Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis

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Summary

Background Malignant tumours arising within the nasal cavity and paranasal sinuses are rare and composed of several histological types, rendering controlled clinical trials to establish the best treatment impractical. We undertook a systematic review and meta-analysis to compare the clinical outcomes of patients treated with charged particle therapy with those of individuals receiving photon therapy.

Methods We identified studies of nasal cavity and paranasal sinus tumours through searches of databases including Embase, Medline, Scopus, and the Cochrane Collaboration. We included treatment-naive cohorts (both primary and adjuvant radiation therapy) and those with recurrent disease. Primary outcomes of interest were overall survival, disease-free survival, and locoregional control, at 5 years and at longest follow-up. We used random-effect models to pool outcomes across studies and compared event rates of combined outcomes for charged particle therapy and photon therapy using an interaction test.

Findings 43 cohorts from 41 non-comparative observational studies were included. Median follow-up for the charged particle therapy group was 38 months (range 5–73) and for the photon therapy group was 40 months (14–97). Pooled overall survival was significantly higher at 5 years for charged particle therapy than for photon therapy (relative risk 1·51, 95% CI 1·14–1·99; p=0·0038) and at longest follow-up (1·27, 1·01–1·59; p=0·037). At 5 years, disease-free survival was significantly higher for charged particle therapy than for photon therapy (1·93, 1·36–2·75, p=0·0003) but, at longest follow-up, this event rate did not differ between groups (1·51, 1·00–2·30; p=0·052). Locoregional control did not differ between treatment groups at 5 years (1·06, 0·68–1·67; p=0·79) but it was higher for charged particle therapy than for photon therapy at longest follow-up (1·18, 1·01–1·37; p=0·031). A subgroup analysis comparing proton beam therapy with intensity-modulated radiation therapy showed significantly higher disease-free survival at 5 years (relative risk 1·44, 95% CI 1·01–2·05; p=0·045) and locoregional control at longest follow-up (1·26, 1·05–1·51; p=0·011).

Interpretation Compared with photon therapy, charged particle therapy could be associated with better outcomes for patients with malignant diseases of the nasal cavity and paranasal sinuses. Prospective studies emphasising collection of patient-reported and functional outcomes are strongly encouraged.

Funding Mayo Foundation for Medical Education and Research.

Lancet Oncol 2014

Published Online
June 27, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70268-2

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(14)70290-6

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Introduction

Primary tumours of the nasal cavity and paranasal sinuses are uncommon; their estimated incidence in the USA is 0·556 cases per 100 000 population per year, with a male:female ratio of 1·8:1.[1] About 3–5% of cancers in the upper respiratory and digestive tract are located in the nasal cavity and paranasal sinuses. The most common histological type is squamous-cell carcinoma (51·6%); other findings include adenocarcinoma (12·6%), olfactory neuroblastoma (6·3%; also known as aesthesioneuroblastoma), adenoid cystic carcinoma (6·2%), melanoma (6·6%), and undifferentiated carcinoma (3·1%). In view of the rarity of cancer at this anatomical site, and because of the multiplicity of histological types, no randomised clinical trials have been completed to generate treatment recommendations.

Management of this heterogeneous group of malignant diseases is challenging. These cancers commonly present as locally advanced disease in close proximity to vital healthy structures of the anterior skull base—eg, the brain, brainstem, eyes, cranial nerves, and optic pathways. Although surgery is the mainstay of treatment for early-stage disease that is resectable, a multimodality approach—with use of postoperative radiation therapy—is needed to augment local control of advanced disease with positive or close surgical margins and perineural spread. Radiation therapy is also used as the primary treatment for patients who are not candidates for definitive surgery and for those with unresectable recurrent disease. The dose of radiation therapy that can be administered safely is, again, limited by the proximity of vital healthy tissue.

Treatment outcomes for patients with tumours of the paranasal sinus and nasal cavity have historically been poor. Technological advances in surgery and conformal targeted radiation therapy—eg, intensity-modulated

radiation therapy and charged particle therapy—give us hope that improvements in treatment outcomes could be achieved by escalating the radiation dose to the tumour target volume and lowering the radiation dose to surrounding vital healthy structures.[2] In a review by Dulguerov and colleagues,[3] the proportion of patients with these cancers who survived for 5 years (regardless of type of radiation therapy) increased from 28% in the 1960s to 51% in the 1990s. The unique physical properties of charged particle therapy—with rapid fall-off of dose beyond the Bragg peak (a sharp deposition of dose at a specific depth in tissue)—and its greater relative biological effectiveness compared with photon therapy might further augment treatment outcomes, not only by reducing the incidence and severity of complications but also by allowing an escalation in radiation dose to improve tumour control and survival, which cannot be achieved with photon therapy. In view of the rarity of paranasal sinus and nasal cavity malignant disease, the time and number of institutions needed to complete a clinical trial, and the current cost of charged particle therapy treatment facilities, undertaking a randomised clinical trial to compare outcomes of photon therapy and charged particle therapy is not feasible. Therefore, we did a systematic review and meta-analysis of published work to compare treatment outcomes with charged particle therapy and photon therapy for management of paranasal sinus and nasal cavity malignant diseases.

Methods

Study design

We developed a protocol that defined inclusion criteria, search strategy, outcomes of interest, and analysis plan. The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[4]

Procedures

To identify studies for inclusion in our systematic review and meta-analysis, we did a broad search of six databases, including Embase, Medline, Medline In-Process & Other Non-Indexed Citations, Scopus, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from the date of inception of every database to April, 2014. A skilled librarian developed and implemented the search strategy, with input from study investigators (appendix pp 1–4).

