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Anti-Tumour Treatment

Systematic review and meta-analysis of radiotherapy in various head and neck cancers: Comparing photons, carbon-ions and protons

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ABSTRACT

Purpose: To synthesize and compare available evidence considering the effectiveness of carbon-ion, proton and photon radiotherapy for head and neck cancer.

Methods: A systematic review and meta-analyses were performed to retrieve evidence on tumor control, survival and late treatment toxicity for carbon-ion, proton and the best available photon radiotherapy.

Results: In total 86 observational studies (74 photon, 5 carbon-ion and 7 proton) and eight comparative in-silico studies were included. For mucosal malignant melanomas, 5-year survival was significantly higher after carbon-ion therapy compared to conventional photon therapy (44% versus 25%; *P*-value 0.007). Also, 5-year local control after proton therapy was significantly higher for paranasal and sinonasal cancer compared to intensity modulated photon therapy (88% versus 66%; *P*-value 0.035). No other statistically significant differences were observed. Although poorly reported, toxicity tended to be less frequent in carbon-ion and proton studies compared to photons.

In-silico studies showed a lower dose to the organs at risk, independently of the tumor site.

Conclusions: For carbon-ion therapy, the increased survival in mucosal malignant melanomas might suggest an advantage in treating relatively radio-resistant tumors. Except for paranasal and sinonasal cancer, survival and tumor control for proton therapy were generally similar to the best available photon radiotherapy. In agreement with included in-silico studies, limited available clinical data indicates that toxicity tends to be lower for proton compared to photon radiotherapy.

Since the overall quantity and quality of data regarding carbon-ion and proton therapy is poor, we recommend the construction of an international particle therapy register to facilitate definitive comparisons.

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Introduction

Head and neck cancer (HNC) covers a heterogeneous group of cancers, which includes paranasal and sinonasal cancer and cancer of the salivary gland, lip, oral cavity, pharynx and larynx. When

considering cancer of the oral cavity, pharynx and larynx in Europe, the annual incidence is approximately 147,500. This represents 4.6% of all cancer cases, accounting for 63,400 deaths.¹

Treatment options for HNC consist of radiotherapy, surgery, chemotherapy or a combination of these modalities. There is a growing body of evidence suggesting that more aggressive treatment regimes, such as altered fractionation schedules for radiotherapy or (concomitant) chemoradiation improve tumor control and survival.^{2–4} Recent meta-analyses showed absolute improvements in 5-year survival of 3% for altered fractionation versus conventional fractionation and of 5% for chemotherapy versus no chemotherapy.^{3,4} However, mainly due to the close proximity of critical organs and the often large irradiation fields, the improved outcomes in these aggressive treatment regimes come at the cost of increased treatment toxicity. Late toxicities (including xerostomia and dysphagia) affect a substantial proportion of HNC patients

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and negatively affects patients' functional outcomes and quality of life.^{5–9}

Particle therapy using carbon-ions or protons is currently gaining importance worldwide.¹⁰ Compared with photons, the in-depth dose distribution of particles allows a more accurate dose administration, resulting in an increased therapeutic ratio. Based on these physical characteristics, it is supposed that less normal tissue will be irradiated compared with photon radiation, presumably resulting in less treatment related toxicity.^{11,12} On the other hand, the increased therapeutic ratio possibly permits dose escalation to the tumor, resulting in a higher tumor control probability. Next to these physical advantages, carbon-ion radiotherapy comprises an increased radiobiological efficacy, especially in the Bragg peak. Hence, to decrease treatment related toxicity and potentially further improve outcome, particle therapy could be a valuable technology in the treatment of HNC. Nevertheless, several reviews indicated that based on clinical evidence it remains unclear, mainly because of the absence of randomized trials, whether particle therapy is superior over radiotherapy with photons in HNC.^{13–20} This makes it difficult to decide whether particle therapy should be implemented as a (routine) treatment in clinical practice.²¹ However, decisions need to be made. In addition to the available clinical evidence, comparative in-silico studies, which analyze computer-predicted dose parameters in radiotherapy treatment planning for different radiation techniques, offer an alternative approach to estimate the potential gain of particle therapy.^{20,22} Our aim was therefore to synthesize all available evidence, from clinical studies as well as comparative in-silico studies. This resulted in the following objectives (1) to review and synthesize available clinical evidence considering the effectiveness (i.e. tumor control, survival and late treatment toxicity) of carbon-ion and proton radiotherapy compared with the best available photon radiation in patients receiving radiotherapy treatment for HNC and, (2) to review available comparative in-silico studies comparing carbon-ion and proton radiotherapy with photon therapy in HNC.

Methods

Search strategy and selection criteria

Systematic literature searches were conducted to identify available clinical particle and photon studies. A first search query was constructed to identify studies using carbon-ions or protons in HNC. Included photon studies were identified using a second (intensity modulated radiotherapy) and third (conventional radiotherapy) search query. The PICO (patient, intervention, comparison and outcome) framework²³ was used to structure all three search queries in Pubmed. MeSH terms as well as free text words were used. The keywords were 'head and neck cancer' AND ('proton radiotherapy' OR 'carbon-ion radiotherapy' OR 'intensity modulated radiotherapy' OR 'radiotherapy') AND ('survival' OR 'adverse effects'). The full search strategy is reported in Appendix 1.

All search queries were updated until February 2010. In addition, manual searches of reference lists were performed to complement all three search queries. For particle therapy, supplementary manual searches of conference proceedings were performed.

Clinical studies were included if they were published after 1990, written in English, examined carbon-ions, protons or photons, examined treatment of primary tumors, examined radical treatment (defined as a treatment with the intent to obtain loco-regional disease control) and had a patient sample ≥ 10 . For photon therapy, if available, only studies using intensity modulated radiotherapy (IMRT) were included. If no IMRT studies were available, studies administering conventional photon therapy were included. Further, photon studies were only included if tumor control or

survival data was reported. In order to collect all available evidence on particle therapy, particle studies were also included if they report toxicity data only. Occasionally data were reported in multiple publications. In case of overlap in data and if both studies reported the required data, only the study with the largest sample size was included.

To identify in-silico studies comparing particle therapy and photon therapy in HNC, a fourth search strategy was constructed. This search query was structured as described above for clinical studies. The search query was equal to the first search query, except for the keyword 'radiotherapy planning' instead of ('survival' OR 'adverse effects') (Appendix 1).

In-silico studies were included if they were published after 1990, written in English, performed a direct comparison of particle therapy (carbon-ions or protons) with photon therapy, examined treatment of primary tumors, reported dose to the organs at risk and had a patient sample ≥ 5 .

Data extraction

General characteristics were extracted from clinical studies: first author, year of publication, treatment type, sample size, dose per fraction, number of fractions, total treatment dose, study population (age, tumor stage, location and histology, percentage of operated patients, and percentage patients of receiving chemotherapy), late treatment toxicity, local control, disease free survival and overall survival outcomes at 2- to 5-year. Since HNC represents a heterogeneous patient group with different treatment modalities and prognosis, the comparisons of clinical studies were categorized according to location or histology. The subgroups were nasopharyngeal cancer, oropharyngeal cancer, paranasal and sinonasal cancer, mucosal malignant melanomas and adenoid cystic carcinomas. Because radiotherapy toxicity is location specific, different types of toxicities were examined for different subgroups. Xerostomia and dysphagia were considered in nasopharyngeal and oropharyngeal cancer, visual toxicity in paranasal and sinonasal cancer, visual, skin and mucosal toxicity in mucosal malignant melanomas and all reported toxicity in adenoid cystic carcinomas. Toxicity data were extracted per type and grade independently of the classification system.

The following characteristics were extracted for included in-silico studies: first author, year of publication, treatment types, sample size, tumor location and/or histology, dose parameters of target volume (coverage, conformity index²⁴ and inhomogeneity) and dose to organs at risk (dose to the optic nerves for paranasal sinus carcinomas and for all other sites dose to the parotid glands and pharyngeal constrictors). These organs at risk were selected since they are associated with visual impairment,²⁵ xerostomia²⁶ and dysphagia.^{27,28}

All data were independently extracted by two reviewers (BR and MPJ), if necessary data were extracted from figures. Discrepancies were solved in consensus meetings with all authors.

Statistical analysis

If tumor control or survival outcomes were available per subgroup for at least two comparators, data from clinical studies were pooled for the longest available follow-up period. Pooling was performed by means of a random effect meta-regression analysis. If corresponding standard errors (se) were not reported in included studies, we calculated them using the standard method for proportions.²⁹ If patients were censored, we used the Peto method.^{30,31} In case the number of censored patients was not reported, we assumed the maximum percentage of censored patients reported in the included studies in the subgroup concerned.

Through relating the outcomes (e.g. survival) to potentially confounding variables (e.g. differences between the included studies in the percentage of patients receiving chemotherapy) in the meta-regression analyses, we explored the effect of these covariates on the outcome.³² We did this by firstly calculating the overall mean for these covariates among all included studies in the subgroup concerned. Secondly, we calculated for each study separately how much the covariate deviated from the overall mean. Finally, this deviation from the overall mean was included in the meta-regression model as an independent covariate. This was done separately for each subgroup for the following covariates: the proportion of patients having T4 tumors, N3 tumors, stage IV tumors, the proportion of patients receiving chemotherapy, the proportion of operated patients and publication year. Only covariates which significantly influenced the outcomes were included in the final meta-regression models.

For comparative in-silico studies, results were reviewed only and no statistical analyses were performed.

All analyses were performed in STATA 9.1 and a P -value ≤ 0.05 was considered statistically significant. Further, this meta-analysis was performed according to proposed guidelines.³³

Results

The three search strategies considering clinical studies identified 86 eligible observational studies: five studies using carbon-ion therapy, seven studies using proton therapy and 74 studies using photon therapy. The fourth search strategy identified eight eligible comparative in-silico studies (Appendix 2). Included and excluded particle studies and in-silico studies were reported in Appendix 3. The characteristics of the clinical studies pooled in the meta-analyses were reported in Appendix 4. Further, results of the meta-analyses are presented in Fig. 1 and Table 1. The eight in-silico studies were reviewed separately from the clinical studies.

