Potential benefits of intensity-modulated proton therapy in head and neck cancer

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Chapter 3

The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature

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Abstract

Purpose: Clinical studies, concerning head and neck cancer patients treated with protons, reporting on radiation-induced side effects are scarce. Therefore, we reviewed the literature regarding the potential benefits of protons compared with the currently used photons in terms of dose reduction to normal tissue and the potential to reduce subsequent radiation-induced side effects with the main focus on *in silico* planning comparative (ISPC) studies.

Materials and Methods: A literature search was performed by two independent researchers on ISPC studies that included proton-based and photon-based irradiation techniques.

Result: Initially, 877 papers were retrieved and 14 relevant and eligible ISPC studies were identified and included for this review. Four studies included paranasal sinus cancer cases, three included nasopharyngeal cancer cases, and seven included oropharyngeal, hypopharyngeal and/or laryngeal cancer cases. Seven studies compared the most sophisticated photon and proton techniques: intensity-modulated photon therapy (IMRT) versus intensity-modulated proton therapy (IMPT). Four studies compared different proton techniques. All studies showed that protons reduced the normal tissue dose, while keeping similar or improved target coverage. Two studies displayed that these dose reductions theoretically translated into a significant reduction of salivary dysfunction.

Conclusion: The results of ISPC studies indicate that protons have the potential to significantly reduce the normal tissue dose, while keeping similar or better target coverage. Scanned IMPT probably offers the most advantage and will allow for a substantial reduction of the probability of radiation-induced side effects. The results of these ISPC studies should be confirmed in properly designed clinical trials.

Introduction

The main objective of modern radiotherapy is to optimize radiation dose delivery in such a way that the tumour will be sterilized while sparing the non-target normal tissues as much as possible. In particular in head and neck cancer, this general objective cannot be easily achieved in the majority of patients, as target volumes are generally large and complex and surrounded by many organs at risk (OARs). Hence, the incidences of severe acute and late radiation-induced side effects are relatively high, in particular when radiation is combined with systemic treatment, such as concomitant chemoradiation [118].

The introduction of advanced photon radiation techniques, such as 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) has already led to a significant progress in dose conformity to the tumour and sparing of normal tissues [186]. However, the physical properties of photon beams do not leave much room for further improvement.

From a physical point of view, charged particles such as protons have an evident advantage over photons. Where photons have a maximum dose near the surface followed by a continuous reduction of dose with depth, protons deposit almost all of their radiation energy in the so-called Bragg peak. By varying the individual proton beam energies, one can produce a spread-out Bragg Peak (SOBP) that covers the tumour accurately and substantially reduces the dose to the normal tissues beyond the tumour. These characteristics allow for an improved target dose conformity than with the currently used photon techniques.

The superior beam properties of protons over photons can be translated into clinical benefits using two different strategies:

First, protons can be used to escalate the tumour dose providing possibilities to improve local tumour control without increasing the healthy surrounding tissue doses and subsequently increasing the risks on radiation-induced side effects. This strategy may be particularly useful when tumour dose escalation is expected to improve local tumour control such as in lung and prostate cancer. It should be noted, that there is virtually no difference in tumour response per unit dose

between protons and photons, which means that the potential benefit of protons in terms of local tumour control can only be the result of physical dose escalation. Moreover, clinically the relative biological effectiveness for protons ($RBE_{protons}$), i.e., the ratio of photon dose required to cause an equivalent biological level of effect as a given proton dose, of 1.1 is generally accepted. Therefore, prescribed proton dose values are expressed in Gy(RBE), i.e., the physical proton dose in Gy multiplied by the $RBE_{protons}$.

Second, protons can be used to reduce the normal tissue dose while keeping the target dose similar. In this case, tumour control is expected to be similar to the results obtained with photons, while radiation-induced side effects will most likely be reduced as the probability and severity of radiation-induced side effects strongly depend on dose and volume irradiated.

At present, all published reviews on the added value of protons over photons [20,30,106,162] mainly focussed on the role of protons in terms of treatment efficacy (i.e., local tumour control and overall survival) rather than on the potential benefits of protons in terms of reduction of radiation-induced side effects. The first step in analyzing if a new radiation technique will have the potential to reduce radiation-induced side effects is by comparing dose distributions that can be obtained with a new technique referenced to the current standard technique, also referred to as *in silico* planning comparative (ISPC) studies. Therefore, the purpose of this study was to review the literature regarding the potential benefits of protons over photons in terms of dose reductions to normal tissues and the potential to subsequently reduce radiation-induced side effects with the main focus on ISPC studies.

Materials and Methods

Selection of studies

A literature search was performed for studies that reported on the potential benefit from proton radiotherapy by comparing dose distributions between protons and photons in the same patient cohort (ISPC studies).

The following keywords were used: synonyms for head and neck neoplasm or synonyms for head and neck cancer and synonyms for proton radiotherapy. These keywords were combined using 'AND'. The literature search was carried out in MEDLINE, Embase and the Cochrane Library databases, in November 2009 and was updated through March 2010. In addition, reference lists of papers were screened in order to retrieve additional relevant papers.

To be selected for this review, studies had to fulfil the following eligibility criteria: 1. cancer of the head and neck area; 2. tumour sites: paranasal sinuses, nasal cavity, oral cavity, oropharynx, hypopharynx, nasopharynx or larynx, and; 3. adult patient population eligible for (chemo) radiotherapy, either primary, adjuvant or in the re-irradiation setting. Review studies or studies published before 1985, only available in abstract form or written in languages other than English were excluded from this review.

Two independent observers assessed the relevant studies from the identified papers. Uncertainties with regard to inclusion of a specific paper or its contents were resolved by consensus between the two other reviewers.

