60 Gy; right/left cochlea: 9.6/7.1 Gy_{RBE} vs. 38.4/35.8 Gy) [73]. The dosimetric advantage conferred by IMPT persisted in the postoperative setting for this case as well as for the second case of locally advanced chondrosarcoma of the sphenoid sinus.

The first long-term report on the use of proton therapy, particularly IMPT, for chordomas and chondrosarcomas was reported by Ares et al. in 2009 [74]. A total of 64 patients with BOS disease were treated with either a spot-scanning proton therapy technique (n = 44) or IMPT (n = 20). The median total dose delivered was 73.5 Gy_{RBE} and 68.4 Gy_{RBE} for chordomas and chondrosarcomas, respectively. With this treatment, 5-year LC rates were high at 81% for chordomas and 94% with chondrosarcomas, and 5-year OS were even higher at 100% and 91%, respectively. Treatment-related toxicities were limited and no brainstem toxicity was reported, making IMPT an ideal RT technique for treatment of BOS tumors.

Reirradiation for recurrent or new primary HNCs

Substantial progress in RT techniques and its application for reirradiation of recurrent or new primary cancers of the head and neck have occurred over the last three decades. Earlier studies using conventional fractionation or brachytherapy in previously irradiated tissues often showed poor to modest local control but at a costly trade-off of highly morbid late complications such as soft tissue necrosis, osteoradionecrosis and carotid blowout [75–77]. IMRT and stereotactic body radiotherapy (SBRT), the latter being a conformal photon-based modality capable of delivering ablative radiation doses over 1–5 fractions with greater dose fall-off than IMRT, have largely replaced traditional 2D/3D RT techniques. Reported 1- to 2-year LRC rates in the literature are approximately 20–60% with 3D RT, 50–60% with IMRT, and 40–80% with SBRT [77].

The ability to deliver conformal definitive doses safely is highly correlative with improved local control and overall survival. Therefore, proton therapy is ideal from a dosimetric standpoint for such cases where minimizing dose exposure to reirradiated normal tissue is critical to reducing the risks of treatment-related toxicities. We have previously summarized the findings of four clinical reirradiation series using proton therapy for squamous cell carcinomas of the head and neck [78]. The majority of these patients were treated with PSPT, and one study (n = 92) reported a 1-year LC and OS of 75% and 65%, respectively, after a PSPT median dose of 60.6 Gy_{RBE}. However, noteworthy grade 3 or higher late skin and dysphagia toxicities were seen in 6 (8.7%) patients and 4 (7.1%) patients, respectively, as well as 2 cases of grade 5 bleeding [10].

Compared to IMRT and PSPT, there is a lack of clinical and toxicity outcomes data after reirradiation using IMPT given the novelty of the technology. Most of the existing information regarding IMPT in the reirradiation setting for HNCs are dosimetric studies such as the one recently published by Eekers et al. [79]. They compared VMAT, IMPT, and ion therapy (IMIT) reirradiation plans prescribed to a second dose of 70 Gy/Gy_{RBE} for 25 patients. Compared to IMRT, IMPT plans were

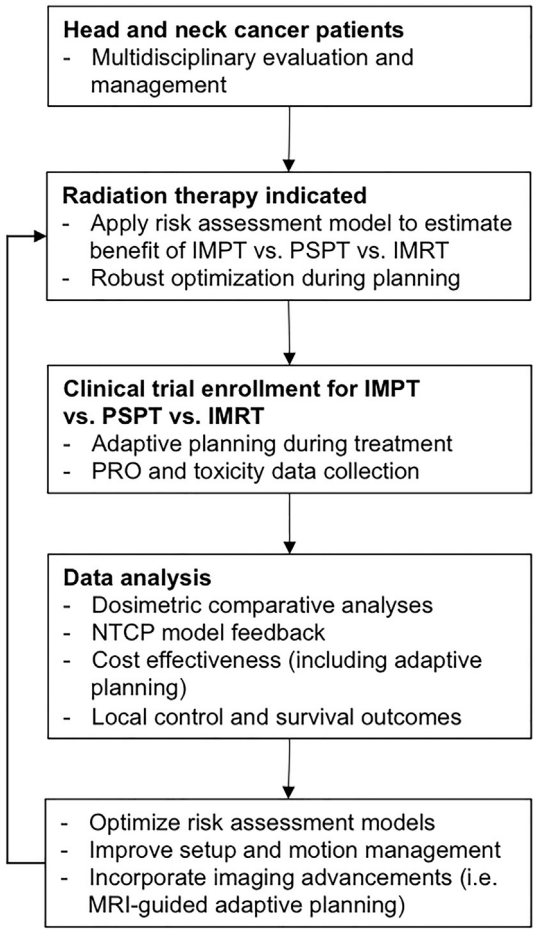

Fig. 4. Proposed methodology to investigate the clinical benefits of IMPT for the management of head and neck cancers. Abbreviations: IMPT, intensity modulated proton therapy; IMRT, intensity modulated radiation therapy; NTCP, normal tissue complication probability; PRO, patient reported outcomes; PSPT, passive scatter proton therapy.