Head and neck cancer

Three studies on particle therapy (two carbon-ion and one proton)^{34–36} and eight studies on IMRT^{37–44} reported on a mixed group (multiple sub-sites) of HNC patients. Local control (LC) rates at 2- and 5 year were 80–85% and 60–70% for carbon-ion therapy, 87% and 74% for proton therapy and 2-year LC ranged between 76% and 100% for IMRT. Disease free survival (DFS) estimates at 2- and 5-year were 56% and 29% for proton therapy and 81–90% at 2-year for IMRT. Overall survival (OS) at 2- and 5-year were respectively 74% and 33–48% for carbon-ion therapy; 69% and 44% for proton therapy and 83–90% at 2-year for IMRT. Due to heterogeneity within and between these studies, these results deemed largely not comparable and outcomes were therefore not pooled in a meta-analysis.

Nasopharyngeal carcinoma

One proton study⁴⁵ and 14 IMRT studies^{46–59} reported results for nasopharyngeal carcinomas. Estimates of 3-year LC were 92% for proton therapy and 95% for IMRT. Pooled 3-year OS estimates were 74% for proton therapy and 90% for IMRT. Both LC and OS were not statistically significantly different (P -values 0.780 and 0.298).

The percentage of T4 patients in the proton study was approximately twice as high as in most IMRT studies (Appendix 4). Nevertheless, this covariate had no statistically significant influence on the outcome. The year of publication had a statistically significant (P -value 0.040) influence on the 3-year LC favoring older studies. The corrected estimates were similar to the uncorrected

estimate for 3-year LC for both IMRT (both estimates were 95%) and proton therapy (decreased from 92% to 90%). As a result, differences in 3-year LC between IMRT and protons remained not statistically significant. The remaining covariates considering disease stage, the proportion of patients receiving chemotherapy or surgery were not statistically significant.

For proton therapy no late xerostomia or dysphagia data were reported, hence it was not possible to perform comparisons considering late treatment related toxicity.

Oropharyngeal carcinoma

One proton study⁶⁰ and 10 IMRT studies^{61–70} reported results for oropharyngeal carcinomas. Estimates of 2- and 5-year LC were 96% and 88% for proton therapy and for IMRT pooled 2-year LC was 95%. For DFS, 2- and 5-year rates were 81% and 65% for proton therapy, pooled 2-year DFS for IMRT was 87%. Both 2-year LC and DFS were not statistically significantly different (P -values 0.782 and 0.570).

No statistically significant covariates were observed.

For proton therapy no late xerostomia or dysphagia data were reported, hence it was not possible to perform comparisons considering late treatment related toxicity.

Paranasal and sinonasal carcinoma

One carbon-ion study³⁵ two proton studies^{71,72} and two IMRT studies^{73,74} reported results for paranasal or sinonasal carcinoma. The pooled estimates of 5-year LC were 49% for carbon-ion therapy, 88% for proton therapy and 66% for IMRT. Differences in 5-year LC between proton therapy and IMRT were statistically significant (P -value 0.035). Five-year DFS was 61% for protons and 54% for IMRT, while 5-year OS was 71% and 52% respectively. Both DFS and OS were not statistically significantly different (P -values 0.682 and 0.323).

It was not possible to include the percentage of patient with T4, N3 or stage IV tumors as covariates in the meta-analyses since none of the included studies reported the number of stage IV tumors and the number of T4 tumors or N3 tumors were only reported in the two photon studies (Appendix 4). None of the other covariates (including the percentage of operated patients) had a statistically significant influence on the outcome.

One proton study reported that no late visual toxicity of RTOG grade 3 or higher was observed.⁷¹ However, another study considering visual outcomes after combined photon/proton therapy reported LENT/CTC v2.0 visual toxicity of grades 1, 2 and 3 of respectively 14%, 17% and 6%.⁷⁵ For IMRT, one study reported CTC v2.0 grade 3 visual toxicity in 9% of the patients, of which four patients (6%) had pre-treatment visual impairment.⁷⁴

Mucosal malignant melanoma

For the treatment of mucosal malignant melanomas, 5-year OS was reported in two carbon-ion studies^{34,76} and 18 studies administering conventional radiotherapy.^{77–94} Analyses showed a 5-year OS of 44% for carbon-ion radiotherapy, this was statistically significantly higher than the pooled estimate of 25% for conventional photon radiotherapy (P -value 0.007).

The percentage of operated patients as well as the percentage of patients with disease stage III could not be incorporated as potentially confounding variables since none of the studies on carbon-ion therapy reported these data (Appendix 4). None of the other covariates were statistically significant.

For carbon-ion therapy one study observed late RTOG grade 2 skin toxicity in 3%, another 3% had grade 2 mucosal toxicity and the remaining patients had grades 0–1 toxicity.⁹⁵ No photon

Fig. 1. Forest plots of random effect meta-regression. *Consisted of only one study and therefore no pooled estimate is reported. †Based on a study population consisting of 85% operated patients. ‡Because of lacking data, it was not possible to correct for surgery for carbon-ions. □ = se retrieved from study, ■ = se calculated (proportion method), ◇ = se calculated (Peto method), ◆ = se calculated (Peto method assuming maximum % censoring reported in the particular sub-analysis). Abbreviations: po = post-operative, bo = biopsy only, ps = partial surgery, cs = complete surgery, and ct = chemotherapy.

studies reported skin or mucosal toxicity with accompanying grades. One study reported grades 3–4 visual toxicity in two (8%) patients (one dry eye syndrome and one optic nerve toxicity resulting in decreased visual acuity) after photon radiotherapy.⁸³ For carbon-ion therapy no visual toxicity data were reported, hence it was not possible to perform comparisons considering late treatment related visual toxicity.

Adenoid cystic carcinoma

For adenoid cystic carcinomas (ACC), one non-randomized comparative study which compared carbon-ion therapy ($n = 29$) with photon radiation ($n = 34$) showed no statistically significant differ-

ences.⁹⁶ Further, two carbon-ion studies (including updated data of the comparative study),^{34,97} one proton study⁹⁸ and 22 conventional photon studies^{99–120} reported results for adenoid cystic carcinomas.

Meta-analyses resulted in a pooled 5-year LC of 69% for carbon-ion therapy, 93% for proton therapy and 75% for conventional photon therapy. Pooled 5-year estimates for OS were 70% for carbon-ion therapy, 77% for proton therapy and 73% for photon therapy. No statistically significant differences were observed between carbon-ion therapy, proton therapy and conventional photon therapy for 5-year LC and OS (see Table 1 for P -values).

The percentage of operated patients had a statistically significant influence on OS (P -value 0.043) favoring studies with higher proportions of operated patients. Therefore 5-year OS estimates

Fig. 1 (continued)

were corrected for this covariate. Due to lacking data, this was not possible for carbon-ion therapy (Appendix 4). The corrected estimate was similar to the uncorrected estimate for 5-year OS for photon therapy (both 73%), but for proton therapy the corrected estimate increased from 77% to 89%. After correcting 5-year OS, the differences between IMRT and protons remained not statistically significant. The covariates considering disease stage and T4 tumors were not reported in the particle studies and were therefore not included in the analyses. The remaining covariates had no statistically significant influence on the outcome.

For carbon-ion radiotherapy, late CTC v3.0 grades 1–2 toxicity was observed in 63% of the patients and no toxicity of grade 3 or higher was reported.⁹⁷ Reported RTOG late grades 1–2 toxicity in photon studies was 64% and 84%^{104,117} and ranged between 4% and 11% for grade 3 and higher toxicity.^{104,109,114,117}

Comparative in-silico studies

Eight comparative in-silico studies were included, one¹²¹ comparing carbon-ion therapy and photon therapy and seven^{122–128} comparing proton therapy and photon therapy.

One in-silico study suggested that for paranasal sinus tumors, carbon-ion therapy has the ability to statistically significantly decrease the dose to the contralateral optic nerve.¹²¹ However, due to unknown differences in relative biological effectiveness for carbon-ion therapy, it is yet unclear how these differences in dose will translate into clinically relevant outcomes. Also, for proton therapy one in-silico study reported a lower dose to the optic nerves compared with IMRT (Table 2).¹²⁴ No information was provided onto what extent this reduced dose would reduce the probability of visual impairment.

For nasopharyngeal, oropharyngeal, hypopharyngeal and squamous cell carcinomas, six comparative in-silico studies consistently showed a lower dose to the parotid glands for proton therapy as opposed to IMRT (Table 2). The decrease in mean dose to the parotid glands between IMRT and proton therapy ranged from 2 GyE to 10 GyE. Based on normal tissue complication probability (NTCP) models, three studies^{123,127,128} predicted probability of complications of the parotid glands (defined as a decrease of the salivary flow to 25% of the pre-treatment salivary flow). The absolute decrease (percentage points) of the complication probability of the parotid glands

Table 1
Results of meta the analyses.

Treatment	Outcome (95% CI)	Comparison	Difference (95% CI)	<i>I</i> ²	<i>P</i> -value ^a
<i>Nasopharyngeal carcinoma</i>					
3Y LC					
IMRT	0.947 (0.923 to 0.970)	Protons – IMRT	−0.027 (−0.232 to 0.178)	19.0%	0.780
Protons ^b	0.920 (0.743 to 1.000)				
3Y OS					
IMRT	0.897 (0.862 to 0.933)	Protons – IMRT	−0.157 (−0.473 to 0.158)	67.5%	0.298
Protons ^b	0.740 (0.471 to 1.000)				
3Y LC corrected for the year of publication					
IMRT	0.946 (0.927 to 0.966)	Protons – IMRT	−0.048 (−0.252 to 0.156)	0.0%	0.609
Protons ^b	0.898 (0.695 to 1.000)				
<i>Oropharyngeal carcinoma</i>					
2Y LC					
IMRT	0.947 (0.898 to 0.995)	Protons – IMRT	0.013 (−0.105 to 0.132)	0.0%	0.782
Protons ^b	0.960 (0.878 to 1.000)				
2Y DFS					
IMRT	0.865 (0.812 to 0.918)	Protons – IMRT	−0.055 (−0.159 to 0.269)	49.9%	0.570
Protons ^b	0.810 (0.662 to 0.958)				
<i>Paranasal and sinonasal carcinoma</i>					
5Y LC					
IMRT	0.662 (0.516 to 0.809)	Carbon-ions – IMRT	−0.172 (−0.600 to 0.256)	0.0%	0.327
Protons	0.878 (0.755 to 1.000)	Protons – IMRT	0.216 (0.025 to 0.407)		0.035 ^c
Carbon-ions ^b	0.490 (0.210 to 0.770)	Protons – carbon-ions	0.388 (−0.033 to 0.809)		0.063
5Y DFS					
IMRT	0.535 (0.162 to 0.907)	Protons – IMRT	0.074 (−0.393 to 0.542)	78.2%	0.682
Protons	0.609 (0.326 to 0.891)				
5Y OS					
IMRT	0.516 (0.154 to 0.878)	Protons – IMRT	0.188 (−0.276 to 0.653)	73.2%	0.323
Protons	0.705 (0.414 to 0.995)				
<i>Mucosal malignant melanoma</i>					
5Y OS					
Photons	0.252 (0.212 to 0.291)	Carbon-ions – photons	0.185 (0.058 to 0.313)	51.7%	0.007 ^c
Carbon-ions	0.437 (0.316 to 0.558)				
<i>Adenoid cystic carcinoma</i>					
5Y LC					
Photons	0.753 (0.635 to 0.870)	Carbon-ions – photons	0.061 (−0.249 to 0.371)	93.7%	0.675
Protons ^b	0.930 (0.797 to 1.000)	Protons – photons	0.177 (−0.252 to 0.607)		0.386
Carbon-ions	0.691 (0.405 to 0.978)	Protons – carbon-ions	0.239 (−0.264 to 0.741)		0.322
5Y OS					
Photons	0.731 (0.674 to 0.789)	Carbon-ions – photons	−0.027 (−0.203 to 0.149)	77.8%	0.752
Protons ^b	0.770 (0.639 to 0.901)	Protons – photons	0.039 (−0.233 to 0.310)		0.769
Carbon-ions	0.704 (0.538 to 0.871)	Protons – carbon-ions	0.066 (−0.248 to 0.379)		0.666
5Y OS corrected for the percentage of operated patient					
Photons	0.728 (0.672 to 0.784)	Protons – photons	0.165 (−0.124 to 0.455)	73.6%	0.245
Protons	0.893 (0.611 to 1.000)				

