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Review Article

Proton therapy for head and neck squamous cell carcinomas: A review of the physical and clinical challenges

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ABSTRACT

The quality of radiation therapy has been shown to significantly influence the outcomes for head and neck squamous cell carcinoma (HNSCC) patients. The results of dosimetric studies suggest that intensity-modulated proton therapy (IMPT) could be of added value for HNSCC by being more effective than intensity-modulated (photon) radiation therapy (IMRT) for reducing side effects of radiation therapy. However, the physical properties of protons make IMPT more sensitive than photons to planning uncertainties. This could potentially have a negative effect on the quality of IMPT planning and delivery. For this review, the three French proton therapy centers collaborated to evaluate the differences between IMRT and IMPT. The review explored the effects of these uncertainties and their management for developing a robust and optimized IMPT treatment delivery plan to achieve clinical outcomes that are superior to those for IMRT. We also provide practical suggestions for the management of HNSCC carcinoma with IMPT. Because metallic dental implants can increase range uncertainties (3–10%), patient preparation for IMPT may require more systematic removal of in-field alien material than is done for IMRT. Multi-energy CT may be an alternative to calculate more accurately the dose distribution. The practical aspects that we describe are essential to guarantee optimal quality in radiation therapy in both model-based and randomized clinical trials.

Radiation therapy is recommended in more than two-thirds of head and neck squamous cell carcinomas (HNSCC). Recent publications have demonstrated the importance of the quality of the radiation therapy offered to HNSCC patients [1–4]. In a randomized clinical trial, Peters *et al.* first demonstrated that HNSCC patients with noncompliant treatment plans could significantly suffer from lower rates of loco-regional control and have an overall survival of two years [5]. Several reviews have already indicated that intensity-modulated proton therapy (IMPT) is promising in the treatment of HNSCC [6–8]. IMPT could reduce the volume of irradiated healthy tissues by more than 25% (Fig. 1), thereby significantly reducing the risk of dysphagia, xerostomia, dysgeusia, and hypothyroidism. Consequently, several clinical studies are currently underway to provide compelling evidence for the clinical benefit of IMPT (*NCT01893307*). However, the physical properties of protons make IMPT more sensitive than IMRT to planning uncertainties, and this could potentially have a negative effect on the quality of IMPT planning and delivery. Thus, building evidence from clinical trials requires that the technical and physical aspects be well understood and managed to ensure the delivery of high-quality IMPT. The goal of the present review was to assess the technical and physical requirements that are specific to PT for HNSCC of usual location (oropharynx, oral cavity, larynx, hypopharynx). A brief explanation of the physical properties of protons is provided. Next, the differences between IMPT and IMRT, especially the effects of the uncertainties associated with IMPT are discussed. Solutions for achieving robust and optimized treatment are proposed. The final section emphasizes the limits of the model-based approaches and randomized clinical trials for IMPT in HNSCC if the uncertainties are not addressed. It is hoped that this article

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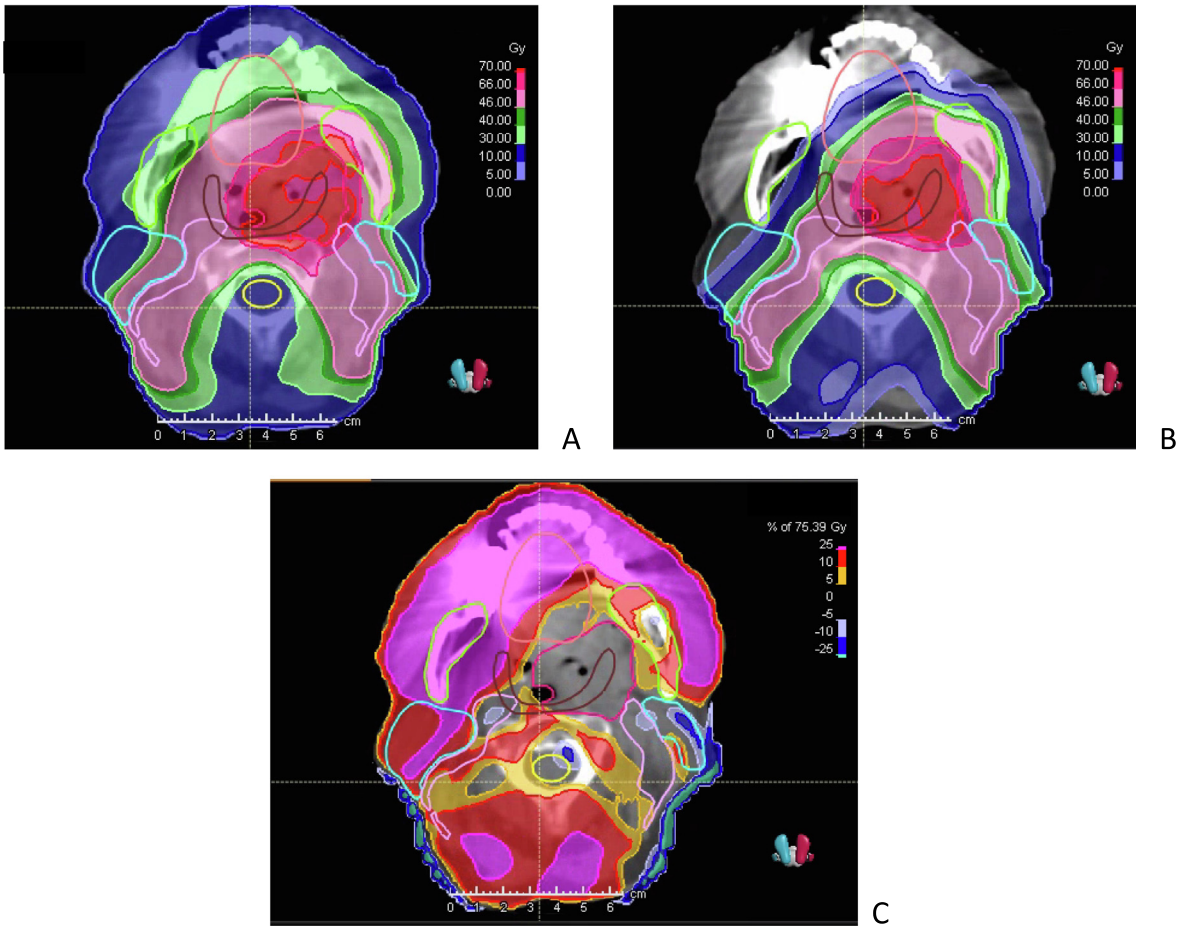