superior as they resulted in significantly reduced mean doses to 15 out of 22 (65%) OARs studied (brainstem D_2, 2.7 Gy_{RBE} vs. 8.2 Gy; spinal cord D_2, 6.7 Gy_{RBE} vs. 16.6 Gy; larynx mean dose, 27.2 Gy_{RBE} vs. 34.1 Gy). Phan et al. have reported on clinical outcomes associated with reirradiation of HNCs with IMPT [11]. From April 2011 to June 2015, 60 patients were treated with proton therapy (IMPT: n = 45, 75%) out of which 35 (58%) patients received upfront surgery, and 44 (73%) received concurrent chemotherapy. The most common retreatment sites for the collective cohort were the oropharynx (40%), nasopharynx (8%), or the neck, orbit, or sinonasal regions (13% each). With a median follow-up of 13.6 months, the 1-year rates of locoregional failure-free survival, OS, PFS, and acute grade 3 toxicities for all patients were 68.4%, 83.8%, 60.1%, and 30%, respectively. While these results are promising, they still highlight the main barrier to reirradiation which is the high rates of toxicity, regardless of RT modality. Therefore, extensive prospective evaluation of IMPT for head and neck reirradiation is required.

Future directions

These are exciting times as proton therapy continues to be validated as a valuable treatment modality for patients with HNCs. The National Comprehensive Cancer Network (NCCN) guidelines already recognizes the dosimetric and clinical advantages protons provide for treating tumors near critical structures and recommends its usage when normal tissue constraints cannot be met with photon-based therapies [44]. With the increase in proton therapy centers worldwide, IMPT will become more readily available, tentatively allowing for increased feasibility in performing larger prospective studies on clinical outcomes and cost-effectiveness analyses [80,81]. Currently, it is still unclear which HNC patients will exhibit a significantly enhanced therapeutic ratio with IMPT over PSPT or IMRT. However in the absence of randomized clinical data, retrospective comparison plans using normal tissue complication probability (NTCP) modeling is providing insight on potential subgrouping categories to properly preselect patients for IMPT. Modern NTCP models take into account the incidence of various toxicities such as acute oral mucositis, aspiration, xerostomia, and dysphagia to compute corresponding NTCP values that can be compared by RT technique. One study has suggested risk reductions of dysphagia with IMPT over IMRT in patients with tumors located in the upper head and neck area as well as risk reductions of acute mucositis in patients with tumors in the larynx [82]. Additional NTCP models are being investigated to estimate the efficacy of IMPT for specific HNCs sub-sites or when IMPT is delivered in a mixed modality treatment [83–86].

Fig. 4 outlines a proposed workflow towards efficiently studying, validating, and refining what we know about and how we use IMPT in oncologic care. First and foremost, all patients presenting with a suspected HNCs should be properly assessed and staged in a multidisciplinary setting [87,88]. Pre-treatment data collection on comorbidities, functional deficits, and disease extent should be performed and integrated into an evolving risk assessment model used to estimate the expected therapeutic ratio using the various RT modalities. Enrollment on clinical trials should be encouraged to prospectively collect and analyze radiographic data (CT, MRI, PET, etc.), quality of life, functional and survival outcomes. Radiomic texture analysis methods are currently being investigated for HNC applications [89] and can be incorporated into developing risk assessment models for future patient stratification and treatments. Overall, having a structured methodology for investigating the value of IMPT, both in the primary and reirradiation settings, is crucial towards providing unbiased information and should be promoted on a national scale.

Conclusions

Proton therapy offers a dosimetric advantage over IMRT in the management of HNCs. IMPT is a highly sophisticated, novel form of proton therapy that is promising for treatment-related toxicity reduction and potential dose escalation while respecting normal tissue dose constraints. The greatest limitation to IMPT is its high sensitivity to radiologic density changes due to setup errors or anatomical changes during or in between fractions. However, advancements with on-board image guidance resources, robust optimization algorithms, and standardization of patient-specific quality assurance programs and CT verification protocols will aid in the establishing of IMPT as a standard of care for HNC treatment. Additional prospective studies are necessary to quantify the clinical benefit of IMPT over IMRT or PSPT, and to provide dynamic feedback on improving current methods used to plan and treat patients with IMPT.

Conflicts of interest

The authors declared that there is no conflict of interest.

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