^a P-value for the difference between the treatments.

^b Consisted of only one study and the study estimated instead of the pooled estimate is therefore reported.

^c Statistically significant difference.

for proton therapy compared with IMRT ranged from 6% to 28% (Table 2).

None of the included in-silico studies reported dose to the pharyngeal constrictors.

The reduced dose to organs at risk for carbon-ion and proton therapy was accomplished with a similar conformity index, dose homogeneity and coverage of the target volume for particle therapy. Hence, the decreased dose to the organs at risk will not result in a reduced tumor control probability.

Discussion

To the best of our knowledge, this review and meta-analysis was the first that reviewed all evidence (clinical and in-silico studies) and pooled the effectiveness of photon, carbon-ion and proton radiotherapy in HNC. Based on currently available evidence, we found that carbon-ion radiotherapy resulted in a statistically

significantly increased 5-year OS compared to conventional photon therapy for mucosal malignant melanomas. Melanomas are considered as relatively radio-resistant tumors.^{129,130} Therefore, our results might indicate that carbon-ion therapy is advantageous in the treatment of relatively radio-resistant tumors in the head and neck region, which profit from the increased relative biological effectiveness (RBE). Because of lacking data, no comparisons were performed considering toxicity in mucosal malignant melanomas. Toxicity data for adenoid cystic toxicity was based on different classification systems (RTOG and CTC), which complicated the comparison. However, the incidence of toxicity for carbon-ion therapy in adenoid cystic carcinomas seemed lower than reported in conventional photon studies.

Outcomes for proton therapy were generally comparable with the best available photon therapy in nasopharyngeal, oropharyngeal and adenoid cystic carcinomas. For paranasal and sinonasal cancer, DFS and OS were comparable for photon and proton ther-

Table 2

Dose to organs at risk and complication probability reported in comparative in-silico studies.

Outcome	First author	N	Tumor histology/site	OAR site	Mean dose in Gray equivalent ^a					Complication probability ^a					
					Photons		Protons	Carbon-ions	Sig. ^b	Photons		Protons	Carbon-ions	Sig. ^b	NTCP model ^c
					3D-CRT	IMRT	Scanned			3D-CRT	IMRT	Scanned			
Parotid gland	Taheri-Kadkhoda et al. ¹²⁶	8	Nasopharynx		–	40	36	–	Yes	–	–	–	–	–	
	Widesott et al. ¹²⁸	6	Nasopharynx	CL	–	29	23	–	Yes	–	22%	5%	–	Yes	Eisbruch et al. ¹³⁶
				IL	–	31	25	–	Yes	–	20%	14%	–	Yes	Roesink et al. ¹³⁷
					–	–	–	–	–	25%	18%	–	Yes	Eisbruch et al. ¹³⁶	
	Van de Water et al. ¹²⁷	10	Oropharynx		–	28	18	–	Yes	–	41%	21%	–	Yes	Roesink et al. ¹³⁷
	Johansson et al. ¹²³	5	Hypopharynx	Left	48	42	33	–	nr	94%	65%	40%	–	nr	Semenenko and Li ¹³⁸
	Right			47	35	33	–	nr	93%	51%	43%	–	nr	Schilstra and Meertens ¹³⁹	
	Cozzi et al. ¹²²	5	Squamous cell carcinomas	Left	49	46	40	–	nr	–	–	–	–	–	–
				Right	48	44	36	–	nr	–	–	–	–	–	–
	Steneker et al. ¹²⁵	5	Squamous cell carcinomas		–	≈55% ^d	≈35% ^d	–	nr	–	–	–	–	–	–
Optic nerve	Mock et al. ¹²⁴	5	Paranasal sinus	CL	66% ^d	62% ^d	51% ^{d,e}	–	nr	–	–	–	–	–	–
				IL	95% ^d	91% ^d	90% ^{d,e}	–	nr	–	–	–	–	–	–
	Amirul Islam et al. ¹²¹	7	Paranasal sinus	CL	42	44	–	24	Yes	–	–	–	–	–	–
				IL	58	58	–	54	No	–	–	–	–	–	–

Abbreviations: CL = contralateral, IL = ipsilateral, OAR = organ at risk, Sig = statistically significance, NTCP = normal tissue complication probability, and nr = not reported.

^a The optimal outcome per study is printed in bold.^b Statistically significance of the comparison IMRT versus proton/carbon-ion therapy (P -value ≤ 0.05 is considered statistically significant).^c Endpoints for the complication probability of the parotid gland: decrease of the salivary flow to 25% of pre-treatment flow at 13 weeks (Schilstra and Meertens¹³⁹), 6 months (Semenenko and Li¹³⁸) or 1 year (Eisbruch et al.¹³⁶ and Roesink et al.¹³⁷) after radiotherapy.^d Dose to organ at risk presented as% of the prescribed dose.^e Protons scattered.

apy. Nevertheless, LC was statistically significantly increased for proton therapy. Besides a higher total treatment dose, this increase may also be influenced by the proportion of patients that received surgery (Appendix 4).⁷² For the remainder, the similar outcomes can be explained since the radiobiological differences between protons and photons are small and the total treatment doses among studies were generally comparable. Considering treatment toxicity in oropharyngeal cancer and nasopharyngeal cancer, no appropriate data concerning xerostomia or dysphagia were available to perform comparisons based on clinical data. Although based on different classification systems, in paranasal and sinusal cancer the incidence of grade 3 visual toxicity seemed lower for proton therapy as compared to photon therapy.

In paranasal carcinomas, one comparative in-silico studies showed a reduced dose to the optic nerves for carbon-ion therapy compared to photon therapy.¹²¹ Nonetheless, it is not yet clear how this decrease in dose translates into clinical outcomes. For proton therapy compared to photon therapy, we found a decreased dose to the optical nerves¹²⁴ and to the parotid glands.^{122–128} Based on NTCP models, this latter dose reduction resulted in a lower complication probability for the parotid glands.^{123,127,128} However, the reported complication probabilities varied largely among the in-silico studies, which is partly due to differences in the applied NTCP models. The decreased dose to the organs at risk was accomplished without compromising on the conformity index, dose homogeneity and coverage of the target volume.^{122–128} This indicates that the main advantage of proton therapy in HNC may currently be the ability to spare organs at risk without decreasing tumor control rates. However, clinical evidence to support this is not yet available.

To explore potential confounding factors and subsequently correct for heterogeneity between studies we included covariates in our analyses. In two analyses, statistically significantly influencing covariates were observed. Firstly, the year of publication was statistically significant in the analyses concerning 3-year LC in naso-

pharyngeal carcinomas, which might reflect changes over time such as the inclusion of more patients with nodal extension in more recent studies (Appendix 4). However, this covariate did not substantially affect the estimated 3-year LC. Secondly, in the analyses considering adenoid cystic carcinomas, the proportion of operated patients had a statistically significant influence on 5-year OS. The estimate for conventional photon therapy remained unchanged whereas the 5-year OS for proton therapy increased substantially (Fig. 1 and Table 1). The remaining analyses did not reveal other covariates which statistically significantly influenced the outcomes.

Radiotherapy was often combined with chemotherapy and/or surgery in the included studies. Since our analyses were restricted to group-level data and study outcomes were not stratified for chemotherapy and surgery, we were not able to clarify the individual impact of chemotherapy or the positioning of surgery. It would be an interesting topic for future research to examine whether and when proton or carbon-ion radiotherapy could best be combined with chemotherapy and/or surgery.

Further, the potential gain of particle therapy in terms of tumor control may rely on higher doses to the tumor while remaining an equal dose to the organs at risk. Correcting for differences in treatment dose would therefore remove the potential gain of particle therapy. For that reason, our analyses were not corrected for differences in radiotherapy dosage schemes.

The present study has some limitations. Most importantly, the evidence on the effectiveness of particle therapy consists of a limited number of (mainly small) observational studies. Also, influencing variables were not always reported adequately. As a consequence correcting for confounding variables was only possible to a limited extent. These data issues may bias the comparisons as a result of differences in setting or treatment properties. This is considered a main drawback of meta-analysis of observational studies.^{33,131} However, in the absence of randomized trials, meta-analysis of observational studies is one of the

few methods to synthesize effectiveness and present uncertainty³³ and follows the recommendation that all relevant studies should be taken into account.¹³² Another data concern was the scarcely reported toxicity data among studies, and as a result it was not possible to adequately compare late treatment toxicity based on clinical data.

Implications for practice

It has been subject of debate whether the high initial and treatment costs of particle therapy are justified given the currently available evidence surrounding its effectiveness.²¹ Based on the available evidence, particle therapy seems as least as effective as photon therapy in tumor control, and may have advantages in sparing organs at risk. However, with regard to the paucity of available proton and carbon-ion studies and the potential bias of comparisons between (small) observational studies, the superiority of particle therapy in terms of tumor control and survival as well as the question whether the benefits outweighs the costs remains uncertain.