Fig. 1. Treatment planning comparison between IMRT and IMPT for the treatment of a right tonsillar squamous cell carcinoma. This figure illustrates a comparison between an IMRT treatment planning (A) and an IMPT treatment planning (B). The picture C shows the subtraction of the two treatment plannings. IMPT allows a better OAR sparing, such as the oral cavity (pink line), the mandible (green line) and the contralateral parotid (blue line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

provides a basis for future clinical trials (the model-based approach and randomized trials).

Materials and methods

The references for this review were identified through searches of PubMed for the terms "Proton therapy AND Head and Neck Squamous Cell Carcinoma," "Proton therapy AND Oropharynx Squamous Cell Carcinoma," "Proton therapy AND Larynx Squamous Cell Carcinoma," "Proton therapy AND Hypopharynx Squamous Cell Carcinoma," "Proton therapy AND Oral cavity Squamous Cell Carcinoma". We excluded articles that referred to other specific locations and histologies such as sino-nasal carcinoma or nasopharyngeal carcinoma. The time period was 2000 to April, 2019. Articles were also identified through searches of the authors' files. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Results

Physical considerations of proton therapy for the treatment of head and neck SCC

Head and neck carcinomas (HNC) are characterized by complex anatomy and are always surrounded by many organs at risk. The physical properties of protons are very useful for the treatment of these cancers. Indeed, in a uniform medium, monoenergetic protons travel a well-defined distance, losing energy at an increasing rate before coming to a halt. This forms the characteristic Bragg peak. Distal penumbra is limited and well adapted to the treatment of HNC. Besides this, a therapeutic beam can be produced by: (1) passively scattered PT (PSPT), i.e., accurately modulating the energy of the initially narrow monoenergetic beam with a range modulation wheel and scattering it laterally to cover the tumor volume; or (2) pencil beam scanning (PBS), i.e., scanning the narrow (pencil) beams magnetically by energy layers. Both PSPT and PBS use the sum of pristine Bragg peaks to produce a homogeneous depth dose, the spread-out Bragg peak (SOBP). PSPT is not well adapted to the complex anatomies of HNSCC compared to PBS. Indeed, in PSPT, the dose distribution is conformed laterally with an aperture; however, in PBS, magnetic scanning is sufficient. Moreover, in PSPT, range uncertainties are minimized through range compensator smearing. For complex (convex) tumor anatomies, field junctions, known as beam patching, can be used. However, beam patching is technically demanding and sensitive to set-up uncertainties [9]. Besides, most medical accelerators produce energies of 100 (rarely 70) to 250 MeV, thus requiring either an additional energy degrader (range shifter) in the nozzle, or a snout to cover the superficial (subcutaneous) areas. The addition of a collimator is not common in PBS techniques; however, it could be considered for reducing the lateral margins. Because the magnetic scanning of thin pencil beams provides greater flexibility

and facilitates intensity modulation, PBS is adequate for the development of PT for complex HNSCC anatomies. In PBS, there are two different optimization techniques: single-field optimization (SFO) and multi-field optimization (MFO/IMPT). In the SFO approach, each beam is optimized independently to achieve a uniform dose to the target while minimizing the dose outside the tumor. SFO is quite robust to changes. With IMPT, the optimization process simultaneously optimizes the intensities of the spots from all of the beams, thereby irradiating the tumor heterogeneously with each beam but providing a uniform dose to it. IMPT is therefore more relevant for the complex HNSCC anatomy and OAR constraints, and it has been shown to have a better ability to spare some OAR [10]. However, because the dose gradients are very steep in each field and the field gradients must match perfectly between the beams, IMPT is clearly less robust than SFO in the presence of uncertainties. Uncertainties in the exact position of the distal dose gradient (+/−3%) arise from: (1) the calibration uncertainties between the Hounsfield unit (HU) values and the proton stopping powers in the tissues, (2) the contribution of linear transfer energy and radiobiology to the dose assessment, (3) the positional or setup variations, (4) the interfraction and intrafraction variations in anatomy (including organ motion and tissue changes), and (5) the approximations in the dose computation models [7,11–13]. Several methods for reducing uncertainties, particularly in HNSCC, are presented below and summarized in Fig. 2.