See Online for appendix

To be eligible for inclusion in our systematic review and meta-analysis, study populations (referred to hereafter as cohorts) had to meet all the following criteria: 1) patients with malignant disease of either the paranasal sinuses (ie, frontal, sphenoid, ethmoid, or maxillary) or the nasal cavity; 2) treatment with photon therapy, charged particle therapy, or combined photon therapy and charged particle therapy; 3) reported outcomes of interest (ie, tumour control, survival, and complications); and 4) from an original study (ie, randomised controlled trial, non-randomised clinical trial, observational studies, or case series). We defined charged particle therapy as radiation therapy using beams of protons, carbon ions, helium ions, or other charged particles. Photon therapy included any type of photon therapy, using either two-dimensional (2D), three-dimensional (3D), or intensity-modulated radiation therapy techniques. We classed patients who received both photon therapy and charged particle therapy as a charged particle therapy cohort.

We excluded studies of photon therapy published before 1990 to ensure we included work incorporating modern radiation therapy techniques. We did not limit by time for charged particle therapy studies. We did not restrict our search to language, country, patients' characteristics, or underlying disease status (ie, primary disease, recurrent disease, primary charged particle therapy or photon therapy, or adjuvant charged particle therapy or photon therapy). We included all malignant histological types, except lymphomas. We excluded case reports with fewer than five patients, reviews, notes, letters, errata, commentaries, and studies published only as abstracts.

Independent reviewers, working in pairs, screened the titles and abstracts of potentially relevant studies. We retrieved the full text of relevant studies for further review by the same pair of reviewers. A third senior investigator resolved any discrepancies between reviewers. If reviewers suspected an overlap of cohorts in a report, they contacted the corresponding author for clarification; we excluded studies with a clear overlap. We did a sensitivity analysis, excluding studies that reviewers either were unable to confirm had a population overlap or had

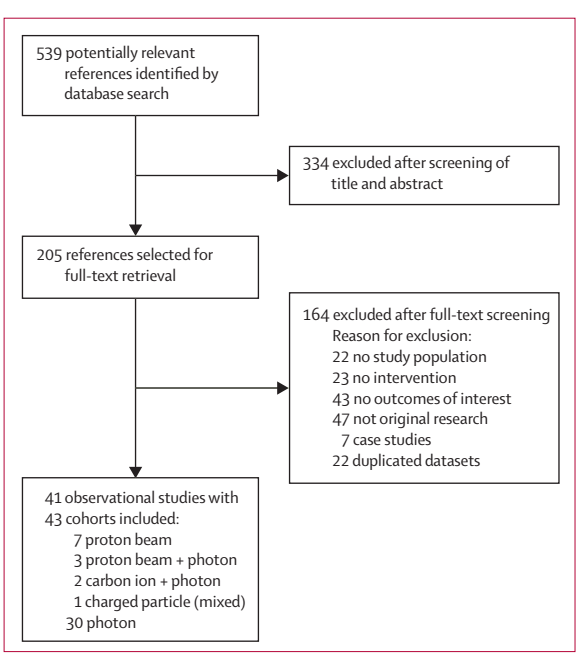

Figure 1: **Trial profile**

judged with a potential slight overlap, to ascertain if our findings would have changed.

The same pair of reviewers extracted study details independently, using a standardised pilot-tested form. A third investigator reviewed all data entries. We extracted the following data: study design, institution and country, study period, inclusion and exclusion criteria, patients' characteristics (sex, age, histological type, and concurrent and previous treatment), interventions (radiation dose, fractionation schedule, duration, surgery, and chemotherapy), sample size, length of follow-up, and outcomes of interest. We defined outcomes of interest as overall survival, disease-free survival, locoregional control, toxic effects, functional status, and quality of life. We assessed survival and recurrence outcomes at both 5 years and the longest duration of complete follow-up. For all other outcomes, we extracted outcomes at the longest follow-up.

	Centre (country)	Study period	Patients (n)*	Radiation (n)	Age (years)	Men (%)	Study inclusion and exclusion criteria	Histological type	Treatment phase
Allen, 2008[14]	MD Anderson (USA)	1969–2000	68	2D/3D CRT (59), brachytherapy (9)	Median 59 (range 19–93)	62%	Inclusion: cancer of nasal cavity or nasal septum Exclusion: skin cancer, tumour of paranasal sinuses, neuroendocrine cancer, melanoma	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma	Treatment-naive
Al-Mamgani, 2012[15]	Erasmus MC, Daniel den Hoed Cancer Center (Netherlands)	1999–2010	82	3D CRT (25), IMRT (57)	Median 62 (range 28–86)	67%	Inclusion: no previous treatment, curative intent Exclusion: nasal vestibule cancers, secondary or recurrent disease, distant metastasis, melanoma, sarcoma, plasmacytoma	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma, mucoepidermoid carcinoma	Treatment-naive
Buiret 2012[16]	Léon Bérard Cancer Center (France)	1985–2009	11	3D CRT, IMRT	Mean 60 (range 42–79)	73%	Inclusion: both inverted papilloma and carcinoma of nasal cavity or paranasal sinus Exclusion: metachronous carcinoma	Squamous-cell carcinoma, adenosquamous carcinoma	Treatment-naive
Castro 1988[17]	University of California, Lawrence Berkeley Laboratory (USA)	1975–85	10	CPT (helium, carbon, neon, and silicon ions)	Unknown	Unknown	Inclusion: malignant disease of the head and neck Exclusion: palliative treatment of recurrent cancer, relative biological effectiveness studies only	Squamous-cell carcinoma, mucosal melanoma, adenoid cystic (and other minor salivary-gland cancers), neuroepithelioma, osteosarcoma	Unknown
Christopherson 2014[18]	University of Florida (USA)	1992–2010	23	Photon therapy (18), photon + proton therapy (5)	Median 56·5 (range 23–83)	61%	Inclusion: sinonasal undifferentiated carcinoma Exclusion: metastatic disease or palliative treatment	Sinonasal undifferentiated carcinoma	Treatment-naive
Combs 2007[19]	University of Heidelberg (Germany)	1999–2004	8	IMRT	Median 45 (range 18–74)	50%	Inclusion: mucosal melanoma, previous surgery, recurrent disease Exclusion: none	Mucosal melanoma	Recurrent
Daly 2007[20]	University of California, San Francisco (USA)	1998–2004	36	IMRT	Median 57 (range 27–84)	47%	Inclusion: malignant disease of paranasal sinus or nasal cavity; Exclusion use of conventional radiation, recurrent disease, inadequate follow-up	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma, olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive
Demizu 2014[21]	Hyogo Ion Beam Medical Center (Japan)	2003–11	62	Proton therapy (33), carbon ion therapy (29)	Median 70 (range 39–86) *vs* 72 (range 33–89)	42% *vs* 45%	Inclusion: head and neck mucosal melanoma Exclusion: distant metastasis	Mucosal melanoma	Treatment-naive
Dirix 2010[22]	University Hospitals Leuven, Gasthuisberg (Belgium)	1992–2008	40	IMRT	Mean 63 (range 37–84)	85%	Inclusion: tumours of the nasal cavity or paranasal sinus, previous surgery Exclusion: none	Squamous-cell carcinoma, adenocarcinoma, olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive
Duprez 2012[23]	Ghent University Hospital (Belgium)	1998–2009	130	IMRT	Median 62 (range 24–80)	82%	Inclusion: sinonasal tumour treated with IMRT Exclusion: distant metastasis	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma, olfactory neuroblastoma (aesthesioneuroblastoma), myoepithelial	87% treatment-naive, 13% recurrent