Implications for research

Particles are used in the treatment of cancer since 1954.¹³³ However, the number of published studies which administer particle therapy in HNC is limited and much of the currently available data have been gathered in less than optimal physic-based settings. Therefore, it is difficult to establish the potential effectiveness of particle therapy in more optimal clinical settings. Studies evaluating the effectiveness of particle therapy in HNC stratified by location and/or histology are therefore needed.

Curative radiation therapy for HNC is often accompanied with a trade-off between radiation toxicity and survival. The length of survival alone is therefore insufficient to determine the success of a treatment, and the quality of survival needs to be considered simultaneously.¹³⁴ However, complete (late) treatment toxicity data is infrequently and inconsistently reported. Hence, there is a need for studies to systematically examine both minor and severe radiation toxicity per type and grade. This is especially important if decreasing treatment toxicity is regarded as the potential benefit of particle therapy in HNC.

As recommended previously,¹⁵ to facilitate comparisons on both survival and treatment toxicity between particle therapy and photon radiation; the construction of an international particle therapy register, which contains anonymous data from patients who have been treated with particle therapy, would be a straightforward and effective solution. Such registries become particularly evident if randomized trials comparing photon therapy and particle therapy are not to be expected.¹³⁵

For now, in the absence of comprehensive toxicity data, comparative in-silico studies combined with dose-response models offer a complementary way of estimating the potential added value of particle therapy in HNC in relation to its costs.^{20,22}

Conclusions

Currently available clinical evidence for HNC indicates that survival for carbon-ion radiotherapy in mucosal malignant melanomas is statistically significantly increased as opposed to photon radiation. This suggests that carbon-ion radiotherapy, with its increased biological efficacy, might be advantageous in the treatment of relatively radio-resistant tumors. Besides local control in paranasal and sinonasal cancer, survival and tumor control outcomes for proton therapy were to a large extent similar to the best available photon radiation. Based on limited data, this review indi-

cates that a clinically relevant benefit of proton therapy probably lies in reducing treatment toxicity in HNC. This finding is in accordance with available comparative in-silico studies.

Since the overall quantity and quality of data regarding carbon-ion and proton therapy is poor and considering the risk of bias in comparisons between (small) observational studies, the reported results do not allow for definite conclusions. Therefore, we recommend the construction of an international particle therapy register to facilitate definitive comparisons on both survival and treatment toxicity between particle and photon radiotherapy.

Conflict of interest statement

No actual or potential conflicts of interest exist.

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Appendix 1. Detailed overview of the search queries

Search query 1: particle therapy studies.

Patient	
#1	“Salivary gland” OR “oropharyngeal” OR “oropharynx” OR “nasopharynx” OR “nasopharyngeal” OR “paranasal sinus” OR “paranasal” OR “hypopharynx” OR “pharynx” OR “oral cavity”
#2	(Neoplasm) OR “cancer” OR “tumor” OR “tumour” OR (malignan) OR (oncol) OR (carcinoma) OR (head and neck neoplasms [mesh])
#3	#1 AND #2
#4	(Carcinoma, adenoid cystic/radiotherapy [mesh]) OR (neoplasms, squamous cell [mesh]) OR (melanoma [mesh]) OR “adenoid cystic” OR “squamous cell” OR “melanoma” OR “cancer” OR (neoplasm) OR “tumor” OR “tumour” OR (malignan) OR (oncol)
#5	((“Cancer” OR (neoplasm) OR “tumor” OR “tumour” OR (malignan) OR (oncol) OR (carcinoma)) AND head neck) OR (head and neck neoplasms [mesh])
#6	#4 AND #5
#7	((Head and neck neoplasms [mesh]) OR (salivary gland neoplasms [mesh]) OR (oropharyngeal neoplasms [mesh]) OR (nasopharyngeal neoplasms [mesh]) OR (pharyngeal neoplasms [mesh]) OR (paranasal sinus neoplasms [mesh]))
#8	#3 OR #6 OR #7
Intervention and comparison	
#9	(proton therap) OR “proton”
#10	“particle” OR (heavy ion) OR (light ion) OR “hadron” OR “carbon”
#11	“beam irradiation” OR “radiation” OR “irradiation” OR “beam radiation” OR (radiotherap) OR (beam therap)
#12	#11 OR (ion therap)
#13	#9 AND #11
#14	#10 AND #12
#15	(Protons/therapeutic use [mesh]) OR (carbon radioisotopes/therapeutic use [mesh])
#16	#13 OR #14 OR #15

Outcome

- #17 “Mortality” OR (adverse effect) OR (adverse event) OR (side effect) OR (toxicity) OR (xerostomia) OR “disease free survival” OR “overall survival” OR “local control” OR “tumour control” OR “tumour control”
- #18 (Mortality [mesh]) OR (head and neck neoplasms/mortality [mesh]) OR (treatment outcome [mesh]) OR (“outcome assessment (health care)” [mesh]) OR (adverse effects [subheading]) OR (radiotherapy/adverse effects [mesh]) OR (sickness impact profile [mesh]) OR (survival rate [mesh]) OR (“xerostomia” [mesh]) OR (disease free survival [mesh])
- #19 #17 OR #18
- PICO = #8 AND #16 AND #19

Search query 2: intensity modulated radiotherapy studies.

Patient

- #1 “Salivary gland” OR “oropharyngeal” OR “oropharynx” OR “nasopharynx” OR “nasopharyngeal” OR “paranasal sinus” OR “paranasal” OR “hypopharynx” OR “pharynx” OR “oral cavity”
- #2 (Neoplasm*) OR “cancer” OR “tumor” OR “tumour” OR (malignant*) OR (oncol*) OR (carcinoma*) OR (head and neck neoplasms [mesh])
- #3 #1 AND #2
- #4 (Carcinoma, adenoid cystic/*radiotherapy [mesh]) OR (neoplasms, squamous cell [mesh]) OR (melanoma [mesh]) OR “adenoid cystic” OR “squamous cell” OR “melanoma” OR “cancer” OR (neoplasm*) OR “tumor” OR “tumour” OR (malignant*) OR (oncol*)
- #5 (“Cancer” OR (neoplasm*) OR “tumor” OR “tumour” OR (malignant*) OR (oncol*) OR (carcinoma*)) AND head neck) OR (head and neck neoplasms [mesh])
- #6 #4 AND #5
- #7 ((head and neck neoplasms [mesh]) OR (salivary gland neoplasms [mesh]) OR (oropharyngeal neoplasms [mesh]) OR (nasopharyngeal neoplasms [mesh]) OR (pharyngeal neoplasms [mesh]) OR (paranasal sinus neoplasms [mesh]))
- #8 #3 OR #6 OR #7

Intervention and comparison

- #9 ((Intensity modulated) AND ((radiotherap*) OR (radiotherapy [subheading]) OR (radiotherapy [mesh]))) OR “IMRT” OR (radiotherapy, intensity modulated [mesh])

Outcome

- #10 “Mortality” OR (adverse effect*) OR (adverse event*) OR (side effect*) OR (toxicity*) OR (xerostomia*) OR “disease free survival” OR “overall survival” OR “local control” OR “tumor control” OR “tumour control”
- #11 (Mortality [mesh]) OR (head and neck neoplasms/*mortality [mesh]) OR (treatment outcome [mesh]) OR (“outcome assessment (health care)” [mesh]) OR (adverse effects [subheading]) OR (radiotherapy/adverse effects [mesh]) OR (sickness impact profile [mesh]) OR (survival rate [mesh]) OR (“xerostomia” [mesh]) OR (disease free survival [mesh])
- #12 #10 OR #11
- PICO = #8 AND #9 AND #12

*For mucosal malignant melanoma and adenoid cystic carcinomas, no studies using intensity modulated radiotherapy were available.

Search query 3: conventional radiotherapy studies for mucosal malignant melanoma and adenoid cystic carcinomas*.

Patient

- #1 “Salivary gland” OR “oropharyngeal” OR “oropharynx” OR “nasopharynx” OR “nasopharyngeal” OR “paranasal Sinus” OR “paranasal” OR “hypopharynx” OR “pharynx” OR “oral cavity”
- #2 (Neoplasm*) OR “cancer” OR “tumor” OR “tumour” OR (malignant*) OR (oncol*) OR (carcinoma*) OR (head and neck neoplasms [mesh])
- #3 #1 AND #2
- #4 (Melanoma [mesh]) OR “melanoma” OR (carcinoma, adenoid cystic/*radiotherapy [mesh]) OR “adenoid cystic”
- #5 (“Cancer” OR (neoplasm*) OR “tumor” OR “tumour” OR (malignant*) OR (oncol*) OR (carcinoma*)) AND head neck) OR (head and neck neoplasms [mesh])
- #6 #4 AND #5
- #7 ((Head and neck neoplasms [mesh]) OR (salivary gland neoplasms [mesh]) OR (oropharyngeal neoplasms [mesh]) OR (nasopharyngeal neoplasms [mesh]) OR (pharyngeal neoplasms [mesh]) OR (paranasal sinus neoplasms [mesh]))
- #8 (#3 OR #7) AND (#6)

Intervention and comparison

- #9 (Radiotherap*) OR (radiotherapy [subheading]) OR (radiotherapy [mesh])

Outcome

- #10 “Mortality” OR (adverse effect*) OR (adverse event*) OR (side effect*) OR (toxicity*) OR (xerostomia*) OR “disease free survival” OR “overall survival” OR “local control” OR “tumor control” OR “tumour control”
- #11 (Mortality [mesh]) OR (head and neck neoplasms/*mortality [mesh]) OR (treatment outcome [mesh]) OR (“outcome assessment (health care)” [Mesh]) OR (adverse effects [subheading]) OR (radiotherapy/adverse effects [mesh]) OR (sickness impact profile [mesh]) OR (survival rate [mesh]) OR (“xerostomia” [mesh]) OR (disease free survival [mesh])
- #12 #10 OR #11
- PICO = #8 AND #9 AND #12

*For mucosal malignant melanoma and adenoid cystic carcinomas, no studies using intensity modulated radiotherapy were available.

Search query 4: comparative in-silico studies.