Treatment planning computed tomography scans

PT planning for the treatment of HNSCC is based on computed tomography (CT) images. Typically, the CT scan is acquired through the use of a single energy spectrum, e.g., single-energy CT. It relies on a calibration process to obtain the proton-stopping power ratio (SPR) from the HU on the basis of the stoichiometric composition of the tissues [14]. However, in single-energy CT, the data are limited to a single dimension per voxel. This is problematic because the HU–SPR calibration curves do not have a one-to-one relationship for human tissues. Calibration uncertainties can be critical in HNSCC in the presence of materials with uncertain stoichiometric composition (such as those in metal implants and dental fillings) and complex heterogeneities. Materials in the beam entry produce range uncertainties because of imaging artifacts. Dual-energy CT or multi-energy CT has the potential to improve the conversion of the CT values to SPR and could decrease the range uncertainties below 1%. It may be particularly applicable in situations in which implanted materials are responsible for increased calibration uncertainties [15–17]. Dual-energy CT should therefore be particularly relevant to HSNCC in the coming years. Besides dual-energy CT, MRI-based CT, which improves proton range calculation accuracy, was recently developed [18]. The reliability of pseudo-CT methods is sensitive to metal-induced MRI distortions; thus, these methods may not solve the problems posed by metallic implants in HNSCC patients. Thus, PT planning may be more demanding in terms of dental care before irradiation. The advances in proton CT are still at the preliminary stage; however, specific proton probes might be a new solution for selected uncertain beam paths [19,20]. In brief, HU or SPR calibration uncertainties and the prevalence of metal materials in patients require caution in the use of CT in HNSCC. Therefore, HNSCC is a relevant area of investigation for improved planning imaging.

Beam line accessories

The superiority of PT over IMRT relies on its physical dose distribution. However, range uncertainties limit the use of distality, and lateral penumbra may be substantially broadened if treatment delivery is not optimized. A clinically relevant question is the acceptable lateral penumbra to ensure the superior performance of IMPT over IMRT in terms of high-dose conformality. Because of the minimal produced energy of 100 MeV cyclotrons, a range shifter remains somewhat necessary for covering the superficial parts of the HNSCC volumes. The preliminary experience with automatically removable range shifters to avoid broadening the

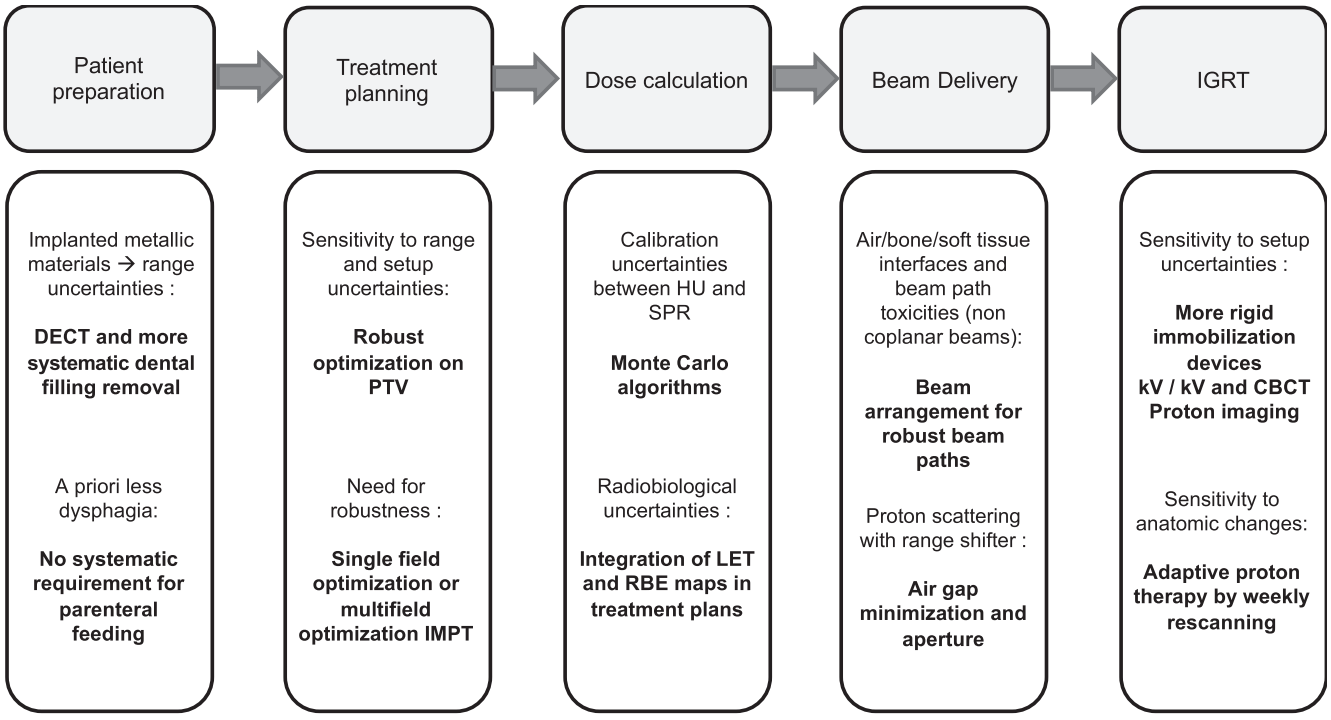

Fig. 2. Optimization and robustness of the workflow comparing IMPT with IMRT for head and neck carcinoma. DECT: Dual-Energy CT, IMPT: Intensity-modulated proton therapy, HU: Hounsfield Unit, SPR: Stopping Power Ratio, IGRT: Image guided radiation therapy CBCT: Cone beam CT.

lateral penumbra in deeper layers has been reported. However, most commercial machines do not provide this option. TPS-integrated Monte Carlo codes allow for more accurate dose computations in air gap conditions and can show the effects of a larger air gap on the lateral penumbra. Air gap minimization below 10 cm or 5 cm is not consensual; thus, a snout is required. Another option is to use collimation in the same way that it is used in PSPT [21]. Finally, the optimization of the lateral penumbra is an essential aspect of proton plan quality in HNSCC given their location under the skin surface and in-depth.