In silico planning comparative (ISPC) studies

In the last decades, radiation techniques in head and neck cancer have evolved dramatically from rather simple 2-dimensional techniques based on direct simulation to more advanced techniques such as 3D-CRT, intensity-modulated radiotherapy (IMRT) and/or helical tomotherapy (HT) enabling improved conformity of the high dose area to the target volume. In addition, protons can also be delivered using different techniques, from 3D conformal proton therapy (3D-CPT) to the more sophisticated intensity-modulated proton therapy (IMPT). In general, protons can be delivered by two main different techniques, including passive scattering and the more sophisticated active scanning technique [67]. With scattered protons each single beam delivers a uniform dose to the target. As for each field the length of the SOBP is fixed and conformed to the distal edge of the target, this technique does not provide good conformity to the proximal target side. However, with scanned protons, a single beam can deliver any desired non-uniform

dose distribution to the target and multiple non-uniform scanned proton beams can be combined to deliver a more uniform dose to the target (referred to as IMPT). Moreover, the length of the SOBP is not fixed providing more degrees of freedom with regard to OAR-sparing and target dose coverage. As a consequence, interpretation of ISPC studies may be influenced because different kinds of photon techniques and proton techniques have been compared. Therefore, for each ISPC study, the different radiation techniques were specified as well.

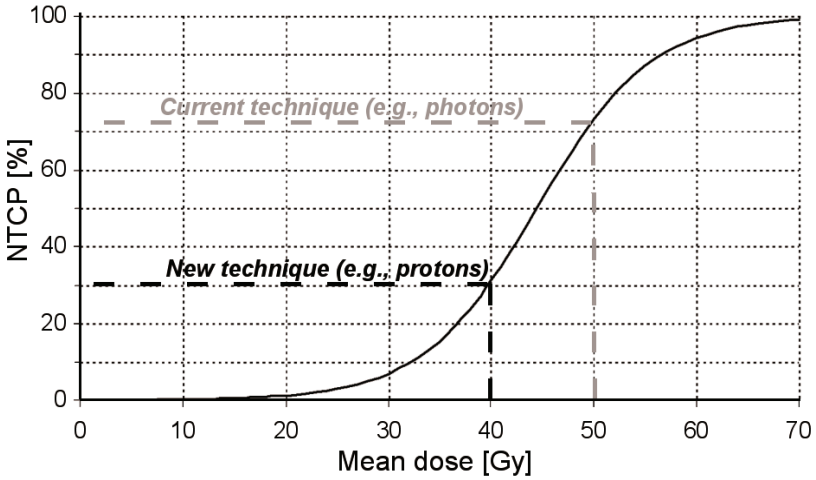

Figure 1. Example of a possible NTCP model with the risk on a given complication (NTCP in %) as a function of radiation dose (in this case the mean dose). NTCP models can be used to estimate the risk on a certain complication as a function of dose and thus also to translate differences in dose into differences in risk on side effects. In this example, the reduction of dose that can be obtained with the new technique (-10 Gy) translates into a risk reduction of -42%. Note that in case of a dose reduction from 30 to 20 Gy, the benefit in terms of risk reduction will be much less.

Normal tissue complication probability (NTCP) models

Lower delivered doses to normal tissues do not always translate into clinical benefits, that is, a lower incidence of radiation-induced side effects. The ultimate estimate of a lower incidence of side effects depends on the shape of the normal tissue complication probability (NTCP) curve (Figure 1). NTCP models describe the relationship between radiation dose distribution parameters and the risk of a given

side effect and may vary between different kinds of side effects. The final step to determine to what extent an optimized physical dose distribution will translate into an expected beneficial effect, in terms of a lower probability of radiation-induced side effects, data from ISPC studies should be combined with NTCP models (Figure 1). When reported, these results were also included in this review.

Results

Literature search

The initial literature search identified 877 papers that included 17 ISPC studies. After screening these papers, 14 ISPC studies that fulfilled the eligibility criteria were ultimately included in this review (Figure 2). The 3 excluded studies concerned 2 ISPC studies only reporting on proton therapy and 1 ISPC study that was not completed.

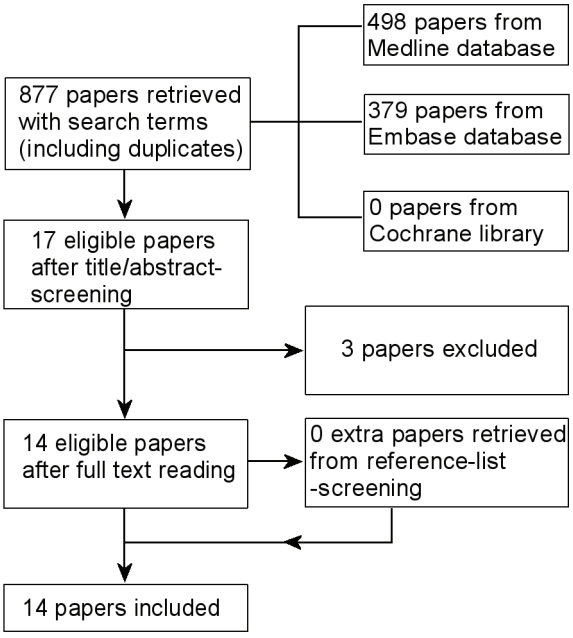

Figure 2. Papers retrieved from the literature search.

Because radiotherapy treatment of different tumour locations involves irradiation of different relevant OARs, we stratified the ISPC studies in three groups: 1. nasopharyngeal cancer, closely surrounded by critical neural tissues like the visual structures, the brain and brainstem, the pituitary gland, the auditory apparatus, the parotid glands, the larynx and the oral cavity; 2. paranasal sinuses cancer, closely surrounded by similar OARs as mentioned in group 1 except for the more caudal structures like the larynx; and 3. a rest group with oropharyngeal, hypopharyngeal and/or laryngeal cancer, particularly surrounded by all major salivary glands, structures in the oral cavity, the spinal cord, the larynx and thyroid gland.