(Table 1 continues on next page)

	Centre (country)	Study period	Patients (n)*	Radiation (n)	Age (years)	Men (%)	Study inclusion and exclusion criteria	Histological type	Treatment phase
(Continued from previous page)									
Fitzek 2002[24]	Massachusetts General Hospital (USA)	1992–98	19	Proton beam + photon therapy	Median 44 (range 26–67)	74%	Inclusion: olfactory neuroblastoma or neuroendocrine carcinoma Exclusion: distant metastases	Olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive
Fukumitsu 2012[25]	University of Tsukuba (Japan)	2001–07	17	Proton beam	Median 62 (range 30–83)	77%	Inclusion: unresectable nasal cavity or paranasal sinus cancer Exclusion: none	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), undifferentiated, myoepithelial	88% treatment-naive, 12% recurrent
Guan 2013[26]	Fudan University (China)	2004–11	59	Photon therapy	Median 56 (range 19–83)	70%	Inclusion: sinonasal squamous-cell cancer Exclusion: none	Squamous-cell carcinoma	Treatment-naive
Herr 2014[27]	Massachusetts General Hospital (USA)	1997–2013	22	Proton beam	Median 46 (range 11–77)	50%	Inclusion: olfactory neuroblastoma (aesthesioneuroblastoma) Exclusion: none	Olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive
Hinerman 2011[28]	University of Florida (USA)	1969–2006	54	2D radiation therapy (51), 3D CRT (2), IMRT (1)	Median 62 (range 36–79)	63%	Inclusion: squamous-cell carcinoma of the maxilla Exclusion: non-squamous-cell carcinoma, non-maxilla cancer	Squamous-cell carcinoma	94% treatment-naive, 6% recurrent
Homma 2009[29]	Hokkaido University (Japan)	1999–2006	47	3D CRT	Median 56 (range 25–73)	77%	Inclusion: age <75 years, performance status 0–2, T3 or T4 disease Exclusion: none	Squamous-cell carcinoma, adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma	Treatment-naive
Hoppe 2008[30]	Memorial Sloan Kettering Cancer Center (USA)	1990–2006	39	Conventional radiation therapy (9), 3D CRT (18), IMRT (12)	Median 59 (range 28–82)	51%	Inclusion: unresectable carcinoma Exclusion: melanoma, sarcoma, lymphoma, rhabdomyosarcoma, olfactory neuroblastoma (aesthesioneuroblastoma), plasmacytoma, metastatic disease, non-invasive disease	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), neuroendocrine	Treatment-naive
Hoppe 2008[31]	Memorial Sloan Kettering Cancer Center (USA)	2000–06	36	IMRT	Unknown	Unknown	Inclusion: disease close to optic pathway and had surgery Exclusion: previous radiation therapy, melanoma, radiation treatment at another facility	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma, olfactory neuroblastoma (aesthesioneuroblastoma), sarcoma	Treatment-naive
Jang 2010[32]	Seoul National University (South Korea)	1990–2007	42	2D radiation therapy (32), 3D CRT (9), IMRT(1)	Median 60 (range 21–81)	86%	Inclusion: unresectable disease Exclusion: none	Squamous-cell carcinoma	Treatment-naive
Jensen 2011[33]	Heidelberg Ion Therapy Centre (Germany)	2009–10	29	Carbon ion therapy + IMRT (25), carbon ion therapy (4)	Median 57 (range 20–77)	Unknown	Inclusion: malignant tumours of the paranasal sinuses and nasal cavity Exclusion: none	Adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma, malignant melanoma, chordoma, chondrosarcoma, osteosarcoma, ameloblastic carcinoma, malignant peripheral-nerve-sheath tumour	69% treatment-naive, 31% recurrent
Jimbo 2010[34]	Mita Hospital (Japan)	NR	19	2D radiation therapy (2), 3D CRT (14), IMRT (3)	Mean 64 (range 39–77)	79%	Inclusion: sinus or skull-base malignant disease Exclusion: none	Squamous-cell carcinoma, salivary-duct carcinoma, chondrosarcoma	Treatment-naive
Kaur 2013[35]	University of California, San Francisco (USA)	1995–2009	11	IMRT (6), EBRT (5)	Median 49·2 (range 31–63)	82%	Inclusion: Kadish stage C olfactory neuroblastoma (aesthesioneuroblastoma) Exclusion: none	Olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive
Luo 2011[36]	Xijing Hospital (China)	2006–08	84	Photon therapy	Median 48 (range 17–72)	60%	Inclusion: T3 and T4 with locally advanced nasal cavity and paranasal sinus carcinoma Exclusion: none	Squamous-cell carcinoma, adenocarcinoma	Treatment-naive
McLean 2007[37]	Emory University (USA)	1991–2006	21	IMRT	Unknown	Unknown	Inclusion: olfactory neuroblastoma Exclusion: none	Olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive

(Table 1 continues on next page)

	Centre (country)	Study period	Patients (n)*	Radiation (n)	Age (years)	Men (%)	Study inclusion and exclusion criteria	Histological type	Treatment phase
(Continued from previous page)									
Mendenhall 2009[38]	University of Florida (USA)	1964–2005	109	EBRT (107), EBRT + brachytherapy (2)	Unknown	60%	Inclusion: no previous treatment, nasal cavity or paranasal sinus cancer Exclusion: maxillary sinus cancers	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma, olfactory neuroblastoma (aesthesioneuroblastoma), carcinoma not otherwise specified, mucoepidermoid carcinoma, miscellaneous minor salivary-gland cancer, transitional-cell carcinoma	Treatment-naive
Moreno 2010[39]	MD Anderson (USA)	1993–2004	33	3D CRT (25), IMRT (3), three-field radiation therapy (5)	Unknown	Unknown	Inclusion: sinonasal mucosal melanoma Exclusion: none	Mucosal melanoma	Treatment-naive
Okano 2012[40]	National Cancer Center Hospital East, Chiba (Japan)	2006–12	13	Proton beam	Median 47 (range 28–60)	69%	Inclusion: T4b N0 nasal cavity or sinonasal cancers Exclusion: none	Squamous-cell carcinoma, adenocarcinoma, sinonasal undifferentiated carcinoma, olfactory neuroblastoma (aesthesioneuroblastoma), small-cell carcinoma	Treatment-naive
Rajapurkar 2013[41]	Amrita Institute of Medical Sciences (India)	2004–09	14	IMRT, 3D CRT	Median 51 (range 32–85)	60%	Inclusion: sinonasal tumours with orbital involvement Exclusion: orbital exenteration and benign tumours	Squamous-cell carcinoma	Treatment-naive
Slevin 1996[42]	Christie Hospital (UK)	1984–93	9	Photon therapy	Mean 66 (range 46–84)	22%	Inclusion: olfactory neuroblastoma Exclusion: none	Olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive
Takeda 1999[43]	Keio University Hospital (Japan)	1982–96	25	2D radiation therapy, 3D CRT	Median 62 (range 31–67)	72%	Inclusion: nasal or paranasal sinus tumours with the eye in the treatment field Exclusion: none	Squamous-cell carcinoma, adenoid cystic (and other minor salivary-gland cancers)	Treatment-naive
Thariat 2011[44]	University of Nice Sophia Antipolis (France)	1991–2006	25	2D radiation therapy, 3D CRT	Median 73 (range 45–91)	24%	Inclusion: sinonasal melanoma Exclusion: none	Mucosal melanoma	Treatment-naive
Truong 2008[45]	Massachusetts General Hospital (USA)	1991–2005	20	Proton beam	Median 53 (range 17–78)	50%	Inclusion: locally advanced primary sphenoid sinus malignant disease Exclusion: none	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers)	Treatment-naive
Uchida 2005[46]	Hokkaido University (Japan)	1976–2002	25	IMRT	Median 58 (range 35–78)	56%	Inclusion: squamous-cell carcinoma and undifferentiated carcinoma of the ethmoid sinus Exclusion: none	Squamous-cell carcinoma, undifferentiated	Treatment-naive
Van der Laan 2013[47]	University Medical Center, Groningen (Netherlands)	1980–2010	12	IMRT, 3D CRT, 2D radiation therapy	Median 69 (range 54–87)	67%	Inclusion: Sinonasal cancer with neuroendocrine differentiation Exclusion: none	Sinonasal undifferentiated carcinoma, sinonasal neuroendocrine carcinoma, and small-cell neuroendocrine carcinoma	Treatment-naive
Van Gerven 2011[48]	University Hospitals Leuven (Belgium)	1992–2004	44	3D CRT (31), IMRT (8); did not complete RT (5)	Mean 62	98%	Inclusion: candidates for endoscopic resection Exclusion: none	Adenocarcinoma	Treatment-naive
Weber 2006[49]	Massachusetts General Hospital (USA)	1991–2001	36	Proton beam + photon therapy	Median 54 (range 24–76)	56%	Inclusion: squamous-cell carcinoma, adenoid cystic carcinoma, olfactory neuroblastoma (aesthesioneuroblastoma), primitive neuroectodermal tumour, or sarcoma subtypes Exclusion: advanced stage (T3–4/N0–1, Kadish B–C) or recurrent nasal cavity and paranasal sinus tumours	Squamous-cell carcinoma, adenoid cystic (and other minor salivary-gland cancers), olfactory neuroblastoma (aesthesioneuroblastoma), primitive neuroectodermal tumour, or sarcoma	92% treatment-naive, 8% recurrent

(Table 1 continues on next page)