Beam angle optimization

Currently, beam angles and numbers are chosen manually, and they are equipment- or team-dependent (Table 1). In HNSCC, patients undergoing bilateral neck PT are treated with left and right anterior oblique beams and a single posterior beam. Other ballistics include left and right posterior oblique beams with one anterior subclavicular beam, left and right anterior and posterior oblique beams, or three or four anterior beams only ([22–24]; Fig. 3). These configurations may be dependent upon the couch characteristics (heterogeneous components not traversed by the beams) and air gap modelling (between the range shifter in the nozzle and the patient surface), which rely on the use of dose algorithms (Monte Carlo use to better account for air/-couch/patient interfaces or proton scattering in the air gap after a range shifter) or other technical and physical parameters rather than clinical factors. By selecting the appropriate beam angles, the sensitivity of an IMPT plan to lateral tissue heterogeneities can be reduced. In 2016, Toramatsu et al. developed a fast and accurate method of beam angle selection for PBS and showed in three clinical cases of HNSCC that by selecting a field with a low mean heterogeneity number, target dose coverage and robustness against setup and range errors were improved [25]. Automatic beam angle optimization is now integrated into some treatment planning software and may provide computationally efficient, dosimetrically superior, and reduced delivery-friendly IMPT plans for HNSCC [26].

Table 1
Physic characteristics of the four reported cohorts of classical HNSCC patients treated with proton therapy.

	Slater et al. (2005)	Frank et al. (2014)	Takayama et al. (2015)	Gunn et al. (2016)
Dose in High Risk - CTV (Gy RBE)	75.9	70	55.8 to 73	70
Dose in Low Risk - CTV (Gy RBE)	50.4 (3D photon)	57	30 (3D photon)	54–63
Passive or active beam delivery	PSPT	PBS	PSPT	PBS
Beams: Number and angles	Single posterior oblique field	BNI: left and right anterior oblique + single posterior beam INI: two to three ipsilateral beam angles	NA	BNI: left and right anterior oblique + single posterior beam
Proton therapy planning	_	IMPT	_	IMPT or SFO (unilateral case)
SIB	Yes	Yes	NA	Yes
Method of artefacts management	NA	Artefact delineation and average HU value assignment	NA	NA
IGRT	NA	2D, Daily	2D, Daily	2D, Daily
Adaptive proton therapy: Rescan	NA	CT, Weekly	NA	CT, At least week 1 and

Abbreviations: NA: Not available, PSPT: passively-scattered proton therapy, PBS: pencil beam scanning, BNI: Bilateral neck irradiation, INI: Ipsilateral neck irradiation, IMPT: Intensity modulated proton therapy, SFO: Single Field optimization, SIB: Simultaneous Irradiated boost, IGRT: Image guided radiotherapy, 2D: orthogonal X-ray projective 2D images.

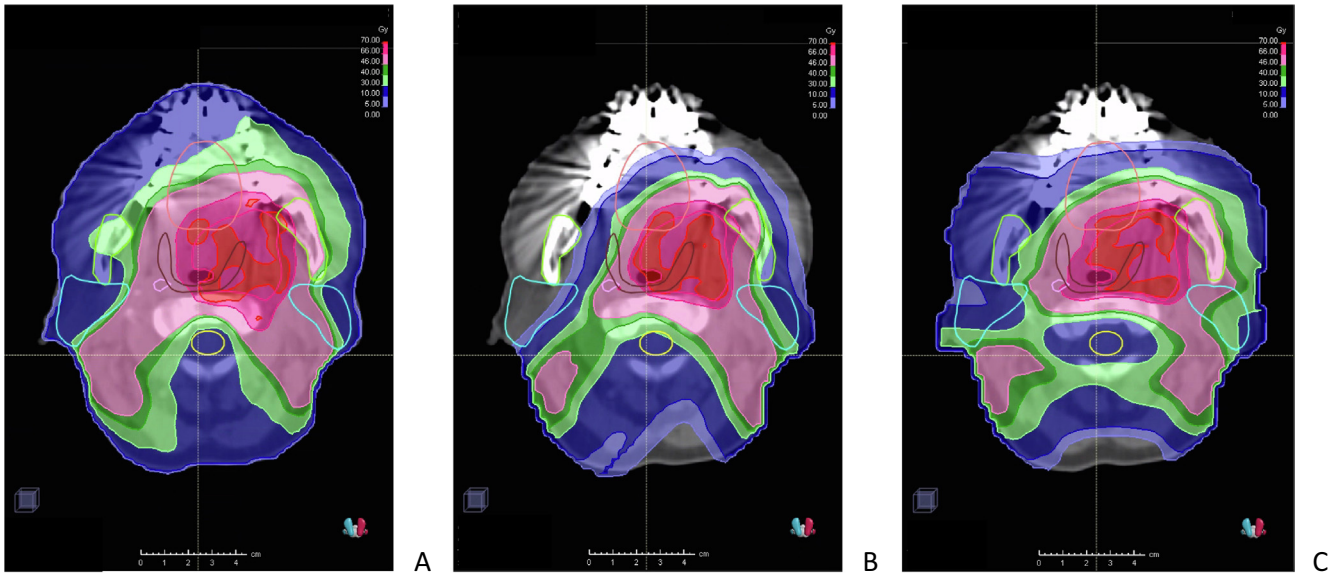

Fig. 3. Comparison between two ballistics of IMPT for the treatment of an oropharyngeal squamous cell carcinoma. The ballistics used in proton therapy to treat head and neck carcinoma are heterogeneous and team dependant. This figure illustrates a comparison between three treatment plannings: A. IMRT, B. IMPT with both left and right posterior oblique beams, C. IMPT with three anterior beams. Both IMPT treatment plannings allow a better organ at risk sparing than IMRT. Both ballistics used for IMPT cause very different treatment plannings, with different organ at risk sparing. The choice of a ballistic allows also to take account for the artefacts.