Paranasal sinus cancer

Four studies were identified reporting on ISPC studies among patients with paranasal sinus cancer (Table 1a), including a total number of 8 patients. In most studies, 3D-CRT photons [122,126] and/or IMRT [31,126] were compared with scattered protons [31,122,126]. In one study, only mixed photon/scattered proton plans were compared with 3D-CRT [122]. There was only one study that compared IMRT with spot-scanning protons (IMPT) [117].

In three out of four studies, the dose coverage to the planning target volume (PTV) obtained with protons was similar to that with photons [31,122,126] (Table 2a). Lomax et al. [117] carried out different comparisons between IMRT and spot-scanning IMPT, showing that increasing dose constraints to the OARs resulted in highly inferior dose coverage of the PTV with IMRT, while PTV dose coverage remained within acceptable limits when IMPT was used. Thus, in contrast to IMRT, IMPT enabled radiation dose escalation to the target without exceeding the tolerance dose of critical structures such as the optic chiasm and optic nerves. The dose to most OARs could be markedly reduced with protons compared with photons, even for the OARs for which no dose constraints were defined (Table 2a). Miralbell et al. showed that by increasing the weight for protons in the mixed photon/proton plans, a further reduction of the dose to OARs could be achieved [122].

Table 1 (a). Description of *in silico* planning comparative studies on paranasal sinus cancer patients.

Study	*n* of patients	Radiotherapy techniques				Target dose prescription	OAR constraints
		Photons		Protons			
		3D-CRT	IMRT	3D-CPT	IMPT		
Paranasal sinus cancer							
Miralbell et al. [122]	1	6 fields		Mixed photons/scattered protons		PTV boost, 64 Gy(RBE); PTV elective, 45 Gy	Lacrimal glands, ≤ 45 Gy(RBE); retina, ≤55 Gy(RBE); optic chiasm and nerves, ≤ 60 Gy(RBE); brainstem center, ≤53 Gy(RBE); brainstem surface, ≤64 Gy(RBE).
Lomax et al. [117]	1		9 fields		9-fields spot scanning	PTV1, 76 Gy(RBE); PTV2, 66 Gy(RBE); PTV3, 54 Gy(RBE) (CTVs not specified)	IMPT plan and IMRT plan I: eyeballs, ≤50 Gy(RBE); brainstem, ≤53 Gy(RBE); optic nerves, ≤56 Gy(RBE). IMRT plan II: same as IMRT plan I, but tighter dose constraints to the eyeballs. IMRT plan III: more tight constraints to all five OARs.
Mock et al. [126]	5	Plan I, 3 fields; plan II, 7 fields	6 or 7 fields	2- or 3-field scattered protons		PTV boost, 60 Gy(RBE) or 70 Gy(RBE)	IMRT plan dose constraints: optic nerves and chiasm, < 55 Gy. Exact dose constraints for other OARs not specified. Reported tolerance doses for several OARs: optic nerves and chiasm, 50 Gy; brain, 55 Gy; pituitary glands, 20Gy; lacrimal glands, 30 Gy; lenses, 10 Gy; retinae, 45 Gy.
Chera et al. [31]	1		5 fields	5-field scattered protons		PTV boost, 74.4 Gy(RBE)	Exact dose constraints not specified. Used OARs in plan optimization: lens, retina, optic nerves, optic chiasm, brainstem, brain, temporal lobes, pituitary gland, spinal cord, lacrimal glands, parotid glands.

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; CTV, clinical target volume; Dmax, maximum dose; Gy(RBE), physical proton dose in Gy multiplied by the RBE of protons; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; OAR, organ at risk; PTV, planning target volume; PTV boost, PTV enclosing GTV and involved lymph nodes; SIB, Simultaneous integrated boost.

Table 1 (b). Description of *in silico* planning comparative studies on nasopharyngeal cancer patients.

Study	*n* of patients	Radiotherapy techniques				Target dose prescription	OAR constraints
		Photons		Protons			
		3D-CRT	IMRT	3D-CPT	IMPT		
Nasopharyngeal cancer							
Brown et al. [22]	2	5 fields		Mixed photons/ scattered protons		3D-CRT: PTV boost, 65-70 Gy(RBE); PTV, elective 48-57 Gy	Exact dose constraints not specified.
						Combined techniques: PTV boost, 70 Gy(RBE) (case I) or 75 Gy(RBE) (case II); PTV elective, 48-57 Gy(RBE)	Spinal Cord, shielded. Reported two tolerance doses for two OARs: optic chiasm ≤ 50 Gy; brainstem ≤ 60 Gy.
Taheri-Kadkhoda et al. [172]	8		9-field SIB		3-field SIB	GTV, 72.6 Gy(RBE); PTV boost, 66 Gy(RBE); PTV elective, 52.8 Gy(RBE)	Spinal cord, ≤ 50 Gy(RBE); optic chiasm and nerves, ≤ 45 Gy(RBE); brainstem, ≤ 60 Gy(RBE); temporal lobes, ≤ 65 Gy(RBE); oral cavity and pituitary gland, as low as possible; parotid glands (single gland), D_{mean} ≤ 26 Gy(RBE).
Widesott et al. [192]	6		HT SIB		3-field SIB	PTV boost, 66 Gy(RBE); PTV elective, 54 Gy(RBE)	Several, including: spinal cord, ≤ 40 Gy(RBE); optic chiasm and nerves, ≤ 45 Gy(RBE); brainstem, ≤ 50 Gy(RBE); parotid glands, D_{mean} < 30 Gy(RBE) (as low as possible); mucosa outside target, dose as low as possible.