	Centre (country)	Study period	Patients (n)*	Radiation (n)	Age (years)	Men (%)	Study inclusion and exclusion criteria	Histological type	Treatment phase
(Continued from previous page)									
Wiegner 2012[50]	Stanford University (USA)	2000–09	52	IMRT	Median 63 (range 11–87)	47%	Inclusion: nasal cavity and paranasal sinus cancer Exclusion: rhabdomyosarcoma, radiation-induced sarcomas, non-Hodgkin lymphoma, mucosal melanoma, chondrosarcoma, Langerhans cell histiocytosis, benign inverted papilloma, and benign inflammatory myofibroblastic process	Squamous-cell carcinoma, adenocarcinoma, adenoid cystic (and other minor salivary-gland cancers), sinonasal undifferentiated carcinoma, olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive
Wu 2010[51]	Memorial Sloan Kettering Cancer Center (USA)	1992–2007	24†	Conventional radiation therapy (10), 3D CRT (4), IMRT (13)†	Unknown	Unknown	Inclusion: localised mucosal melanoma of the head and neck Exclusion: none	Mucosal melanoma	Treatment-naive
Yoshida 2013[52]	University of California, Davis (USA)	1999–2009	10	Chemo-radiotherapy	Unknown	Unknown	Inclusion: sinonasal undifferentiated carcinoma Exclusion: none	Sinonasal undifferentiated carcinoma	Treatment-naive
Zenda 2011[53]	National Cancer Center Hospital East, Chiba (Japan)	2004–07	14	Proton beam	Median 73 (range 56–79)	50%	Inclusion: N0M0 clinical status, performance status of 2 or less, adequate organ function, and no active concomitant malignant disease Exclusion: none	Mucosal melanoma	Treatment-naive
Zenda 2011[54]	National Cancer Center Hospital East, Chiba (Japan)	1999–2006	39	Proton beam	Median 57 (range 22–84)	56%	Inclusion: unresectable malignant tumours of the nasal cavity, paranasal sinuses, or skull base, no lymph-node metastases or distant metastases Exclusion: none	Squamous-cell carcinoma, mucosal melanoma, adenoid cystic (and other minor salivary-gland cancers), olfactory neuroblastoma (aesthesioneuroblastoma)	Treatment-naive

Outcome data for every study are presented in the appendix (pp 5–6). 2D=two-dimensional. 3D=three-dimensional. CPT=charged particle therapy. CRT=conformal radiation therapy. EBRT=external-beam radiation therapy. IMRT=intensity-modulated radiation therapy. NR=not reported. RT=radiation therapy. *Number of patients included in our analysis. †Numbers differ because we excluded three patients from our analysis who did not meet our inclusion criteria; it is not clear which radiation technique was used for those three patients.

Table 1: **Characteristics of included studies**

To assess quality, since we included non-comparative (uncontrolled) studies in our systematic review and meta-analysis, we used the Newcastle-Ottawa quality assessment scale.[5] We selected items that focused on representativeness of study patients, demonstration that the outcome of interest was not present at the start of the study, adequate assessment of outcome, sufficient length of follow-up to allow outcomes to arise, adequacy of follow-up (loss due to treatment), and source of study funding.

Statistical analysis

We prespecified the analysis plan in the protocol. We analysed all patients who started photon therapy or charged particle therapy, regardless of their adherence to treatment. We calculated event rates of outcome (the proportion of patients who developed outcomes of interest) from the included cohorts for both charged particle therapy and photon therapy, and we estimated 95% CIs with the Jeffreys method.[6] We pooled log-transformed event rates with DerSimonian and Laird random-effect models and assessed heterogeneity using the Mantel-Haenszel test.[7] We used the test of interaction proposed by Altman and Bland to compare log-transformed rates of outcomes between charged particle therapy and photon therapy.[8] When the difference between treatments was significant, we calculated the number needed to treat (NNT) from the absolute difference of the pooled estimates between the two groups.

We did an ad-hoc subgroup analysis to compare primary outcomes for proton beam therapy with those for intensity-modulated radiation therapy. We also undertook planned subgroup analyses of treatment history and grades of toxic effect. We could not do prespecified analyses for histological type, use of chemotherapy, and tumour stage because data from the included cohorts were limited.

We created multivariable random-effects meta-regression models to compare outcomes between charged particle therapy and photon therapy, by adjusting for tumour stage among treatment-naive patients. We calculated p values with Monte Carlo permutation tests.[9] We judged two-sided p less than 0·05 significant. To account for the potential effect of publication bias, we used the Duval and Tweedie non-parametric trim-and-fill method.[10,11] To measure overall heterogeneity across the included cohorts, we calculated the I^2 statistic, with I^2 greater than 50% indicating high heterogeneity.[12] We assessed potential publication bias by visual inspection of the symmetry of funnel plots and with the Egger regression asymmetry

test.[13] We did all statistical analyses with Stata version 12.1 (StataCorp, College Station, TX, USA).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all raw data and the corresponding author had final responsibility for the decision to submit for publication.

Results

539 studies were identified from the database search, of which 205 reports were retrieved for full-text evaluation. 41 non-comparative observational studies met the inclusion criteria and were included in this systematic review (figure 1). We did not find randomised controlled trials or controlled studies that compared charged particle therapy with photon therapy directly. Table 1 shows the characteristics of the included studies.

From the 41 studies, 43 cohorts were identified. 30 cohorts were treated with photon therapy (1186 patients) whereas 13 received charged particle therapy (286 patients; table 2). Overall, 1472 patients were included, with a mean age of 57·7 years (range 44–73) for the charged particle therapy group and 59·2 years (45–73) for the photon therapy group. Sex, advanced disease (stage IV or Kadish stage C), histological type, radiation dose, or median duration of follow-up did not differ between groups. Loss to follow-up was not reported adequately for the included cohorts; when these numbers were reported, loss to follow-up was 2·7–6·8%.