Treatment planning

Defining the target volume

The definition of the target volume in IMPT for HNSCC is currently similar to that for IMRT. A PTV is generated by geometrically expanding a CTV with fixed and predefined margins on the basis of setup error models [27]. However, such an approach does not account for the beam-path uncertainties in tissue composition. In 2012, Park et al. proposed a beam-specific PTV method for designing and evaluating proton plans [28]. In the first step of the creation on this beam-specific PTV, a "geometrical miss" of the CTV resulting from a lateral setup error is addressed by a lateral (relative to the beam direction) expansion of the CTV. Second, systematic range uncertainties are addressed by adding distal and proximal margins for each ray trance from the beam source to the distal and proximal surfaces of the CTV. Third, range error resulting from misaligned tissue heterogeneity is addressed by adding extra margins from a density correction kernel. This beam-specific PTV design seems to outperform those using the conventional PTV approach and can be particularly useful in complex anatomies found in HNSCC. Usually, the addition of an automatic margin around the CTV is used to take into account setup uncertainties. The optimization is done on this PTV, resulting in the irradiation of a large volume of healthy tissue at full dose. In IMPT, the latest developments include a robust optimization method that takes into account individual setup and range uncertainties directly during the spot weight optimization process to ensure CTV coverage without the use of a PTV. Therefore, it does not require extra volume to be irradiated, and could allow better OAR sparing. In Liu et al. (2013), two sets of IMPT plans were generated for 14 HNSCC cases: one being PTV-based conventionally optimized and the other CTV-based robustly optimized [29]. The CTV-based robustly optimized plans exhibited better target coverage, improved dose homogeneity, and lower equivalent dose to OAR than the conventional PTV approach. These robust CTV-based prescription modalities may be particularly relevant to challenging HNSCC cases and should be investigated further for both conformality and robustness. The current literature rarely provides sufficient data on treatment planning methods despite their possible significant dosimetric effects. The standardized reporting on these prescription methods would be very useful to define new ICRU guidelines dedicated to harmonize the dose reporting in proton therapy, with correct definition of the relevant target volume.

Dose definition and fractionation

A mean relative biological effectiveness (RBE) of 1.1 is currently applied in TPS to achieve a dose scheme that is similar to that used in IMRT for HNSCC [30]. For PT, most centers use conventional fractionation, with 1.8 Gy as the physical dose (corresponding to 2 Gy RBE). Because of the increasing RBE with the decreasing dose per fraction, a theoretical concern for any given total dose is the possible increase in toxicity in the critical serial organs with low α/β [31]. In most HNSCCs, IMRT is currently performed with a simultaneous integrated dose (SIB) approach because of its superior potential over the sequential approach regarding conformality. Despite the lack of clinical evidence of the risks and the inadequacy of the data regarding sequential planning, this approach should be considered in the design of SIB PBS plans.

Physical and radiobiological optimization

The physical dose (number of protons per mass unit) is not equivalent to the linear energy transfer (LET). This means that the ionization density and a more clinical notion are the dose-averaged LET (LETd) to reflect the effects of PT. Indeed, the proton RBE increases as the LETd increases. The RBE increases with depth in the SOBP: from ~1.1 in the entrance region to ~1.15 in the center, ~1.35 at the distal edge, and ~1.7 in the distal fall-off [32–35]. As *Paganetti* points out, these averages for all cell lines are not necessarily representative for clinically relevant tissues [35]. Nevertheless, there may well be a significant increase in the RBE between the entrance and the distal fall-off of the SOBP. Disregarding this variation could have negative clinical implications, particularly when an OAR is located near the distal end of a tumor [36,37]. Rorvik et al. proposed a phenomenological dose model on the basis of the LET spectra [38]. Advances in TPS and processors now allow for the integration of physical uncertainties to deliver robust plans for HNSCC. Several teams have indeed investigated the feasibility of incorporating the LET into the optimization of IMPT plans [39,40]. In Cao's study, LET-based objectives were added to the classic optimization for maximizing the LET in target volumes and minimizing it in critical structures and healthy tissues. Software and processors allowing clinically relevant calculation times are becoming available in routine practice [41]. Some TPS include patient-specific quality assurance for PBS [42]. A new calculation tool developed at the Heidelberg and Pavia Ion Beam Therapy Centers incorporates LET and RBE maps through the use of a graphics processing unit for fast and accurate calculation [43].

Other important parameters of the biological efficacy of protons include cell type, α/β, and therapeutic parameters, such as the dose per fraction. Advances in TPS and processors now allow for the integration of radiobiological uncertainties to deliver robust plans for HNSCC. The use of a generic spatially invariant RBE of 1.1 within tumors and normal tissues ignores the evidence that proton RBE varies with several other endpoints (cf. [30,35]). Therefore, beam selection based on biological dose and robustness could be superior to geometric substitute measures. Because the superposition of dose distributions from different directions almost always decreases the dose-weighted LET, the RBE robustness of multifield plans can be improved [44]. A variable RBE correction with LET-dependent tissue-specific parameters based on the α/β ratio might be used to assess the RBE-corrected dose-volume histograms and to show the higher normal tissue complication probability (NTCP) values for the non-target healthy tissues than those expected with an RBE of 1.1 [34,36,45]. In Yepes et al.'s study (2019), the variable RBE values in IMPT were integrated in four ways [46]. One was a fast-dose Monte Carlo calculator with fixed RBE, and three were the RBE calculated on the basis of three models: McNamara, Wedenberg, and repair–misrepair–fixation. For the OAR, the two LET-based models systematically predicted RBE > 1.1 for most structures in HNSCC. In another study, the average RBE within CTV was 1.06–1.16 [47]. Variable RBE values could therefore be a critical factor, especially in NTCP-based comparisons of proton and photon plans.