Patient

- #1 “Salivary gland” OR “oropharyngeal” OR “oropharynx” OR “nasopharynx” OR “nasopharyngeal” OR “paranasal Sinus” OR “paranasal” OR “hypopharynx” OR “pharynx” OR “oral cavity”
- #2 (Neoplasm) OR “cancer” OR “tumor” OR “tumour” OR (malignant) OR (oncol) OR (carcinoma) OR (head and neck neoplasms [mesh])
- #3 #1 AND #2
- #4 (Carcinoma, adenoid cystic/radiotherapy [mesh]) OR (neoplasms, squamous cell [mesh]) OR (melanoma [mesh]) OR “adenoid cystic” OR “squamous cell” OR “melanoma” OR “cancer” OR (neoplasm) OR “tumor” OR “tumour” OR (malignant) OR (oncol)
- #5 (“Cancer” OR (neoplasm) OR “tumor” OR “tumour” OR (malignant) OR (oncol) OR (carcinoma)) AND head neck) OR (head and neck neoplasms [mesh])

(continued on next page)

#6 #4 AND #5

#7 ((Head and neck neoplasms [mesh]) OR (salivary gland neoplasms [mesh]) OR (oropharyngeal neoplasms [mesh]) OR (nasopharyngeal neoplasms [mesh]) OR (pharyngeal neoplasms [mesh]) OR (paranasal sinus neoplasms [mesh]))

#8 #3 OR #6 OR #7

Intervention and comparison

#9 (Proton therap) OR “proton”

#10 “Particle” OR (heavy ion) OR (light ion) OR “hadron” OR “carbon”

#11 “Beam irradiation” OR “radiation” OR “irradiation” OR “beam radiation” OR (radiotherap) OR (beam therap)

#12 #11 OR (ion therap)

#13 #9 AND #11

#14 #10 AND #12

#15 (Protons/therapeutic use [mesh]) OR (carbon radioisotopes/therapeutic use [mesh])

#16 #13 OR #14 OR #15

Outcome

#17 Planning AND (radiotherapy OR (radiotherapy [mesh]))

#18 Radiotherapy planning, computer-assisted/methods [mesh]

#19 #17 OR #18

PICO = #8 AND #16 AND #19

Appendix 2. Flow chart of the inclusion and exclusion process for the search strategies

* Data/sub-analysis extracted from two carbon-ion studies were used in multiple subgroups

Abbreviations: Pr = Proton therapy, Ci/C-ions = carbon-ion therapy, MM = mucosal malignant melanomas, ACC = adenoid cystic carcinomas

* Search query specified for mucosal malignant melanomas and adenoid cystic carcinomas (for these subgroups no IMRT studies were available).

Abbreviations: IMRT = intensity modulated radiotherapy, MM = mucosal malignant melanomas, ACC = adenoid cystic carcinomas

Abbreviations: Pr = Proton therapy, Ci/C-ion = carbon-ion therapy, ACC = adenoid cystic carcinomas

Appendix 3. Included and excluded particle studies and in-silico

Included clinical studies.

First author	Year	Comparison(s) (outcomes)
Resto	2009	Paranasal and sinonasal carcinoma (LC, DFS and OS)
Nishimura	2009	Paranasal and sinonasal carcinoma (LC, DFS, OS, and toxicity)
Mizoe	2009	Mucosal malignant melanoma (OS)
Mizoe	2009	Head and neck cancer (LC and OS), mucosal malignant melanoma (OS), adenoid cystic carcinoma (LC and OS)
Munter	2009	Adenoid cystic carcinoma (LC, OS and toxicity)
Yanagi	2009	Mucosal malignant melanoma (toxicity)
Pommier	2006	Adenoid cystic carcinoma (LC and OS)
Weber	2006	Paranasal and sinonasal carcinoma (toxicity)
Slater	2005	Oropharyngeal carcinoma (LC and DFS)
Chan	2004	Nasopharyngeal carcinoma (LC and OS)
Mizoe	2004	Head and neck cancer (LC and OS), paranasal and sinonasal carcinoma (LC)
Tokuuye	2004	Head and neck cancer (LC, DFS and OS)

Excluded clinical studies.

First author	Year	Reason(s) for exclusion
Truong	2009	Overlap in patient sample (with Resto et al., 2008)
Takagi	2007	Overlap in patient sample (with Mizoe et al., 2009)
Chan	2004	Overlap in patient sample (with Resto et al., 2008)
Schulz-Ertner	2005	Overlap in patient sample (with Munter et al., 2009)
Schulz-Ertner	2004	Overlap in patient sample (with Munter et al., 2009)
Schulz-Ertner	2003	Overlap in patient sample (with Munter et al., 2009)
Fitzek	2002	Overlap in patient sample (with Resto et al., 2008)
Lin	1999	Re-treatment
Thornton	1998	Overlap in patient sample (with Resto et al., 2008)
Tsujii	1992	Overlap in patient sample (with Tokuuye et al., 2004)
Castro	1988	Published before 1990 and other particles than protons and carbon-ions only (including He, C, Ne and Si)
Munzenrider	1985	Published before 1990
Castro	1982	Published before 1990

Included comparative in-silico studies.

First author	Year	Tumor site/histology
Amirul Islam	2008	In close proximity of the optic pathways
Taheri-Kadkhoda	2008	Nasopharynx
Van de Water	2008	Oropharynx
Widesott	2008	Nasopharynx
Steneker	2006	Squamous cell carcinoma
Johansson	2004	Hypopharynx
Mock	2004	Paranasal sinus
Cozzi	2001	Squamous cell carcinoma

Excluded comparative in-silico studies.

First author	Year	Reason(s) for exclusion
Chera	2009	Patients sample <5
Thorwarth	2008	Patients sample <5
Muzik	2008	Patients sample <5
Flynn	2008	Patients sample <5
Lomax	2003	Patients sample <5
Schulz-Ertner	2003	Dose to the organs at risk was not reported
Lomax	1999	Patients sample <5 and no comparison of particle therapy and photons
Lomax	1999	Patients sample <5
Slater	1992	Patients sample <5
Mirabell	1992	Patients sample <5
Brown	1989	Patients sample <5 and published before 1990

Appendix 4A. Characteristics of nasopharyngeal and oropharyngeal studies*

	N	Modality	Number of fractions [†]	Total treatment dose (GyE) [†]	Age [†]	% Ct	% Operated patients	% T3/T4	% T4	% N+	% N3	% Stage IV
<i>Nasopharynx</i>												
Chan et al. (2004) ⁴⁵	17	P-rt + X-rt	46	73.6	41	59%	0%	100%	100%	53%	6%	100%
Zheng et al. (2010) ⁵⁹	59	X-rt	33	70.7	48	100%	nr	50%	28%	85%	20%	43%
Kim et al. (2009) ⁴⁹	25	X-rt	30	67.5	44	100%	0%	44%	24%	96%	24%	48%
Lee et al. (2009) ⁵²	68	X-rt	33	70.0	49	84%	0%	34%	19%	74%	12%	28%
Lin et al. (2009) ⁵⁴	323	X-rt	30/31	66.0/69.8	nr	91%	0%	61%	24%	91%	6%	29%
Nishimura et al. (2009) ⁵⁵	35	X-rt	28–35	68.0	56	89%	nr	46%	26%	66%	11%	34%
Tham et al. (2009) ⁵⁶	195	X-rt	35	70.0	52	56%	0%	nr	26%	nr	nr	30%
Wong et al. (2009) ⁵⁸	175	X-rt	33	70.0	48	73%	0%	35%	15%	72%	9%	24%
Fang et al. (2008) ⁴⁷	110	X-rt	36–42	64.8–75.6	nr	57%	0%	25%	11%	68%	1%	12%
Koom et al. (2008) ⁵⁰	24	X-rt	27	64.8	46	100%	0%	29%	13%	96%	25%	33%
Wolden et al. (2006) ⁵⁷	74	X-rt	30	70.2	45	93%	0%	51%	31%	78%	24%	47%
Chong et al. (2004) ⁴⁶	104	X-rt	25–30	64.0–70.0	43	nr	nr	nr	nr	nr	nr	16%
Kam et al. (2004) ⁴⁸	63	X-rt	33	66.0	48	30%	0%	51%	19%	70%	5%	22%
Kwong et al. (2004) ⁵¹	33	X-rt	34	68.0–70.0	43	0%	0%	3%	0%	18%	0%	0%
Lee et al. (2002) ⁵³	67	X-rt	nr	65.0–70.0	49	75%	0%	43%	21%	78%	12%	37%
<i>Oropharynx</i>												
Slater et al. (2005) ⁶⁰	29	P-rt + X-rt	45	75.9	nr	0%	0%	55%	21%	83%	10%	62%
Daly et al. (2010) ⁷⁰	107	X-rt	30	60.0/66.0	nr	80%	21%	47%	29%	91%	11%	86%
Eisbruch et al. (2009) ⁶²	67	X-rt	30	66.0	56	0%	0%	0%	0%	43%	0%	0%
Lawson et al. (2008) ⁶⁵	34	X-rt	33	70.3	61	100%	0%	41%	29%	91%	9%	85%
Rusthoven et al. (2008) ⁶⁷	32	X-rt	33	69.3	nr	100%	0%	41%	19%	97%	3%	84%
Schoenfeld et al. (2008) ⁶⁸	64	X-rt	42	67.5/72.0	nr	54% [‡]	0%	42% [‡]	20% [‡]	70% [‡]	5% [‡]	63% [‡]
Garden et al. (2007) ⁶³	51	X-rt	30	63.0–66.0	54	10%	0%	0%	0%	67%	4%	53%
Lee et al. (2006) ⁶⁶	41	X-rt	40/42	70.0–72.0	55	100%	0%	39%	nr	90%	5%	85%
Yao et al. (2006) ⁶⁹	66	X-rt	nr	60.0–74.0	53	70%	6%	41%	29%	88%	14%	88%
Chao et al. (2004) ⁶¹	74	X-rt	35	66.0/70.0	55	23%	58%	45%	nr	84%	nr	70%
Huang et al. (2003) ⁶⁴	41	X-rt	33	70.0	55	73%	7%	17%	7%	76%	5%	68%

Appendix 4B. Characteristics of paranasal and sinonasal and mucosal malignant melanoma studies*