Methodological quality of the included studies was fair; most studies provided adequate outcome ascertainment, enrolled a representative sample of patients, and had an acceptable length of follow-up (figure 2). However, comparative evidence was at high risk of bias because we compared data across studies not within them, and selection bias was likely to be present. Assessment of publication bias was not done because data would be unreliable in view of the few studies included for each treatment group and high heterogeneity (I^2 >50%) in most analyses.[55]

Survival and recurrence outcomes reported in the included studies are listed in the appendix (pp 5–6). The pooled event rate of overall survival for charged particle therapy was significantly higher than that for photon therapy at the longest duration of follow-up (relative risk 1·27, 95% CI 1·01–1·59; p=0·037) and at 5 years (1·51, 1·14–1·99; p=0·0038; table 3). Locoregional control was also significantly better at the longest duration of follow-up for patients treated with charged particle therapy than for those receiving photon therapy (1·18, 1·01–1·37; p=0·031), but not at 5 years (1·06, 0·68–1·67; p=0·79). The pooled 5-year disease-free survival event rate was significantly higher for charged particle therapy than for photon therapy (1·93, 1·36–2·75; p=0·0003), but not at longest follow-up (1·51, 1·00–2·30; p=0·052).

37 cohorts included treatment-naive patients (either exclusively or forming around 90% of the cohort; table 1). In ten of these cohorts, charged particle therapy was administered; the remaining 27 cohorts received photon therapy. One cohort receiving photon therapy consisted of patients with recurrent disease only; none of the cohorts receiving charged particle therapy included only individuals with recurrent disease. For treatment-naive patients, charged particle therapy was associated with significantly higher overall survival and locoregional control than with photon therapy, at 5 years and at longest duration of follow-up (appendix p 7); 5-year disease-free survival was also significantly higher for charged particle therapy in this group of patients. We could not do a subgroup analysis for recurrent patients because data were insufficient.

Table 4 shows the comparison of primary outcomes for cohorts receiving proton beam therapy versus those given intensity-modulated radiation therapy. Disease-free survival at 5 years and locoregional control at longest follow-up were significantly higher in the proton beam therapy group. However, no other difference was noted

	Charged particle therapy	Photon therapy	p
Cohorts (n)	13	30	..
Patients (n)	286	1186	..
Treatment-naive patients (%)	80%	85%	0·10
Age (years)	57·7 (range 44–73)	59·2 (range 45–73)	0·61
Men (%)	57%	64%	0·28
Patients with advanced tumour (%)*	63%	57%	0·55
Patients with high-risk histological type (%)†	27%	50%	0·06
Median (range [IQR]) radiation dose (GyE)‡	60·1 (48–69 [55–67])	61·4 (31–70 [60–67])	0·66
Median (range [IQR]) follow-up (months)	38 (5–73 [23–55])	40 (14–97 [28–52])	0·72

RBE=relative biological effectiveness. *Included stage IV or Kadish stage C. †Included squamous-cell carcinoma, sinonasal undifferentiated carcinoma, and poorly differentiated or undifferentiated. ‡GyE=RBE×Gy; RBE of proton beam is 1·1; RBE of carbon ion is 3.

Table 2: **Baseline characteristics of charged particle therapy cohorts and photon therapy cohorts**

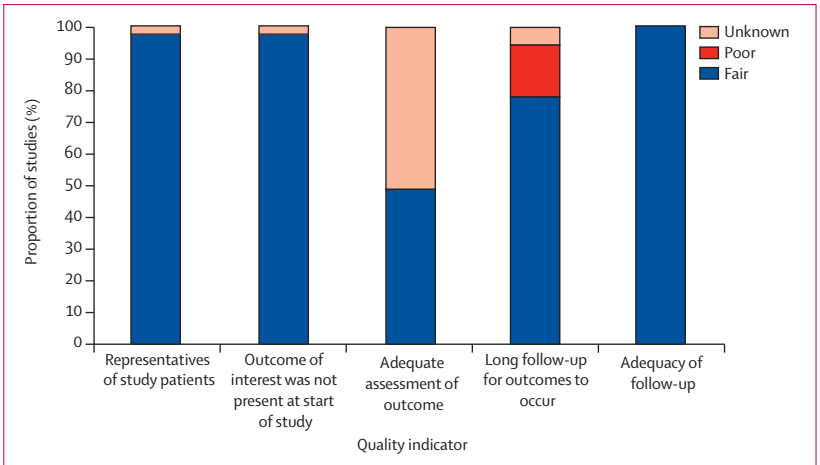

Figure 2: **Selected methodological quality indicator**

	Cohorts (n)	Patients (n)	Event rate (95% CI)	I^2	Relative risk (95% CI)	p	NNT* (95% CI)
Overall survival†							
CPT	10	242	0·66 (0·56–0·79)	77·5%	1·27 (1·01–1·59)	0·037	7·09 (3·57–480·55)
Photon therapy	26	1120	0·52 (0·46–0·60)	86·0%	..	..	..
5-year overall survival							
CPT	6	146	0·72 (0·58–0·90)	80·1%	1·51 (1·14–1·99)	0·0038	4·12 (2·37–15·60)
Photon therapy	15	779	0·48 (0·40–0·57)	84·1%	..	..	..
Disease-free survival†							
CPT	3	78	0·67 (0·48–0·95)	79·4%	1·51 (1·00–2·30)	0·052	..
Photon therapy	8	411	0·44 (0·35–0·56)	76·5%	..	..	..
5-year disease-free survival							
CPT	2	58	0·80 (0·67–0·95)	41·6%	1·93 (1·36–2·75)	0·0003	2·60 (1·74–5·15)
Photon therapy	6	341	0·41 (0·30–0·56)	80·9%	..	..	..
Locoregional control†							
CPT	10	208	0·76 (0·68–0·86)	54·0%	1·18 (1·01–1·37)	0·031	8·55 (4·40–143·44)
Photon therapy	14	736	0·65 (0·59–0·71)	60·3%	..	..	..
5-year locoregional control							
CPT	3	58	0·66 (0·43–1·02)	81·2%	1·06 (0·68–1·67)	0·79	..
Photon therapy	8	546	0·62 (0·55–0·71)	73·0%	..	..	..