Automated dose optimization

The manual adaptation of priority weights for cost functions is time-consuming. Fully automated optimization can be done if the correct constraints are either known (in the case of plan optimization) or discoverable on the basis of rules (lexicographic-ordering approach [44]). Repetitive steps, such as image registration, delineation of the healthy tissue, and dose optimization, can be automated with templates. Machine learning approaches, i.e., knowledge-based planning from previous patients, can be added. This method predicts the plan quality metrics, treatment plan parameters, or voxel-by-voxel dose distributions on the basis of previous plans and explanatory variables that quantify the geometry of the new patient of interest. This automated dose optimization can be of great interest. Firstly, it can allow a quick comparison of different plans and the selection of the one that provides the best target coverage and OAR sparing [48]. It may also be particularly useful in the case of machine breakdown because the repopulation of HNSCC is a significant issue over 4-day interruptions. This can also be useful in the case of significant weight loss,

which is common in patients being treated for HNSCC, requiring very rapid replanning. McIntosh found that for oropharyngeal HNSCC patients treated with IMRT, a fully automated treatment plan that used a voxel-based dose prediction and dose-mimicking method exhibited increased OAR sparing and better target coverage or uniformity in 12–13 minutes without any user interaction [49]. Similarly, new plans with another treatment machine, a different treatment technique, and an alternative treatment modality can automatically be created to reproduce the dose distribution of the original reference plan. The comparison between an IMRT plan and an IMPT plan can in this case be facilitated and this approach makes it possible to quickly choose the optimal technique. Automatic knowledge-based planning could be useful for IMPT treatment plans for HNSCC patients [50].

Image-guided and adaptive proton therapy

Image-guided radiation therapy (IGRT), which relies on orthogonal projective 2D images or volumetric 3D images (in-room CT or cone-beam CT [CBCT]), is critical to the success of IMPT. Most machines are equipped with 2D-IGRT systems only, and their adequacy for 2D imaging for HNSCC is a matter of debate. In most HNSCC studies, the setup accuracy was assessed with the daily X-ray orthogonal verification of the isocenter on the basis of the bony anatomy. CBCT was not used (Table 1). Nevertheless, comparative 2D and 3D data have shown that sensitivity to setup errors could be more performant for detecting and measuring translational errors with 3D IGRT. This method would be useful for HNSCC [51,52]. Another concern with HSNCC is patient and tumor anatomy changes. Because 3D imaging is relevant to most tumors but not available in all centers, 2D IGRT with weekly rescanning to address anatomical changes during irradiation is an alternative. Replanning may be even more critical during IMPT than IMRT for the reasons mentioned above [53]. In a Gunn et al. study, because of weight loss and tumor volume changes, adaptive replanning was used in 19 patients (38%), and rescanning was performed at Weeks 1 and 4 or on a case-by-case basis [23]. The replanning–decision trigger could be similar to that for IMRT, with replanning performed if the target coverage is below a given threshold (e.g., D95 < 95% of the prescribed dose) or the OAR constraints are perturbed. Finally, 2D IGRT appears reasonable as long as weekly rescanning is available. Other investigations have focused on CT-to-CBCT deformable image registration. In a preliminary study of six patients, the dose distributions calculated on the deformed CBCT images were comparable to those calculated on corresponding replanned CT [54]. A similar approach in three HNSCC patients demonstrated that proton dose calculations were sensitive to registration errors, particularly in the high-dose gradient regions [55]. In a study of 10 HNSCC patients, the results for deformable image registration and a histogram-matching algorithm demonstrated that HU modifications of CBCT images could reduce the proton dose calculation error [56]. The limitations were the significant artifacts in the CBCT images and the morphologic deformation in the CT and CBCT. Thus, the use of CBCT for adaptive PT does not appear to be mature.

Discussion and conclusion

Prescribing, recording and reporting proton-beam therapy according to ICRU report 78

In 2007, the International Commission on Radiation Units and Measurements (ICRU) published a report on proton therapy [57]. Many aspects including proton radiobiology, dose prescription and reporting, volume definition and dosimetry were reviewed. This report is interesting because it is the first of its kind that has attempted to standardize practices. In view of what we have presented in the previous paragraphs, two points are nonetheless highly questionable. First, the report recommended the use of a constant RBE value of 1.1 in all tissues and over the entire irradiated volume, independent of dose and LET. As explained above, a number of studies have shown varying RBE values in different test systems. This must call into question the use of a single approximate RBE value for protons in clinical practice. Second, the report recommended that the PTV be defined in the traditional sense, including only organ motion and setup errors. However, we believe, as explained above, that the definition of target volumes should also take into account range uncertainties and optimization could directly be done on CTV. The democratization of protons will surely lead to the drafting of new ICRU reports taking into account these observations in particular.