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; CTV, clinical target volume; Dmax, maximum dose; D_{mean}, mean dose; GTV, gross tumour volume; Gy(RBE), physical proton dose in Gy multiplied by the RBE of protons; HT, helical tomotherapy; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; OAR, organ at risk; PTV, planning target volume; PTV boost, PTV enclosing GTV and involved lymph nodes; SIB, Simultaneous integrated boost.

Nasopharyngeal cancer

Three studies were identified reporting on ISPC studies among patients with nasopharyngeal carcinoma (Table 1b), including a total number of 16 patients [22,172,192]. In one study, 3D-CRT was compared with mixed photon/scattered proton plans, while in the other two studies, 3-field IMPT was compared with IMRT and HT, respectively. In one study [22], dose constraints were only defined for the critical neural structures, while in the other two studies dose constraints for several other OARs, including the parotid glands, were taken into account. In two studies [22,172], target dose coverage and dose conformity significantly improved by using protons, while target dose could be escalated without exceeding the tolerance dose of critical structures [22]. In all studies, the dose to all OARs could be markedly reduced (Table 2b). Of note is that the medium-to-low dose volume or the mean dose to the total body could be reduced with IMPT than with IMRT [172,192], although the exact definition of this endpoint remained unclear.

Oropharyngeal, hypopharyngeal and laryngeal cancer

We identified seven studies reporting on ISPC studies among patients with oropharyngeal, hypopharyngeal and laryngeal carcinoma, including a total number of 22 patients [40,61,92,129,168,170,174] (Table 3a and b). In one study, only 3D-CRT using parallel-opposed fields was compared with 3D-CPT [168]. However, in the majority of studies, IMRT or HT was compared with scanned and/or scattered 3D-CPT [40,92] or to IMPT [61,129,170,174]. In general, dose conformity and/or dose coverage to the PTV improved when protons were used (Table 4a and b). In one study [168] the use of scattered protons allowed dose escalation with approximately 10 Gy, without exceeding tolerance dose to the critical structures, which could not be achieved with the photon techniques.

Table 2 (a). Results of the *in silico* planning comparisons in paranasal sinus cancer.

Study	Target coverage	Dose to OARs					Remarks
		OAR parameter	Photons		Protons		
			3D-CRT	IMRT	3D-CPT	IMPT	
Paranasal sinus cancer							
Miralbell et al. [122]	Similar PTV dose coverage	Dmax retina left/right	54 Gy/50 Gy		54 Gy(RBE)/50 Gy(RBE)		All OAR dose constraints were satisfied with both techniques.
		Dmax optic nerve left/right	59 Gy/55 Gy		57 Gy(RBE)/52 Gy(RBE)		
		Dmax brainstem service	< 55 Gy		< 55 Gy(RBE)		
Lomax et al. [117]	Similar PTV dose coverage between IMRT and IMPT plan I.	Right eyeball volume ≥ 20 Gy		plan I, ~88%; plan II, ~42%; plan III, ~12%		~20%	Tightening of the IMRT dose constraints resulted in highly inferior target coverage and increased dose outside the PTV.
	With increasing dose constraints to OARs, PTV coverage with IMRT (plan II-III) compromised.	Brainstem volume ≥ 20 Gy(RBE)		Plan I & II, ~85%; plan III, ~13%		~15%	
		Non-critical normal tissues ≥ 20 Gy(RBE)		~27% all IMRT plans		~12%	
Mock et al. [126]	Similar PTV dose coverage for all 4 plans.	Dmean brain	14% plan I; 17% plan II	15%	5%		None of the treatment planning techniques allowed dose reductions for OARs closely surrounding the PTV below the reported tolerance doses.
		Dmean cntr. optic nerve	77% plan I; 66% plan II	62%	51%		
		Dmean ipsi. optic nerve	96% plan I; 95% plan II	91%	90%		
		Dmean Optic chiasm	77% plan I; 71% plan II	66%	64%		
		Non-target tissues	15% plan I; 17% plan II	15%	9%		
Chera et al. [31]	Similar PTV dose coverage	Dmax cntr. optic nerve		33.3 Gy	15.4 Gy(RBE)		
		Dmax ipsi. optic nerve		61.6 Gy	62.1 Gy(RBE)		
		Dmax optic chiasm		32.2 Gy	12.0 Gy(RBE)		
		Dmax brainstem		45.6 Gy	23.0 Gy(RBE)		
		Dmean cntr. parotid gland		8.4 Gy	0.0 Gy(RBE)		
		Dmean ipsi. parotid gland		20.7 Gy	12.7 Gy(RBE)		

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; D50%, 50% of the volume receives at least this dose level, Dmax, maximum dose; Dmean, mean dose; Gy(RBE), physical proton dose in Gy multiplied by the RBE of protons; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; OAR, organ at risk; PTV, planning target volume; PTV boost, PTV enclosing GTV and involved lymph nodes; SIB, Simultaneous integrated boost; cntr., contralateral; ipsi., ipsilateral.

Table 2 (b). Results of the *in silico* planning comparisons in nasopharyngeal cancer.