	N	Modality	Total treatment dose (GyE) [†]	Age [†]	% Ct	% Operated patients	% T4	% N3	% Stage III [§]
<i>Paranasal and sinonasal</i>									
Resto et al. Cs (2008) ⁷²	20	P-rt + X-rt	67.6	50 [‡]	33% [‡]	100%	nr	nr	na
Resto et al. Ps (2008) ⁷²	50	P-rt + X-rt	75.6	50 [‡]	33% [‡]	100%	nr	nr	na
Resto et al. Bo (2008) ⁷²	32	P-rt + X-rt	75.4	50 [‡]	33% [‡]	0%	nr	nr	na
Nishimura et al. (2007) ⁷¹	14	P-rt	65.0	56	29%	50%	nr	nr	na
Mizoe et al. (2004) ³⁵	10	C-rt	48.6–64.8	60 [‡]	6% [‡]	33% [‡]	nr	nr	na
Madani et al. (2009) ⁷⁴	73	X-rt	70.0	63	0%	89% [‡]	39% [‡]	0%	na
Daly et al. (2007) ⁷³	36	X-rt	70.0	57	22%	89%	69%	0%	na
<i>Mucosal malignant melanoma</i>									
Mizoe et al. (2009) ³⁴	100	C-rt	57.6	57 [‡]	0%	nr	na	na	nr
Mizoe et al. +Ct (2009) ⁷⁶	57	C-rt	57.6	60	100%	nr	na	na	nr
Meleti et al. (2008) ⁸⁷	42	X-rt	30.0	64	2%	90%	na	na	3% [‡]
Nakashima et al. (2008) ⁸⁸	20	X-rt	54.0	62	6%	100%	na	na	0%
Wagner et al. (2008) ⁹³	17	X-rt	66.9	64	0%	76%	na	na	0%
Huang et al. (2007) ⁸¹	15	X-rt	nr	69	20%	93%	na	na	0%
Krengli et al. (2006) ⁸³	74	X-rt	55.1	66	5%	80%	na	na	8%
Bridger et al. (2005) ⁷⁸	27	X-rt	nr	66	0%	100%	na	na	nr
Temam et al. (2005) ⁹²	69	X-rt	64.9	58	0%	100%	na	na	0%
Owens et al. (2003) ⁸⁹	44	X-rt	nr	56	0%	100%	na	na	nr
Yii et al. (2003) ⁹⁴	89	X-rt	nr	64	10%	97%	na	na	7%
Patel et al. (2002) ⁹⁰	59	X-rt	nr	63	0%	100%	na	na	7%
Loree et al. (1999) ⁸⁴	28	X-rt	nr	nr	18%	61%	na	na	4%
Lund et al. (1999) ⁸⁵	58	X-rt	nr	64	16%	100%	na	na	0%
Manolidis and Donald (1997) ⁸⁶	14	X-rt	nr	71	0%	86%	na	na	nr
Kingdom and Kaplan (1995) ⁸²	10	X-rt	nr	nr	0%	100%	na	na	nr
Guzzo et al. (1993) ⁸⁰	48	X-rt	nr	58	29%	90%	na	na	8%
Shibuya et al. (1993) ⁹¹	28	X-rt	nr	nr	0%	0%	na	na	0%
Andersen et al. (1992) ⁷⁷	26	X-rt	54.0	65	0%	77%	na	na	4%
Gilligan and Slevin (1991) ⁷⁹	28	X-rt	45.0–55.0	65	0%	0%	na	na	nr

Appendix 4C. Characteristics of adenoid cystic carcinoma studies*

	N	Modality	Total treatment dose (GyE) [†]	Age [†]	% Ct	% Operated patients	% T4	% N3	% Stage IV
<i>Adenoid cystic carcinoma</i>									
Pommier et al. (2006) ⁹⁸	23	P-rt + X-rt	73.3/76.4	46	4%	52%	nr	0%	nr
Mizoe et al. (2009) ³⁴	107	C-rt	57.6	57 [‡]	nr	nr	nr	nr	nr
Munter et al. (2009) ⁹⁷	59	C-rt + X-rt	72.0	52	nr	nr	nr	nr	nr
Iseli et al. (2009) ¹¹⁰	171	X-rt	60.0–70.0	53	0%	82%	nr	nr	37%
Agarwal et al. (2008) ⁹⁹	76	X-rt	56.0	nr	0%	97%	54%	nr	59%
Gomez et al. (2008) ¹⁰⁴	59	X-rt	63.0	52	10%	92%	34%	nr	nr
Leonetti et al. (2008) ¹¹³	16	X-rt	51.0–60.0	47	0%	100%	nr	nr	nr
Da Cruz Perez et al. (2006) ¹⁰²	18	X-rt	53.6	39	17%	61%	nr	nr	nr
Rhee et al. (2006) ¹¹⁶	35	X-rt	nr	47	9%	77%	49%	nr	nr
Bhattacharyya and Fried (2005) ¹⁰¹	18	X-rt	nr	59 [‡]	nr	nr	nr	nr	nr
Gurney et al. (2005) ¹⁰⁵	33	X-rt	60.0	49	0%	100%	nr	nr	31%
Rapidis et al. (2005) ¹¹⁵	23	X-rt	nr	60	26%	96%	nr	nr	nr
Kokemueller et al. (2004) ¹¹²	74	X-rt	60.0	58	0%	100%	42%	0%	45%
Mendenhall et al. (2004) ¹¹⁴	101	X-rt	10.5–79.2	58	2%	58%	44%	0%	45%
Silverman et al. (2004) ¹¹⁷	75	X-rt	nr	52	0%	100%	31%	0%	31%

Appendix 4C (continued)

	N	Modality	Total treatment dose (GyE) [†]	Age [‡]	% Ct	% Operated patients	% T4	% N3	% Stage IV
Hsu et al. (2003) ¹⁰⁸	25	X-rt	nr	50	0%	100%	nr	nr	12%
Harbo et al. (2002) ¹⁰⁶	26	X-rt	nr	64 [‡]	0%	49% [‡]	7% [‡]	2% [‡]	36% [‡]
Huber et al. (2001) ¹⁰⁹	25	X-rt	64.0	55 [‡]	0%	68%	nr	nr	nr
Khan et al. (2001) ¹¹¹	68	X-rt	nr	52	3%	87%	22%	nr	31%
Takagi et al. (2001) ¹¹⁹	20	X-rt	40.0–65.0	59	35%	85%	nr	nr	nr
Avery et al. (2000) ¹⁰⁰	15	X-rt	nr	53	7%	100%	nr	nr	33%
Therkildsen et al. (1998) ¹²⁰	87	X-rt	60.0–66.0	60 [‡]	0%	91% [‡]	nr	nr	17% [‡]
Garden et al. (1995) ¹⁰³	198	X-rt	60.0	50	0%	100%	nr	nr	nr
Hosokawa et al. (1992) ¹⁰⁷	41	X-rt	40.0–70.0	58	0%	79%	nr	nr	nr
Spiro and Huvois (1992) ¹¹⁸	184	X-rt	nr	57	0%	95%	nr	nr	12% [‡]

[†]Only characteristics of studies included in meta-analyses were reported. [‡]Median/mean value. [‡]Figures are for the whole study sample not only for this subgroup. [§]According to Ballantyne's staging system.

Abbreviations: X-rt = photon radiotherapy, P-rt = proton radiotherapy, C-rt = carbon-ion radiotherapy, Cs = complete surgery, Ps = partial surgery, Bo = biopsy only, Ct = chemotherapy, nr = not reported, na = not applicable.

References

- Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;**18**:581–92.
- Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys* 2006;**64**: 47–56.
- Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006;**368**: 843–54.
- Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;**92**:4–14.
- Duke RL, Campbell BH, Indresano AT, et al. Dental status and quality of life in long-term head and neck cancer survivors. *Laryngoscope* 2005;**115**:678–83.
- Hammerlid E, Silander E, Hornestam L, Sullivan M. Health-related quality of life three years after diagnosis of head and neck cancer – a longitudinal study. *Head Neck* 2001;**23**:113–25.
- Jensen AB, Hansen O, Jorgensen K, Bastholt L. Influence of late side-effects upon daily life after radiotherapy for laryngeal and pharyngeal cancer. *Acta Oncol* 1994;**33**:487–91.
- Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;**26**:3770–6.
- List MA, Bilir SP. Functional outcomes in head and neck cancer. *Semin Radiat Oncol* 2004;**14**:178–89.
- Durante M, Loeffler JS. Charged particles in radiation oncology. *Nat Rev Clin Oncol* 2010;**7**:37–43.
- Glimelius B, Ask A, Bjelkengren G, et al. Number of patients potentially eligible for proton therapy. *Acta Oncol* 2005;**44**:836–49.
- Palm A, Johansson KA. A review of the impact of photon and proton external beam radiotherapy treatment modalities on the dose distribution in field and out-of-field; implications for the long-term morbidity of cancer survivors. *Acta Oncol* 2007;**46**:462–73.
- Brada M, Pijls-Johannesma M, De Ruyscher D. Proton therapy in clinical practice: current clinical evidence. *J Clin Oncol* 2007;**25**:965–70.
- Jereczek-Fossa BA, Krengli M, Orecchia R. Particle beam radiotherapy for head and neck tumors: radiobiological basis and clinical experience. *Head Neck* 2006;**28**:750–60.
- Lodge M, Pijls-Johannesma M, Stirk L, Munro AJ, De Ruyscher D, Jefferson T. A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. *Radiother Oncol* 2007;**83**:110–22.
- Chan AW, Liebsch NJ. Proton radiation therapy for head and neck cancer. *J Surg Oncol* 2008;**97**:697–700.
- Ask A, Bjork-Eriksson T, Zackrisson B, Blomquist E, Glimelius B. The potential of proton beam radiation therapy in head and neck cancer. *Acta Oncol* 2005;**44**:876–80.
- Schulz-Ertner D, Jakel O, Schlegel W. Radiation therapy with charged particles. *Semin Radiat Oncol* 2006;**16**:249–59.
- Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. *J Clin Oncol* 2007;**25**:953–64.
- Brada M, Pijls-Johannesma M, De Ruyscher D. Current clinical evidence for proton therapy. *Cancer J* 2009;**15**:319–24.
- Pijls-Johannesma M, Pommier P, Lievens Y. Cost-effectiveness of particle therapy: current evidence and future needs. *Radiother Oncol* 2008;**89**:127–34.
- Glimelius B, Isacson U, Blomquist E, Grusell E, Jung B, Montelius A. Potential gains using high-energy protons for therapy of malignant tumours. *Acta Oncol* 1999;**38**:137–45.
- Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club* 1995;**123**:A12–3.
- Feuvret L, Noel G, Mazeron JJ, Bey P. Conformity index: a review. *Int J Radiat Oncol Biol Phys* 2006;**64**:333–42.
- Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. *Int J Radiat Oncol Biol Phys* 2010;**76**:S28–35.
- Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. *Int J Radiat Oncol Biol Phys* 2010;**76**:S58–63.
- Caudell JJ, Burnett OL, Schaner PE, Bonner JA, Duan J. Comparison of methods to reduce dose to swallowing-related structures in head and neck cancer. *Int J Radiat Oncol Biol Phys* 2010;**77**:462–7.
- Rancati T, Schwarz M, Allen AM, et al. Radiation dose-volume effects in the larynx and pharynx. *Int J Radiat Oncol Biol Phys* 2010;**76**:S64–9.
- Moore DS, McCabe GP, Craig BA. *Introduction to the practice of statistics*. 6th ed. W.H. Freeman Company; 2009.
- Cantor AB. Projecting the standard error of the Kaplan–Meier estimator. *Stat Med* 2001;**20**:2091–7.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II analysis and examples. *Br J Cancer* 1973;**35**:1–39.
- Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;**21**:1559–73.
- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–12.
- Mizoe JE, Hasegawa A, Bessho H, Jingu K, Kakimoto Y. Head and neck tumors. In: Proceedings of NIRS-ETOILE: joint symposium 2009 on carbon ion radiotherapy. Lyon; 2009.
- Mizoe JE, Tsujii H, Kamada T, et al. Dose escalation study of carbon ion radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2004;**60**:358–64.
- Tokuuye K, Akine Y, Kagei K, et al. Proton therapy for head and neck malignancies at Tsukuba. *Strahlenther Onkol* 2004;**180**:96–101.
- Milano MT, Vokes EE, Kao J, et al. Intensity-modulated radiation therapy in advanced head and neck patients treated with intensive chemoradiotherapy: preliminary experience and future directions. *Int J Oncol* 2006;**28**:1141–51.
- Monroe AT, Young JA, Huff JD, Ernster JA, White GA, Peddada AV. Accelerated fractionation head and neck intensity-modulated radiation therapy and concurrent chemotherapy in the community setting: safety and efficacy considerations. *Head Neck* 2009;**31**:1144–51.
- Rades D, Fehlauer F, Wroblewski J, Albers D, Schild SE, Schmidt R. Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. *Oral Oncol* 2007;**43**:535–43.
- Studer G, Furrer K, Davis BJ, et al. Postoperative IMRT in head and neck cancer. *Radiat Oncol* 2006;**1**:40.
- Seung S, Bae J, Solhjem M, et al. Intensity-modulated radiotherapy for head-and-neck cancer in the community setting. *Int J Radiat Oncol Biol Phys* 2008;**72**:1075–81.
- Laue A, Morris M, Schmidt-Ullrich R, et al. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II – clinical results. *Int J Radiat Oncol Biol Phys* 2004;**60**:374–87.
- Nangia S, Chufal KS, Tyagi A, Bhatnagar A, Mishra M, Ghosh D. Selective nodal irradiation for head and neck cancer using intensity-modulated radiotherapy: application of RTOG consensus guidelines in routine clinical practice. *Int J Radiat Oncol Biol Phys*; 2009.