I^2≥50% suggests high heterogeneity across studies. CPT=charged particle therapy. NNT=number needed to treat. *Calculated when the difference between CPT and photon therapy was significant. †At longest duration of complete follow-up.

Table 3: **Comparison of primary outcomes for charged particle therapy cohorts and photon therapy cohorts**

	Cohorts (n)	Patients (n)	Event rate (95% CI)	I^2	Relative risk (95% CI)	p
Overall survival*						
PBT	8	191	0·63 (0·53–0·76)	59·3%	1·02 (0·77–1·35)	0·89
IMRT	8	348	0·62 (0·50–0·77)	86·9%	..	..
5-year overall survival						
PBT	5	124	0·66 (0·52–0·85)	69·7%	1·39 (0·99–1·94)	0·057
IMRT	4	212	0·48 (0·38–0·60)	45·1%	..	..
Disease-free survival*						
PBT	2	56	0·49 (0·21–1·16)	83·6%	0·98 (0·40–2·42)	0·97
IMRT	3	187	0·50 (0·38–0·67)	69·3%	..	..
5-year disease-free survival						
PBT	1	36	0·72 (0·59–0·89)	..	1·44 (1·01–2·05)	0·045
IMRT	3	187	0·50 (0·38–0·67)	69·3%	..	..
Locoregional control*						
PBT	7	147	0·81 (0·71–0·92)	55·2%	1·26 (1·05–1·51)	0·011
IMRT	4	258	0·64 (0·57–0·72)	33·7%	..	..
5-year locoregional control						
PBT	2	36	0·43 (0·09–2·10)	89·5%	0·73 (0·15–3·58)	0·70
IMRT	2	166	0·59 (0·52–0·67)	0·0%	..	..

I^2 ≥50% suggests high heterogeneity across studies. IMRT=intensity-modulated radiation therapy. PBT=proton beam therapy. *At longest duration of complete follow-up.

Table 4: **Comparison of primary outcomes for proton beam therapy cohorts and intensity-modulated radiation therapy cohorts**

between proton beam therapy and intensity-modulated radiation therapy.

For treatment-naive patients, the multivariable meta-regression models—adjusted for advanced tumours (stage IV and Kadish stage C)—showed that charged particle therapy was associated with a significant increase in overall survival (relative risk 1·41, 95% CI 1·00–1·98; p=0·047) and disease-free survival (1·53, 1·08–2·17; p=0·034) compared with photon therapy, but no difference was recorded for locoregional control (1·21, 0·97–1·52; p=0·059; appendix p 8). The trim-and-fill method was used to adjust for potential publication bias, but findings were similar (data not shown).

	Event rate (95% CI)	I^2	p
Eye			
CPT	0·19 (0·08–0·45)	85·3%	0·12
Photon therapy	0·43 (0·24–0·75)	97·3%	..
Head and neck			
CPT	0·54 (0·24–1·24)	96·5%	0·30
Photon therapy	0·87 (0·62–1·22)	95·6%	..
Nasal			
CPT	0·07 (0·01–0·55)	52·7%	0·66
Photon therapy	0·12 (0·04–0·37)	76·6%	..
Ear			
CPT	0·20 (0·09–0·47)	34·7%	0·56
Photon therapy	0·14 (0·06–0·32)	82·9%	..
Neurological			
CPT	0·20 (0·13–0·31)	0·0%	0·0002
Photon therapy	0·04 (0·02–0·08)	0·0%	..
Miscellaneous			
CPT	0·41 (0·17–1·02)	70·5%	0·78
Photon therapy	0·49 (0·24–1·00)	93·4%	..
Haematological			
CPT	2·31 (1·59–3·36)	..	0·40
Photon therapy	1·92 (1·55–2·37)	..	..

I^2 ≥50% suggests high heterogeneity across studies. Toxic effect group definitions are listed in the appendix (p 10). The difference between treatment event rates was not calculated because of under-reporting of toxic effects in the included studies. CPT=charged particle therapy.

Table 5: **Comparison of toxic effect event rates for charged particle therapy and photon therapy**

A potential overlap of patients with other cohorts was identified in three studies.[18,46,48] All analyses were repeated, excluding these studies, and similar results were shown (appendix p 9).

Table 5 shows the overall (acute and late) occurrence of toxic effects with charged particle therapy versus photon therapy. There were significantly more neurological toxic effects in the charged particle therapy group than in the photon therapy group (p=0·0002). However, the two groups did not differ with respect to other types of toxic effect. Reported toxic effects by type are presented in the appendix (p 10). Data for functional status and quality of life were not reported in any study.

Discussion

The findings of our systematic review and meta-analysis suggest that the theoretical advantages of charged particle therapy might in fact be real. We noted better locoregional control, disease-free survival, and overall survival in all patients (treatment-naive and those with recurrent disease) who were treated with charged particle therapy, compared with those receiving photon therapy, at either 5 years or at longest duration of treatment, or both periods. A non-significant improvement in disease-free survival was seen at longest duration of follow up, which was probably attributable to the scarcity of studies that assessed and reported this endpoint (three cohorts for charged particle therapy and eight cohorts for photon therapy).

Our analysis contains the highest quality data available comparing photon therapy with charged particle therapy for tumours of the nasal cavity and paranasal sinuses. Most patients presented with advanced disease, and at least a third presented with highly aggressive histological types. Use of photon therapy in treatment-naive patients resulted in 5-year overall survival of 47%, disease-free survival of 41%, and locoregional control of disease in 64% (appendix p 7), with treatment-related toxic effects ranging from 4% to 87% depending on the organ at risk (table 5). These findings indicate that prognosis is relatively poor in this group of patients treated with photon therapy, and safer and more effective treatment is needed.