Study	Target coverage	Dose to OARs					Remarks
		OAR parameter	Photons		Protons		
			3D-CRT	IMRT	3D-CPT	IMPT	
Nasopharyngeal cancer							
Brown et al. [22]	Protons provided superior primary target coverage and an increased target dose and improved target dose confromity.	D50% of parotid glands	~60 Gy		plan I & plan II, ~ 50 Gy(RBE)		Better sparing of the spinal cord, brainstem and parotid glands with protons.
		D50% of both parotid glands (case II)	65 Gy		Plan I, 42 Gy(RBE); plan II, 35 Gy(RBE)		
Taheri-Kadkhoda et al. [172]	IMPT significantly improved target coverage and conformation.	Dmax optic chiasm		23.8 Gy		16.1 Gy(RBE)	IMPT also reduced the medium-to-low dose volume (0.33-13.2 Gy(RBE)) > 50% compared with IMRT.
		Dmax brainstem		58.7 Gy		47.3 Gy(RBE)	
		Dmean inner ear		36.4 Gy		13.1 Gy(RBE)	
		Dmean larynx/oesophagus		30.6 Gy		14.3 Gy(RBE)	
		Dmean oral cavity		44.0 Gy		38.1 Gy(RBE)	
		Dmean pituitary gland		42.2 Gy		34.8 Gy(RBE)	
		Dmean parotid gland		40.0 Gy		36.3 Gy(RBE)	
Widesott et al. [192]	Similar PTV dose coverage.	Dmax optic chiasm distal part		25.2 Gy		1.7 Gy(RBE)	
		Dmax optic chiasm proximal part		48.1 Gy		50.3 Gy(RBE)	
		Dmax brainstem		50.4 Gy		35.0 Gy(RBE)	
		Dmean larynx		27.2 Gy		27.1 Gy(RBE)	
		Dmean mucosa outside target		26.2 Gy		18.0 Gy(RBE)	
		Dmean contralateral parotid gland		28.6 Gy		23.0 Gy(RBE)	
		Dmean ipsilateral parotid gland		31.1 Gy		24.7 Gy(RBE)	
		Dmean total body		21.2 Gy		12.6 Gy(RBE)	

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; D50%, 50% of the volume receives at least this dose level, Dmax, maximum dose; Dmean, mean dose; Gy(RBE), physical proton dose in Gy multiplied by the RBE of protons; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; OAR, organ at risk; PTV, planning target volume; PTV boost, PTV enclosing GTV and involved lymph nodes; SIB, Simultaneous integrated boost; cntr., contralateral; ipsi., ipsilateral.

In general, the dose to OARs could be substantially reduced, in particular to the parotid glands [40,61,92,129,168,170], the larynx [61,129] and the spinal cord [40,129,174]. In one study, no difference was noted between 3-, 5- and 9-field scanning IMPT [170]. There was only one study in which scattered protons were compared with scanned protons showing better OAR-sparing with scanning protons [40]. Flynn et al. [61] used distal gradient tracking IMPT (DGT-IMPT), a method designed to deliver non-uniform target dose prescriptions by placing proton Bragg peaks only at locations of dose gradients in the prescribed dose distribution. Dose prescriptions for a hypoxic region in a head and neck squamous cell carcinoma patient were designed to either uniformly boost the region or redistribute the dose based on positron emission tomography (PET) images with a hypoxia tracer. IMRT and IMPT delivered comparable dose distributions within the boost region for both uniform and redistributed boosts. However, dose to the larynx and parotid glands as well as the integral dose to the non-target tissue was reduced substantially when IMPT was used instead of IMRT.

Do lower doses to OARs result in lower NTCP values?

In two studies, the authors tried to translate the differences in dose distributions into clinical benefits in terms of differences in NTCP values by using existing NTCP models [92,192]. The NTCP models used were derived from other studies [1,24,55,59,150,154,160]. This model-based approach indicated that for both parotid glands, scanned protons significantly reduced NTCP values for salivary flow [92,192] and xerostomia [192] (Table 5). The NTCP model for the larynx did not result in significant differences between IMPT and HT [192].

Table 3 (a). Description of *in silico* planning comparative studies on oropharyngeal, hypopharyngeal and laryngeal carcinoma.

Study	*n* of patients	Radiotherapy techniques				Target dose prescription	OAR constraints
		Photons		Protons			
		3D-CRT	IMRT	3D-CPT	IMPT		
Slater et al. [168]	2	Parallel-opposed fields		Parallel-opposed scattered proton fields		Photons: PTV boost, 70-75 Gy; PTV elective, 50 Gy Protons: PTV boost, 70-85 Gy(RBE); PTV elective, 50 Gy(RBE)	Not specified.
Cozzi et al. [40]	5	Plan I, mixed photon/electron; Plan II, 5-field photons	Plan I, 5 fields; Plan II, 9 fields	Plan I, 3-field scattered protons; Plan II, 3-field scanned protons		PTV elective, 54 Gy(RBE)	Spinal cord, ≤ 40.5 Gy(RBE).
Johansson et al. [92]	5	Mixed photon / electron	9 field SIB	4 field SIB scanned protons		Mixed plan: PTV boost, 70 Gy; PTV elective, 50 Gy SIB plans: PTV boost, 71.7 Gy(RBE); PTV elective, 54 Gy(RBE) (30 fractions)	Spinal cord, ≤ 40.5 Gy(RBE).
Steneker et al. [170]	5		5- and 9-field		3-, 5- and 9-field scanned protons; 3-, 5- and 9-field scanned protons with reduced spot size	PTV elective, 54 Gy(RBE)	Gradual tightening of spinal cord and parotid gland constraints, but exact constraints not specified.

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; dIMRT, dynamic IMRT with SIB; Dmax, maximum dose; Dmean, mean dose; EUD, equivalent uniform dose; Gy(RBE), physical proton dose in Gy multiplied by the RBE of protons; HT, helical tomotherapy; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; OAR, organ at risk; PTV, planning target volume; SIB, Simultaneous integrated boost; sIMRT, IMRT with static fields with SIB.

Table 3 (b). Description of *in silico* planning comparative studies on oropharyngeal, hypopharyngeal and laryngeal carcinoma.