44. Saba NF, Edelman S, Tighiouart M, et al. Concurrent chemotherapy with intensity-modulated radiation therapy for locally advanced squamous cell carcinoma of the larynx and oropharynx: a retrospective single-institution analysis. *Head Neck* 2009;**31**:1447–55.
45. Chan AW, Liebsch LJ, Deschler DG, et al. Proton radiotherapy for T4 nasopharyngeal carcinoma. *J Clin Oncol (Meeting Abstracts)* 2004;**22**:5574.
46. Chong Z. Improved local control with intensity modulated radiation therapy in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2004;**60**:S317.
47. Fang FM, Chien CY, Tsai WL, et al. Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy – a longitudinal study. *Int J Radiat Oncol Biol Phys* 2008;**72**:356–64.
48. Kam MK, Teo PM, Chau RM, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. *Int J Radiat Oncol Biol Phys* 2004;**60**:1440–50.
49. Kim K, Wu HG, Kim HJ, et al. Intensity-modulated radiation therapy with simultaneous integrated boost technique following neoadjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma. *Head Neck* 2009;**31**:1121–8.
50. Koom WS, Kim TH, Shin KH, et al. SMART (simultaneous modulated accelerated radiotherapy) for locally advanced nasopharyngeal carcinomas. *Head Neck* 2008;**30**:159–69.
51. Kwong DL, Pow EH, Sham JS, et al. Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. *Cancer* 2004;**101**:1584–93.
52. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol* 2009;**27**:3684–90.
53. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys* 2002;**53**:12–22.
54. Lin S, Pan J, Han L, Zhang X, Liao X, Lu JJ. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. *Int J Radiat Oncol Biol Phys* 2009;**75**:1071–8.
55. Nishimura Y, Shibata T, Nakamatsu K, et al. A two-step intensity-modulated radiation therapy method for nasopharyngeal cancer: the Kinki University experience. *Jpn J Clin Oncol* 2009;**40**:130–8.
56. Tham IW, Hee SW, Yeo RM, et al. Treatment of nasopharyngeal carcinoma using intensity-modulated radiotherapy – The National Cancer Centre Singapore experience. *Int J Radiat Oncol Biol Phys* 2009;**75**:1481–6.
57. Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. *Int J Radiat Oncol Biol Phys* 2006;**64**:57–62.
58. Wong FC, Ng AW, Lee VH, et al. Whole-field simultaneous integrated-boost intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2009;**76**:138–45.
59. Zheng J, Wang G, Yang GY, et al. Induction chemotherapy with nedaplatin with 5-FU followed by intensity-modulated radiotherapy concurrent with chemotherapy for locoregionally advanced nasopharyngeal carcinoma. *Jpn J Clin Oncol* 2010 [Epub ahead of print].
60. Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. *Int J Radiat Oncol Biol Phys* 2005;**62**:494–500.
61. Chao KS, Ozyigit G, Blanco AI, et al. Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. *Int J Radiat Oncol Biol Phys* 2004;**59**:43–50.
62. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat Oncol Biol Phys* 2009.
63. Garden AS, Morrison WH, Wong PF, et al. Disease-control rates following intensity-modulated radiation therapy for small primary oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2007;**67**:438–44.
64. Huang K, Lee N, Xia P, et al. Intensity-modulated radiotherapy in the treatment of oropharyngeal carcinoma: a single institutional experience. *Int J Radiat Oncol Biol Phys* 2003;**57**:S302.
65. Lawson JD, Otto K, Chen A, Shin DM, Davis L, Johnstone PA. Concurrent platinum-based chemotherapy and simultaneous modulated accelerated radiation therapy for locally advanced squamous cell carcinoma of the tongue base. *Head Neck* 2008;**30**:327–35.
66. Lee NY, de Arruda FF, Puri DR, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006;**66**:966–74.
67. Rusthoven KE, Raben D, Ballonoff A, Kane M, Song JI, Chen C. Effect of radiation techniques in treatment of oropharynx cancer. *Laryngoscope* 2008;**118**:635–9.
68. Schoenfeld GO, Amdur RJ, Morris CG, Li JG, Hinerman RW, Mendenhall WM. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2008;**71**:377–85.
69. Yao M, Nguyen T, Buatti JM, et al. Changing failure patterns in oropharyngeal squamous cell carcinoma treated with intensity modulated radiotherapy and implications for future research. *Am J Clin Oncol* 2006;**29**:606–12.
70. Daly ME, Le QT, Maxim PG, et al. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: clinical outcomes and patterns of failure. *Int J Radiat Oncol Biol Phys* 2010;**76**:1339–46.
71. Nishimura H, Ogino T, Kawashima M, et al. Proton-beam therapy for olfactory neuroblastoma. *Int J Radiat Oncol Biol Phys* 2007;**68**:758–62.
72. Resto VA, Chan AW, Deschler DG, Lin DT. Extent of surgery in the management of locally advanced sinonasal malignancies. *Head Neck* 2008;**30**:222–9.
73. Daly ME, Chen AM, Bucci MK, et al. Intensity-modulated radiation therapy for malignancies of the nasal cavity and paranasal sinuses. *Int J Radiat Oncol Biol Phys* 2007;**67**:151–7.
74. Madani I, Bonte K, Vakaet L, Boterberg T, De Neve W. Intensity-modulated radiotherapy for sinonasal tumors: Ghent University Hospital update. *Int J Radiat Oncol Biol Phys* 2009;**73**:424–32.
75. Weber DC, Chan AW, Lessell S, et al. Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. *Radiother Oncol* 2006;**81**:243–9.
76. Mizoe JE, Hasegawa A, Bessho H, Jingu K, Kakimoto Y. Phase II clinical trial for mucosal malignant melanoma of the head and neck combined with chemotherapy (protocol 0007). In: Proceedings of NIRS-ETOILE: joint symposium 2009 on carbon ion radiotherapy. Lyon; 2009.
77. Andersen LJ, Berthelsen A, Hansen HS. Malignant melanoma of the upper respiratory tract and the oral cavity. *J Otolaryngol* 1992;**21**:180–5.
78. Bridger AG, Smee D, Baldwin MA, Kwok B, Bridger GP. Experience with mucosal melanoma of the nose and paranasal sinuses. *ANZ J Surg* 2005;**75**:192–7.
79. Gilligan D, Slevin NJ. Radical radiotherapy for 28 cases of mucosal melanoma in the nasal cavity and sinuses. *Br J Radiol* 1991;**64**:1147–50.
80. Guzzo M, Grandi C, Licitra L, Podrecca S, Cascinelli N, Molinari R. Mucosal malignant melanoma of head and neck: forty-eight cases treated at Istituto Nazionale Tumori di Milan. *Eur J Surg Oncol* 1993;**19**:316–9.
81. Huang SF, Liao CT, Kan CR, Chen IH. Primary mucosal melanoma of the nasal cavity and paranasal sinuses: 12 years of experience. *J Otolaryngol* 2007;**36**:124–9.
82. Kingdom TT, Kaplan MJ. Mucosal melanoma of the nasal cavity and paranasal sinuses. *Head Neck* 1995;**17**:184–9.
83. Krengli M, Masini L, Kaanders JH, et al. Radiotherapy in the treatment of mucosal melanoma of the upper aerodigestive tract: analysis of 74 cases. A Rare Cancer Network study. *Int J Radiat Oncol Biol Phys* 2006;**65**:751–9.
84. Looe TR, Mullins AP, Spellman J, North Jr JH, Hicks Jr WL. Head and neck mucosal melanoma: a 32-year review. *Ear Nose Throat J* 1999;**78**:372–5.
85. Lund VJ, Howard DJ, Harding L, Wei WI. Management options and survival in malignant melanoma of the sinonasal mucosa. *Laryngoscope* 1999;**109**:208–11.
86. Manolidis S, Donald PJ. Malignant mucosal melanoma of the head and neck: review of the literature and report of 14 patients. *Cancer* 1997;**80**:1373–86.
87. Meleti M, Leemans CR, de Bree R, Vescovi P, Sesenna E, van der Waal I. Head and neck mucosal melanoma: experience with 42 patients, with emphasis on the role of postoperative radiotherapy. *Head Neck* 2008;**30**:1543–51.
88. Nakashima JP, Viegas CM, Fassizoli AL, et al. Postoperative adjuvant radiation therapy in the treatment of primary head and neck mucosal melanomas. *ORL J Otorhinolaryngol Relat Spec* 2008;**70**:344–51.
89. Owens JM, Roberts DB, Myers JN. The role of postoperative adjuvant radiation therapy in the treatment of mucosal melanomas of the head and neck region. *Arch Otolaryngol Head Neck Surg* 2003;**129**:864–8.
90. Patel SG, Prasad ML, Escrig M, et al. Primary mucosal malignant melanoma of the head and neck. *Head Neck* 2002;**24**:247–57.
91. Shibuya H, Takeda M, Matsumoto S, Hoshina M, Suzuki S, Takagi M. The efficacy of radiation therapy for a malignant melanoma in the mucosa of the upper jaw: an analytic study. *Int J Radiat Oncol Biol Phys* 1993;**25**:35–9.
92. Temam S, Mamelle G, Marandas P, et al. Postoperative radiotherapy for primary mucosal melanoma of the head and neck. *Cancer* 2005;**103**:313–9.
93. Wagner M, Morris CG, Werning JW, Mendenhall WM. Mucosal melanoma of the head and neck. *Am J Clin Oncol* 2008;**31**:43–8.
94. Yii NW, Eisen T, Nicolson M, et al. Mucosal malignant melanoma of the head and neck: the Marsden experience over half a century. *Clin Oncol (R Coll Radiol)* 2003;**15**:199–204.
95. Yanagi T, Mizoe JE, Hasegawa A, et al. Mucosal malignant melanoma of the head and neck treated by carbon ion radiotherapy. *Int J Radiat Oncol Biol Phys* 2009;**74**:15–20.
96. Schulz-Ertner D, Nikoghosyan A, Diding B, et al. Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques. *Cancer* 2005;**104**:338–44.
97. Munter M, Umthum V, Nikoghosyan A, et al. Combination of intensity modulated radiation therapy (IMRT) and a carbon ion boost for subtotal resected or inoperable adenoid cystic carcinomas (ACC's) of the head and neck region. Heidelberg; 2009 [PTCOG 48].
98. Pommier P, Liebsch NJ, Deschler DG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. *Arch Otolaryngol Head Neck Surg* 2006;**132**:1242–9.
99. Agarwal JP, Jain S, Gupta T, et al. Intraoral adenoid cystic carcinoma: prognostic factors and outcome. *Oral Oncol* 2008;**44**:986–93.
100. Avery CM, Moody AB, McKinna FE, Taylor J, Henk JM, Langdon JD. Combined treatment of adenoid cystic carcinoma of the salivary glands. *Int J Oral Maxillofac Surg* 2000;**29**:277–9.