Local tumour persistence or recurrence is the most common type of treatment failure. Most local recurrences either are within the prescribed dose radiation treatment volume or straddle the margin of this volume.[56] Most marginal and out-of-field local tumour recurrences either are located at the level of the eyes or are more superior (affecting the brain), showing the difficulty of obtaining negative surgical margins and adequate radiation dose in this region when attempting to protect the optic structures, brain, and brainstem.[56]

Charged particle therapy with protons, helium ions, carbon ions, or neon ions has several theoretical advantages compared with photon therapy. First, the physical advantage of the rapid dose fall-off beyond the Bragg peak should allow for more conformal treatment with better targeted dose coverage of the tumour. This improvement allows for dose escalation, resulting in augmented tumour control and prolonged survival, with a lower incidence and severity of toxic effects because the dose delivered to adjacent organs is diminished. Second, the higher relative biological effectiveness of charged particle therapy could result in improved locoregional tumour control and survival. Third, toxic effects did not differ between treatment groups, probably because of the physical advantage of improved organ sparing with charged particle therapy. The higher rate of neurological toxic effects reported in the charged particle therapy group could be accounted for by reporting bias: a significantly higher proportion of studies of charged particle therapy reported toxic effects, compared with photon therapy studies (92% *vs* 57%; p=0·03). Another contributing factor could be referral bias, whereby a greater proportion of anatomically challenging cases are referred to charged particle therapy institutions. Furthermore, the greater relative biological effectiveness of charged particle therapy and higher physical dose could contribute to this difference.

Owing to the heterogeneity of reported data (eg, studies with both definitive and adjuvant patients, and those with combined photon therapy and charged particle therapy), a dose comparison between photon therapy and charged particle therapy in the definitive and adjuvant

setting was not possible. Moreover, a minor portion of the photon series included 2D techniques, which would not be judged acceptable by modern standards. Therefore, we did a subgroup analysis of proton beam therapy versus intensity-modulated radiation therapy, the findings of which indicated a benefit of proton beam therapy with respect to locoregional tumour control and 5-year disease-free survival; a slight increase in 5-year overall survival was also seen. Heterogeneity of data, and few cohorts receiving only proton beam therapy and only intensity-modulated radiation therapy, makes such a comparison difficult.

Our findings could have been confounded by selection bias. The proportion of patients with high-risk histological types treated with charged particle therapy was lower than with photon therapy, which could account for the increase in tumour control and survival recorded in the charged particle therapy group. On the other hand, more patients treated with charged particle therapy had advanced disease. We did not compare outcomes within studies, only across them, which raises concerns about possible confounding and absence of prognostic balance between charged particle therapy and photon therapy groups. Patients with more locally advanced inoperable disease might have been more likely to be selected for charged particle therapy. Furthermore, sampling bias attributable to the few institutions in the charged particle therapy group might affect our findings: most patients receiving charged particle therapy were treated at three institutions (appendix p 11). Also, in our analysis, we could not adjust for variation between institutions, potentially limiting our findings. Another bias that must be considered is treatment indication preference: various factors can affect a patient's selection for charged particle therapy. Gaining access to individual patients' data might alleviate such biases.

Technological advances in the delivery of photon beams account for the progression from conventional 2D treatment to state-of-the-art intensity-modulated radiation therapy. We should keep in mind that the charged particle therapy group represents not only heterogeneous charged particles (eg, carbon ion, proton) but also heterogeneous delivery techniques. In the case of proton beam therapy, technological advances have been made that include moving from passive scattering to use of an active scanning beam; very few institutions use an active scanning beam to deliver intensity-modulated proton therapy.

Our study highlights the need for continued comprehensive reporting of outcomes from the growing number of institutions delivering charged particle therapy. Future studies of charged particle therapy should be designed to gather more detailed outcomes (clinician-reported and patient-reported), particularly in terms of late effects, quality of life, function, and cost. Sinonasal cancer patients have a substantial amount of physical, functional, and psychosocial detriments attributable to the disease and the side effects of treatment.[57] Measurement of quality-of-life outcomes is paramount to allow for assessment of treatment options.[58] As more patients are treated with charged particle therapy with prospective collection of outcomes, we might be able to ascertain if one charged particle provides better outcomes than another. Heavier charged particles have a sharper lateral beam penumbra and greater relative biological effectiveness, which might reduce complications further and increase tumour control and survival. Undertaking randomised trials in patients with tumours of the nasal cavity and paranasal sinuses is challenging because of the rarity of this set of malignant diseases and the diminished likelihood of future clinical trial support. International collaboration is necessary to implement a prospective trial that can define the best treatment for these diseases. High-quality patient registries, with independent and prospective enrolment and rigorous collection of prognostic variables, are another possibility and should be encouraged.

Comparing clinical outcomes recorded in charged particle therapy studies with those reported in photon therapy studies suggests that charged particle therapy might be associated with better outcomes for malignant diseases of the nasal cavity and paranasal sinuses. The growing number of institutions providing charged particle therapy are encouraged to collaborate and report their outcomes.

Contributors

SHP and ZW contributed equally to this study. SHP helped to design the study; contributed to collection, analysis, and interpretation of data; and wrote the report. ZW helped to design the study; did the literature search; contributed to collection, analysis, and interpretation of data; and wrote the report. WWW, SES, and RLF helped to design the study and contributed to collection and interpretation of data. MHM helped to design the study and contributed to analysis and interpretation of data. CRB contributed to collection and interpretation of data. KM did the literature search and contributed to collection and analysis of data. FA, OA, and MN did the literature search and contributed to collection and analysis of data.

Declaration of interests

SES received a grant from the Alliance cooperative research group for travel-related expenses as vice chair of the respiratory committee. All other authors declare no competing interests.

Acknowledgments

This study was funded by the Mayo Foundation for Medical Education and Research.

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