Dosimetric and clinical studies comparing IMRT and proton therapy in HNSCC

A substantial body of evidence indicates that for head and neck malignancies, proton-based plans can produce similar or better target coverage and conformity than IMRT [7,58–60]. Early dosimetric studies of PBS for oropharyngeal and oral-cavity HNSCC exhibited better OAR sparing with PT [61,62]. Indeed, both IMRT and PT achieved 100% of the dose to the CTV and 95% to the PTV in all of the cases, and the mean PTV conformity indexes were comparable. However, the mean doses to the contralateral submandibular and contralateral parotid glands, oral cavity, spinal cord, and brainstem were significantly lower in the proton plans. In the subgroup with unilateral treatment, IMPT exhibited dramatically better sparing of the contralateral salivary glands. Interestingly, recent comparisons of IMRT and IMPT plans that use posterior proton beams for oropharyngeal HNSCC have indicated that with IMPT, only the contralateral salivary glands and oral cavity were spared. The brainstem and spinal cord were not spared, thus demonstrating the importance of including technical details to facilitate the understanding of outcomes [24]. The results of the three studies are summarized in Table 2 [24,61,63]. A major criticism on all these dosimetric studies is that they compare planned dose and not delivered dose. The observed differences between IMRT and IMPT could become smaller if all the setup errors, movements and anatomical changes at each fraction were taken into account. Clinical studies are therefore needed to affirm that the differences observed in the dosimetric studies are real. However, no valid data are yet available to compare clinical outcomes after IMRT and IMPT in HNSCC. Indeed, only a small number of teams have studied PT prospectively or retrospectively in cohorts of a small number of patients with classic HNSCC. Table 3 summarizes the main results of four studies on this topic, although comparison is difficult because the dose, technique, and eligibility criteria are different [22,23,64,65]. In the majority of these studies, no unexpected toxicities have been observed with IMPT for HNSCC.

Impact of uncertainties in clinical trial (model based and randomized trial) comparing IMRT and IMPT for the treatment of HNSCC

The dosimetric and clinical results should be confirmed through clinical trial comparisons of IMRT and IMPT. Currently, two types of clinical studies exist: the model-based approach and the classical randomized clinical trial. As was previously described, the RT-QA is essential for limiting the risk of the misinterpretation of the results of these trials [4]. As was demonstrated by Peters et al. in 2010, the quality of radiation therapy is a major prognosticator. Radiation therapy has been shown to influence the outcomes of patients in trials of new drugs (such as tirapazamin). Deviations in protocol compliance can lead to negative trials [5]. Thus, quality assessment is critical in the evaluation of new forms of radiation. The quality of radiation therapy is important for

Table 2
Treatment planning comparing IMRT and IMPT for the treatment of classical HHSCC.

	Kandula et al. (2013)	Stromberger et al. (2016)	Apinorasethkul et al. (2017)
Technique			
Photon	IMRT	IMRT (HT or RA)	IMRT (RA)
Proton	IMPT	IMPT	SFO
Beams (Number and angles)	2 or 3 beams, angles NA	2 to 4 beams, angles NA	2, left and right posterior oblique beams
Prescribed Dose (Gy RBE)	70	70.4	60
Location			
Oral cavity	1/5	13/20	
Oropharynx	3/5	2/20	7/7
Dose in OAR (Gy RBE): **proton** vs. photon			
Spinal Cord (Dmax)	**20 Gy** *vs.* 37 Gy	**37 Gy** *vs.* 38 Gy (HT) / 42 Gy (RA)	**44 Gy** *vs.* 40 Gy
Brainstem (Dmax)	**14 Gy** *vs.* 34 Gy	NA	**41 Gy** *vs.* 37 Gy
CL Submandibular gland (Dmean)	**0.04 Gy** *vs.* 6 Gy	**1 Gy** *vs.* 15 Gy (HT) / 20 Gy (RA)	**33 Gy** *vs.* 36 Gy
CL Parotid gland (Dmean)	**0.5 Gy** *vs.* 5 Gy	**< 0.01 Gy** *vs.* 6 Gy (HT) / 10 Gy (RA)	**14 Gy** *vs.*18 Gy
Oral Cavity (Dmean)	**5 Gy** *vs.*18 Gy	NA	**2 Gy** *vs.*18 Gy
Larynx (Dmean)	**16 Gy** *vs.* 26 Gy	**18 Gy** *vs.* 19 Gy (HT) / 27 Gy (RA), *NS or p < 0.05*	**26 Gy** *vs.* 24 Gy

Abbreviations: IMRT: intensity-modulated photon therapy, IMPT: Intensity-modulated proton therapy, HT: helical tomotherapy, RA: RapidArc therapy, SFO: single field optimization, NA: Not available, RBE: relative biological effectiveness, CL: Contralateral.

Table 3
Characteristics, outcomes and toxicities of the four reported cohorts of classical HNSCC patients treated with proton therapy.

	Slater et al. (2005)	Frank et al. (2014)	Takayama et al. (2015)	Gunn et al. (2016)
Characteristics				
Type	Prospective	Prospective	Prospective	Prospective
Period	1991–2002	NA	2009–2012	2011–2014
Patients (number)	29	15	33	50
TNM	II-IV	NA	III-IVb	III-IV
Location	OP (100%)	OP (53%), NP (27%), NC (13%)	OC (100%)	OP (100%)
SCC	100%	66%	100%	100%
Treatment				
Surgery (%)	0	0	0	3
NAC (%, type)	NA	33 (Taxane and Platinum)	100 (5FU)	40 (Taxane and Platinum)
AC	NA	0	0	0
CCT (%, type)	NA	80 (cisplatin, carboplatin or cetuximab)	100 (intra-arterial cisplatin)	64 (cisplatin, carboplatin or cetuximab)
Follow-up				
Months	28	28	43	29
LRC (2-year, 5-year)	93%, 84%	93%, NA	90%, NA	NA
OS (2-year, 5-year)	NA	NA	NA	94.5%, NA
PFS (2-year, 5-year)	81%, 65%	NA	NA	88.6%, NA
Grade $\geq$ 3 Toxicities (%)				
Acute				
Mucositis	NA	40	79	58
Dermatitis	NA	NA	33	46
Dysphagia	NA	38	NA	24
Weight Loss	NA	13	6	2
GTP	NA	14	27	22
Late				
Dysphagia	NA	NA	NA	12
Trismus	3	NA	NA	NA
Osteoradionecrosis	0	NA	0	NA
Xerostomia	0	6	0	2