101. Bhattacharyya N, Fried MP. Determinants of survival in parotid gland carcinoma: a population-based study. *Am J Otolaryngol* 2005;**26**:39–44.
102. Da Cruz Perez DE, Pires FR, Lopes MA, de Almeida OP, Kowalski LP. Adenoid cystic carcinoma and mucoepidermoid carcinoma of the maxillary sinus: report of a 44-year experience of 25 cases from a single institution. *J Oral Maxillofac Surg* 2006;**64**:1592–7.
103. Garden AS, Weber RS, Morrison WH, Ang KK, Peters LJ. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 1995;**32**:619–26.
104. Gomez DR, Hoppe BS, Wolden SL, et al. Outcomes and prognostic variables in adenoid cystic carcinoma of the head and neck: a recent experience. *Int J Radiat Oncol Biol Phys* 2008;**70**:1365–72.
105. Gurney TA, Eisele DW, Weinberg V, Shin E, Lee N. Adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation. *Laryngoscope* 2005;**115**:1278–82.
106. Harbo G, Bundgaard T, Pedersen D, Sogaard H, Overgaard J. Prognostic indicators for malignant tumours of the parotid gland. *Clin Otolaryngol Allied Sci* 2002;**27**:512–6.
107. Hosokawa Y, Ohmori K, Kaneko M, et al. Analysis of adenoid cystic carcinoma treated by radiotherapy. *Oral Surg Oral Med Oral Pathol* 1992;**74**:251–5.
108. Hsu HC, Huang EY, Wang CJ. Postoperative adjuvant radiotherapy for adenoid cystic carcinoma of the head and neck: treatment results and prognostic factors. *Chang Gung Med J* 2003;**26**:646–53.
109. Huber PE, Debus J, Latz D, et al. Radiotherapy for advanced adenoid cystic carcinoma: neutrons, photons or mixed beam? *Radiother Oncol* 2001;**59**:161–7.
110. Iseli TA, Karnell LH, Graham SM, et al. Role of radiotherapy in adenoid cystic carcinoma of the head and neck. *J Laryngol Otol* 2009;1–8.
111. Khan AJ, DiGiovanna MP, Ross DA, et al. Adenoid cystic carcinoma: a retrospective clinical review. *Int J Cancer* 2001;**96**:149–58.
112. Kokemueller H, Eckardt A, Brachvogel P, Hausamen JE. Adenoid cystic carcinoma of the head and neck – a 20 years experience. *Int J Oral Maxillofac Surg* 2004;**33**:25–31.
113. Leonetti JP, Marzo SJ, Agarwal N. Adenoid cystic carcinoma of the parotid gland with temporal bone invasion. *Otol Neurotol* 2008;**29**:545–8.
114. Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Hinerman RW, Villaret DB. Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. *Head Neck* 2004;**26**:154–62.
115. Rapidis AD, Givalos N, Gakiopoulou H, et al. Adenoid cystic carcinoma of the head and neck. Clinicopathological analysis of 23 patients and review of the literature. *Oral Oncol* 2005;**41**:328–35.
116. Rhee CS, Won TB, Lee CH, et al. Adenoid cystic carcinoma of the sinonasal tract: treatment results. *Laryngoscope* 2006;**116**:982–6.
117. Silverman DA, Carlson TP, Khuntia D, Bergstrom RT, Saxton J, Esclamado RM. Role for postoperative radiation therapy in adenoid cystic carcinoma of the head and neck. *Laryngoscope* 2004;**114**:1194–9.
118. Spiro RH, Huvos AG. Stage means more than grade in adenoid cystic carcinoma. *Am J Surg* 1992;**164**:623–8.
119. Takagi D, Fukuda S, Furuta Y, et al. Clinical study of adenoid cystic carcinoma of the head and neck. *Auris Nasus Larynx* 2001;**28**(Suppl.):S99–S102.
120. Therkildsen MH, Christensen M, Andersen LJ, Schiodt T, Hansen HS. Salivary gland carcinomas—prognostic factors. *Acta Oncol* 1998;**37**:701–13.
121. Amirul Islam M, Yanagi T, Mizoe JE, Mizuno H, Tsujii H. Comparative study of dose distribution between carbon ion radiotherapy and photon radiotherapy for head and neck tumor. *Radiat Med* 2008;**26**:415–21.
122. Cozzi L, Fogliata A, Lomax A, Bolsi A. A treatment planning comparison of 3D conformal therapy, intensity modulated photon therapy and proton therapy for treatment of advanced head and neck tumours. *Radiother Oncol* 2001;**61**:287–97.
123. Johansson J, Blomquist E, Montelius A, Isacson U, Glimelius B. Potential outcomes of modalities and techniques in radiotherapy for patients with hypopharyngeal carcinoma. *Radiother Oncol* 2004;**72**:129–38.
124. Mock U, Georg D, Bogner J, Auberger T, Potter R. Treatment planning comparison of conventional, 3D conformal, and intensity-modulated photon (IMRT) and proton therapy for paranasal sinus carcinoma. *Int J Radiat Oncol Biol Phys* 2004;**58**:147–54.
125. Steneker M, Lomax A, Schneider U. Intensity modulated photon and proton therapy for the treatment of head and neck tumors. *Radiother Oncol* 2006;**80**:263–7.
126. Taheri-Kadkhoda Z, Bjork-Eriksson T, Nill S, et al. Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons. *Radiat Oncol* 2008;**3**:4.
127. Van de Water T, Lomax A, Bijl H, et al. Comparative treatment planning study between scanned intensity modulated proton therapy and photon therapy in complex oropharyngeal carcinoma. ESTRO. Göteborg; 2008.
128. Widesott L, Pierelli A, Fiorino C, et al. Intensity-modulated proton therapy versus helical tomotherapy in nasopharynx cancer: planning comparison and NTCP evaluation. *Int J Radiat Oncol Biol Phys* 2008;**72**:589–96.
129. Krengli M, Jereczek-Fossa BA, Kaanders JH, Masini L, Beldi D, Orecchia R. What is the role of radiotherapy in the treatment of mucosal melanoma of the head and neck? *Crit Rev Oncol Hematol* 2008;**65**:121–8.
130. Overgaard J. The role of radiotherapy in recurrent and metastatic malignant melanoma: a clinical radiobiological study. *Int J Radiat Oncol Biol Phys* 1986;**12**:867–72.
131. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol* 1999;**28**:1–9.
132. National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. London: NICE; 2008.
133. PTCOG. Statistics of patients treated in hadron therapy centers worldwide; 2009. Available from: http://ptcog.web.psi.ch/patient_statistics.html [accessed 2009].
134. Sayed SI, Elmiyeh B, Rhys-Evans P, et al. Quality of life and outcomes research in head and neck cancer: a review of the state of the discipline and likely future directions. *Cancer Treat Rev* 2009.
135. Goitein M. Trials and tribulations in charged particle radiotherapy. *Radiother Oncol* 2010;**95**:23–31.
136. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1999;**45**:577–87.
137. Roesink JM, Moerland MA, Hoekstra A, Van Rijk PP, Terhaard CH. Scintigraphic assessment of early and late parotid gland function after radiotherapy for head-and-neck cancer: a prospective study of dose-volume response relationships. *Int J Radiat Oncol Biol Phys* 2004;**58**:1451–60.
138. Semenenko VA, Li XA. Lyman–Kutcher–Burman NTCP model parameters for radiation pneumonitis and xerostomia based on combined analysis of published clinical data. *Phys Med Biol* 2008;**53**:737–55.
139. Schilstra C, Meertens H. Calculation of the uncertainty in complication probability for various dose-response models, applied to the parotid gland. *Int J Radiat Oncol Biol Phys* 2001;**50**:147–58.