Study	*n* of patients	Radiotherapy techniques				Target dose prescription	OAR constraints
		Photons		Protons			
		3D-CRT	IMRT	3D-CPT	IMPT		
Muzik et al. [129]	1		9-field sIMRT		2-field SIB	PTV boost, 60 Gy(RBE); PTV elective, 54 Gy(RBE)	Right parotid gland, Dmean ≤ 11 Gy(RBE).
			9-field dIMRT				Serial EUD constraints: spinal cord, 33 Gy(RBE); brainstem, 33 Gy(RBE); larynx, 44 Gy(RBE).
			HT				
Thorwarth et al. [174]	3		9-field SIB; HT SIB		3-field SIB	PTV dose escalation: uniform and non-uniform dose prescriptions. PTV1, 70 Gy(RBE); PTV2, 60 Gy(RBE); PTV elective, 54 Gy(RBE)	EUD constraints defined for parotid glands, spinal cord and spinal cord extended with 3 mm.
Flynn et al. [61]	1		9-field SIB; HT SIB		3-field SIB; 7-field SIB distal gradient tracking (DGT-IMPT)	PTV dose escalation: 3 uniform/3 non-uniform dose prescriptions; PTV60, 60 Gy(RBE).	Larynx, < 20 Gy(RBE) to 30% volume; oral cavity, < 25 Gy(RBE) to 30% volume, Dmax < 50 Gy(RBE); parotid gland left, Dmean < 26 Gy(RBE); Spinal cord < 25 Gy(RBE) to 30% volume, Dmax < 45 Gy(RBE); brainstem < 25 Gy(RBE) to 20% volume, Dmax < 40 Gy(RBE).

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; dIMRT, dynamic IMRT with SIB; Dmax, maximum dose; Dmean, mean dose; EUD, equivalent uniform dose; Gy(RBE), physical proton dose in Gy multiplied by the RBE of protons; HT, helical tomotherapy; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; OAR, organ at risk; PTV, planning target volume; SIB, Simultaneous integrated boost; sIMRT, IMRT with static fields with SIB.

Table 4 (a). Results of the *in silico* planning comparisons in oropharyngeal, hypopharyngeal and laryngeal cancer.

References	Target coverage	Dose to OARs					Remarks
		OAR parameter	Photons		Protons		
			3D-CRT	IMRT	3D-CPT	IMPT	
Slater et al. [168]	Scattered protons improved target dose conformity and allowed a dose escalation of about 10 Gy.	Dmax contralateral parotid gland case I	~65 Gy		~20 Gy(RBE)		
		Dmax contralateral parotid gland case II	~70 Gy		~50 Gy(RBE)		
Cozzi et al. [40]	The mixed 3D-CRT plan showed inferior results. Target coverage was comparable for all other plans, but target homogeneity was better with protons.	D_{max} spinal cord	Plan I, 39.7 Gy; Plan II, 38.8 Gy	Plan I, 31.1 Gy Plan II, 26.2 Gy	Plan I, 20.4 Gy(RBE) Plan II, 17.6 Gy(RBE)		With regard to OAR-sparing, scanned protons displayed the best results.
		Dose to 2/3 parotid gland	Plan I, 51.5 Gy Plan II, 46.4 Gy	Plan I, 43.3 Gy Plan II, 41.1 Gy	Plan I, 28.4 Gy(RBE) Plan II, 23.2 Gy(RBE)		
Johansson et al. [92]	IMRT and protons had a 17% higher tumour control probablility than 3D-CRT.	D_{max} spinal cord	44.2 Gy	46.2 Gy	42.7 Gy(RBE)		Protons also allowed for a reduced dose to the nontarget tissue.
		D_{mean} parotid glands	48 Gy	38 Gy	33 Gy(RBE)		
Steneker et al. [170]	IMPT had a better target homogeneity preservation; significant advantage was seen for 9-field compared with 5-field IMRT, whereas for 3, 5 and 9-field IMPT similar results were obtained.	D_{mean} parotid glands in % of prescribed PTV dose at similar target homogeneity levels		~55% (9 fields)		~35% (small spots)	Planning was only caried out for the elective dose level without a boost to the high-dose area.

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; dIMRT, dynamic IMRT with SIB; Dmax, maximum dose; Dmean, mean dose; DGT-IMPT, distal gradient tracking IMPT; EUD, equivalent uniform dose; Gy(RBE), physical proton dose in Gy multiplied by the RBE of protons; HT, helical tomotherapy; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; OAR, organ at risk; PTV, planning target volume; sIMRT, IMRT with static fields with SIB.

Table 4 (b). Results of the *in silico* planning comparisons in oropharyngeal, hypopharyngeal and laryngeal cancer.

References	Target coverage	Dose to OARs					Remarks
		OAR parameter	Photons		Protons		
			3D-CRT	IMRT	3D-CPT	IMPT	
Muzik et al. [129]	Similar target coverage results were obtained for all techniques, with exception of sIMRT, which was slightly inferior.	D_{mean} spinal cord		10.1-11.4 Gy[a]		1.2 Gy(RBE)	
		D_{mean} brainstem		24.5-25.6 Gy[a]		7.7 Gy(RBE)	
		D_{mean} larynx		37.7-38.4 Gy[a]		13.6 Gy(RBE)	
		D_{mean} right parotid gland		10.3-10.9 Gy[a]		0.4 Gy(RBE)	
		D_{mean} nontarget tissue		5.3-6.0 Gy[a]		1.5 Gy(RBE)	
Thorwarth et al. [174]	HT and IMPT provided more accurate target coverage than IMRT; IMPT allowed for the highest local dose escalation.	Spinal cord volume ≥ 20 Gy(RBE)		65%		19%	
		Parotid gland volume ≥ 20 Gy(RBE)		58-65%		55%	
Flynn et al. [61]	IMRT and IMPT target coverage results for the dose-escalated PTV were similar for both uniform and nonuniform (dose-painted) prescriptions.	D_{mean} larynx		12.7-14.1 Gy[a]		6.0-6.1 Gy(RBE)	DGT-IMPT further improved results obtained with standard IMPT.
		D_{mean} left parotid gland		20.6-23.1 Gy[a]		0.1-0.1 Gy(RBE)	
		D_{mean} oral cavity		19.3-20.4 Gy[a]		21.6-21.9 Gy(RBE)	
		D_{mean} normal tissue		17.9-20.1 Gy[a]		8.2-8.5 Gy(RBE)	

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; dIMRT, dynamic IMRT with SIB; Dmax, maximum dose; Dmean, mean dose; DGT-IMPT, distal gradient tracking IMPT; EUD, equivalent uniform dose; Gy(RBE), physical proton dose in Gy multiplied by the RBE of protons; HT, helical tomotherapy; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; OAR, organ at risk; PTV, planning target volume; sIMRT, IMRT with static fields with SIB.