MDA: MD Anderson Cancer Center, MGH: Massachusetts General Hospital, OP: Oropharynx, NP: Nasopharynx, NC: Nasal Cavity/paranasal sinus, SB: Skull base, OC: Oral cavity, HP: Hypopharynx/larynx, SCC: squamous cell carcinoma NAC: Neoadjuvant chemotherapy, AC: adjuvant chemotherapy, CCT: Concurrent chemoradiation, LRC: Locoregional Control Rate, OS: Overall Survival, PFS: Progression free survival GTP: Gastrostomy tube placement.

achieving optimal treatment outcomes in the combined modality treatment of advanced HNSCC. The previous section described many of the uncertainties surrounding IMPT, particularly in HNSCC treatment. These uncertainties can result in poor quality radiation therapy, thereby leading to the risk of the misinterpretation of the results of clinical trial comparisons of IMPT and IMRT in model-based approaches and randomized clinical trials [66]. It must be noted that in Frank's study, patient-specific quality assurance measurements facilitated the determination that the range uncertainty resulting from the stopping power conversion error, CT artifacts, and patient anatomy changes was 3.5% of the nominal beam ranges [22].

The NTCP is a statistical model that estimates the probability of a given side-effect, i.e., the NTCP value, on the basis of the dose–volume relationships within a specific OAR with the assumption of an equivalent uniform dose. On the assumption that randomized clinical trials are not always ethical or applicable for evaluating the benefit of a new treatment technology [67], proton centers in the Netherlands have proposed an approach that uses the data from both the planning and the NTCP studies to predict the probability of a predetermined toxicity in a given patient [68]. This has been adopted by the Health Council of the Netherlands for selecting patients for PT. This approach is very attractive, particularly in HNSCC, because it could facilitate the identification of the patients

for whom IMPT would be more beneficial than IMRT [69–71]. Nevertheless, this first phase of this model-based approach, i.e., selecting patients who may benefit from IMPT, has some limitations.

In the first step, an NTCP-model is chosen. Usually, the most reliable dose–volume parameters are obtained from prospective cohort studies and should preferably be validated in independent cohorts. However, the relationship between the dose distribution parameters and the side effects may vary across different patient populations, and individual patient information may be integrated into the model [72]. The uncertainties of NTCP models may have consequences for the accuracy of patient selection [73]. In addition, changes in the distributions because of the differences in radiation delivery techniques may affect the predictive power of NTCP models. Thus, it is not evident that the results obtained from photon studies could be directly reliable to IMPT [74]. Blanchard et al. recently validated photon-derived NTCP models for patients treated with IMPT [75]. The evaluated models remained valid, thus suggesting that this source of uncertainty, unlike those in model coefficients, can be ignored. Nevertheless, treatment-related toxicities should be captured prospectively to validate the NTCP models for IMPT.

In the second step, in silico planning comparative studies facilitate the assessment of the possible differences in the relevant dose distribution parameters to the target volumes and OARs in radiation delivery techniques: at either the population or individual patient level. Using this type of study, Vergeer et al. demonstrated that in patients with HNSCC, the reduction of the mean dose to the salivary glands obtained by IMRT resulted in lower estimates of patient- and physician-rated xerostomia than those obtained by 3D radiation therapy [76]. This result was later confirmed by Nutting et al. in a prospective randomized comparative trial [77]. To be applicable to IMPT, the uncertainties exposed in the second chapter and their solutions (e.g., robust optimization and LET dependent on RBE) must be considered. Currently, dose uncertainty is likely not given sufficient attention [73]. In addition, the uncertainties resulting from interfraction and intrafraction variations in anatomy (including organ motion and tissue changes) and the means for their control (IGRT and adaptive radiation therapy) may not be integrated into the model-based approach.

Finally, in the third step, the estimation of the clinical benefit of a dose reduction is possible only if the threshold that must not be exceeded is known. For IMPT, this is not always evident. Because of the sensitivity or proton to uncertainties, not only the technical and physical details of PT planning but also the patient preparation requirements should be specified in clinical studies. As was previously mentioned, metallic implants may result in a significantly greater deterioration of the plan quality with IMPT than with IMRT. It is therefore recommended that comprehensive dental preparation and extractions be performed before IMPT.

Strategy was not included in any of the reports of the clinical studies of PT. Conversely, a reduction in the weight loss rate could necessitate the updating of the indications for feeding tube placement before IMPT. In 2016, an MDA case-matched comparative analysis of IMRT and IMPT exhibited equivalent survival rates and reduced rates of tube feeding or severe weight loss [78]. The MDA Phase II or III trial was initiated with a physician-reported toxicity endpoint [79]. The authors reduced the symptom burden with chemo-IMPT ($N = 35$) or chemo-IMRT ($N = 46$) during the subacute recovery phase following treatment. Caution should be exercised in the preliminary interpretation of the effects of symptoms on quality of life [80]. A prospective randomized clinical trial (*NCT01893307*) is underway to determine the value of IMPT in HNSCC. IMPT likely reduces acute toxicities, such as mucositis, dysgeusia, dysphagia, and fatigue. It should also reduce the late xerostomia and dysphagia rates.

IMPT is a promising addition to our current technical treatment options for HNSCC patients because it can substantially reduce side effects compared to IMRT thanks to the physical characteristics of protons that allow more effective sparing of OAR. This should be carefully considered during treatment planning, and comprehensively recorded during and after treatment for reporting of outcomes to allow for inter-comparisons of clinical practice in real life and in clinical studies. We support the conduct of ongoing and new well-designed randomized and model-based clinical trials that are expected to provide a strong level of evidence in the coming years.

Conflict of interest

None declared.

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CYCLHAD.

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