[a] = range of sIMRT, dIMRT and HT.

Table 5. Translation of differences in dose distributions to differences in NTCP values.

References	NTCP model endpoint	OAR	Estimated NTCP value			
			Photons		Protons	
			3D-CRT	IMRT	3D-CPT	IMPT
Johansson et al. [92]	Reduced salivary flow to <25% of the pretreatment flow at 13 weeks [160]	Left parotid gland	93.5%	65.2%	39.5%	
		Right parotid gland	92.7%	51.2%	42.6%	
	Myelitis [1]	Spinal cord	0%	0%	0%	
Widesott et al. [192]	Reduced salivary flow to <25% of the pretreatment flow at 1 year [55]	Contralateral parotid gland		20.2%		4.8%
		Ipsilateral parotid gland		25.3%		14.3%
	Reduced salivary flow to <25% of the pre-treatment flow at 1 year [154]	Contralateral parotid gland		21.7%		13.5%
		Ipsilateral parotid gland		41.5%		17.6%
	Xerostomia [59, 24]	Contralateral parotid gland		1.0%		0.4%
		Ipsilateral parotid gland		3.2%		1.5%
	Salivary excretion factor < 25% at 1 year after RT [154]	Contralateral parotid gland		10.3%		6.9%
		Ipsilateral parotid gland		13.0%		9.0%
	Larynx edema ≥grade 2 within 15 months after RT [150]	Larynx		1.4%		1.9%

Abbreviations: 3D-CPT, 3-dimensional conformal proton therapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon therapy; NTCP, normal tissue complication probability; OAR, organ at risk; RT, radiotherapy.

Discussion

The findings of this review on ISPC studies showed that irradiation with protons in head and neck cancer generally results in a reduction of the dose to the normal tissues while target dose distributions improve, offer more opportunities for dose-escalation and/or at least remain similar in terms of homogeneity and conformity. This physical advantage may theoretically allow for improving the therapeutic ratio by reducing the risk on radiation-induced side effects while keeping the target dose the same or by target dose escalation without increasing the risk of radiation-induced side effects.

An ISPC study is one of the first and necessary steps in the development of emerging radiation techniques which allow for a comparison of physical dose distributions between the current standard and new radiation techniques and thus for assessing the potential of improving the therapeutic ratio. If performed properly, the study outcome may serve as the basis for the hypothesis and design of future clinical studies that should confirm the benefit of the new technique. However, proper interpretation of the outcome of ISPC studies requires a critical view on some methodological issues.

An important prerequisite for an ISPC study is that the new technique is compared with the best currently available technique. In addition, a valuable estimation of the new technique's benefit can only be properly determined if the new technique is tested using its full potential properties. In the treatment of head and neck cancer, we consider IMRT as the current standard, while the most optimal approach using protons remains to be determined. In this respect, there were only a few studies in which different proton techniques were compared [22,40,61,170]. Brown et al. [22] compared two different mixed 3D-CRT/3D-CPT techniques and showed that OAR-sparing improved with the mixed technique that used the highest proton weight. However, this technique used protons only partly during the radiation course and therefore did not fully use their potential benefits with regard to sparing of the OARs. More recent studies did use protons for the full course. Cozzi et al. [40] showed that scanned 3D-CPT improved OAR-sparing

compared with scattered 3D-CPT. As previously discussed, IMPT (non-uniform dose fields) allows for more freedom with regard to OAR-sparing than scanned 3D-CPT (uniform dose fields). Given the relatively large and complex-shaped PTVs close to OARs in head and neck cancer, IMPT is more likely to obtain a more optimal dose distribution than scanned 3D-CPT. Steneker et al. [170] found that using IMPT, OAR-sparing was most optimal with 3-field IMPT using the smallest spot size. Increasing the number of fields neither improved target dose homogeneity nor further reduced the parotid gland dose. Flynn et al. [61] investigated further refinement of IMPT by comparing DGT-IMPT with IMPT for dose painting and showed that DGT-IMPT provided the most optimal results. Overall, these findings suggest that IMPT provides the most optimal results with regard to OAR-sparing while keeping good target coverage results.

In total, seven of the 14 ISPC studies compared the most sophisticated photon technique (IMRT), with the most sophisticated proton technique (IMPT) [61,117,129,170,172,174,192]. Therefore, these studies provide the most reliable information with regard to the potential benefit of protons versus photons to spare critical structures. The results of these studies all showed marked reduction of the dose to different OARs with similar or even improved dose distributions to the target volume. Of note is that different tumour sites had been included in the 7 studies and that a certain variety was observed in the dose distribution results. However, although all results point in the same direction, it cannot be ruled out that some bias occurred resulting from the fact that most studies were written by authors from centers with proton therapy.

There were some limitations with regard to the design and required or reported dose distribution results of some ISPC studies. For example, Steneker et al. and Cozzi et al. only used a total dose of 54 Gy(RBE) for the elective nodal areas and the primary site without a boost to the high risk areas. On the other hand, Chera et al. and Mock et al. only took into account the high risk areas. As this is not according to what is currently considered standard, translation of these results to clinical practice is severely hampered.

Second, some authors did not clearly specify their planning objectives with regard to target coverage acceptance, e.g., the recommendations of the International Commission on Radiation Units and Measurements Report 50 [84], or defined other target coverage criteria than currently considered standard [22,61,117,122,129,168,170,174].

Third, most authors only presented averaged results for all cases [40,126,170,172,192]. It should be noted that the benefit of a new technique in terms of dose distributions in targets and OARs will depend on a number of factors, such as the volume and shape of the target, the position of the target reference to OARs and/or the amount of overlap of the PTV with a given OAR. Moreover, the translation of a reduction in dose to an estimated NTCP value reduction strongly depends on the shape of the NTCP curve and the initial dose parameters as obtained by the currently available technique as illustrated in Figure 1. Therefore, ISPC studies should also report on the results of individual patients in order to get more insight in the percentage of patients that will eventually benefit from protons in terms of reducing the risk of radiation-induced side effects.

In almost all ISPC studies attempts were made to spare various OARs, including the spinal cord, brainstem, optic structures and parotid glands (Tables 1-4). More recently, it has been recognised that, in addition to xerostomia, dysphagia is also an important side effect that adversely affects quality of life after radiotherapy of the head and neck area [47,105]. Therefore, sparing of the structures related to both complications, including the salivary glands and pharyngeal constrictor muscles [47], is of importance. Of note is that most ISPC studies did report on the dose in the parotid glands, however, none of the studies reported on the dose in the pharyngeal constrictor muscles. Furthermore, OAR dose constraints used in the optimization process differed among the different studies. Moreover, the exact OAR dose constraints were not always clearly specified in all studies [31,126,170]. Of note is that the more recently published studies often included more OARs in their planning optimization.

To compare possibilities of different radiotherapy techniques with respect to target coverage and OAR-sparing different strategies can be handled depending on

the study's aim. This makes it hard to allow fair comparisons across different treatment planning studies. To compare the possibilities of different radiotherapy techniques with respect to OAR-sparing at similar target coverage in a fair manner, target dose and OAR dose prescriptions and acceptance criteria should be identical for the different techniques, otherwise the obtained dose differences could also be a consequence of different dose prescriptions. Of note is that in order to obtain the best plan with different radiation techniques, the dose-volume constraints used during plan optimization may have to be different for the different techniques. On the other hand, if the study aim is to examine whether with a less advanced technique (e.g. IMRT in [117]) similar OAR-sparing could be obtained as achieved with a more advanced technique (e.g. IMPT in [117]) dose prescriptions and acceptance criteria do not have to be the same. These latter studies also focus on the techniques' possible limitations or benefits, though, not all treatment plans obtained with this study strategy will be suitable for clinical practice. However, both discussed treatment planning comparison strategies are important to investigate differences between radiotherapy techniques.

Furthermore, in general, if no attempts are made to reduce OAR doses as much as possible, the achieved results will not necessarily be the best results that can be achieved with the specific techniques [117,192]. Consequently, the obtained differences in NTCP can not be used to adequately determine which technique is best to spare a specific OAR (e.g. the larynx structure spared by Widesott et al.).

The question arises: What would be the most optimal way to deliver protons with regard to fractionation? Cozzi et al. [41] reported on the results of an ISPC study investigating the potential benefit of a full simultaneous integrated boost technique (SIB) in proton therapy compared with conventional fractionation with sequential (SEQ) boost and a mixed SEQ/SIB technique. The final results showed a dosimetric advantage for the SEQ/SIB technique in terms of target coverage while keeping similar OAR dose results. The authors concluded that the clinical introduction of this technique appears promising given the logistic advantages (lower number of fractions) and limited availability of proton therapy facilities.

In addition to fractionation issues, the clinical introduction of proton therapy in head and neck cancer may be hampered by a number of other problems. In general, protons are more sensitive to density heterogeneities (like air gaps, air-tissue-bone transitions) than photons [115,113,114]. Hence, image-guidance and patient positioning are even more important. None of these ISPC studies reported on IMRT and IMPT plan-robustness-analysis comparisons, though such studies would be of interest with regard to clinical application of these techniques. Furthermore, as there is not much experience with advanced proton techniques and due to the fact that proton therapy-based clinical studies reporting on radiation-induced side effects are scarce, the remaining question is whether the potential clinical benefit of proton therapy is worth the additional costs? Goitein et al. and Peeters et al. estimated that the proton versus photon treatment costs were ~2.4 or ~3.2, respectively [71,142], but could be reduced to ~1.7 [71]. Note that the treatment specific costs and the costs per fraction highly depend on the specific disease site, the treatment technique's complexity, the patient throughput and clinical experience. As clinical experience with the advanced proton techniques like IMPT is poor, there is still room to further optimize the application of this technique (also with regard to the used treatment schedules [41]). Remark furthermore, that the cost analyses studies did note take into account the additional costs for treating radiation-induced side effects or for caring for not-cured patients. Additional costs for combined treatments like chemoradiotherapy were also not considered. The ISPC studies indicated that protons have the ability to reduce the probability of side effects [92,192] and may improve application of dose escalation [174], that subsequently may improve tumour control. Protons also reduced the integral dose that is of major importance for treatment of pediatric patients [107,123]. Therefore the total costs for proton treatment could be much less than the estimated values. Finally, clinical data should provide the answer to the question whether the potential clinical benefit of proton therapy is worth the additional costs.

Conclusion

ISPC studies indicate that protons have the potential to reduce the dose to several OARs significantly, while keeping similar or even better target coverage. Given the complexity of the target volume in head and neck cancer patients, scanned IMPT probably offers the most advantage and will allow for a substantial reduction of the probability of radiation-induced side effects. The results of these ISPC studies should be confirmed in properly designed clinical trials with a focus on uniform accepted toxicity endpoints.