Received: 5 July 2020 | Revised: 27 August 2020 | Accepted: 2 September 2020

DOI: 10.1111/cas.14650

ORIGINAL ARTICLE

Cancer Science WILEY

Carbon ion radiation therapy for sinonasal malignancies: Promising results from 2282 cases from the real world

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Funding information
Program of Shanghai Academic/Technology Research Leader, Grant/Award Number: 18XD1423000; Science and Technology Commission of Shanghai Municipality, Grant/Award Number: 19411951000; National Key Research and Development Program of China, Grant/Award Number: 2018YFC0115700

Abstract

The aim of this study is to compare the effectiveness of carbon ion radiation therapy (CIRT), proton radiation therapy (PRT), and photon-based intensity-modulated radiation therapy (IMRT) in the treatment of sinonasal malignancies. We identified studies through systematic review and divided them into three cohorts (CIRT group/PRT group/IMRT group). Primary outcomes of interest were overall survival (OS) and local control (LC). We pooled the outcomes with meta-analysis and compared the survival difference among groups using Chi^2 (χ^2) test. A representative sample of 2282 patients with sinonasal malignancies (911 in the CIRT group, 599 in the PRT group, and 772 in the IMRT group) from 44 observation studies (7 CIRT, 16 PRT, and 21 IMRT) was included. The pooled 3-year OS, LC, distant metastasis–free survival, and progression-free survival rates were 67.0%, 72.8%, 69.4%, and 52.8%, respectively. Through cross-group analysis, the OS was significantly higher after CIRT (75.1%, 95% CI: 67.1%-83.2%) than PRT (66.2%, 95% CI: 57.7%-74.6%; $\chi^2 = 13.374$, $P < .0001$) or IMRT (63.8%, 95% CI: 55.3%-72.3%; $\chi^2 = 23.814$, $P < .0001$). LC was significantly higher after CIRT (80.2%, 95% CI: 73.9%-86.5%) than PRT (72.9%, 95% CI: 63.7%-82.0%; $\chi^2 = 8.955$, $P = .003$) or IMRT (67.8%, 95% CI: 59.4%-76.2%; $\chi^2 = 30.955$, $P < .0001$). However, no significant difference between PRT and IMRT for OS and LC was observed. CIRT appeared to provide better OS and LC for patients with malignancies of nasal cavity and paranasal sinuses. A prospective randomized clinical trial is needed to confirm the superiority of CIRT in the treatment of sinonasal tumors.

KEYWORDS

carbon ion radiation therapy, intensity-modulated radiation therapy, meta-analysis, proton radiation therapy, sinonasal malignancy, survival

1 | INTRODUCTION

Primary tumors originating from the nasal cavity and paranasal sinuses are rare but represent a heterogeneous group of histologies with substantially diverse biological behaviors. In total, sinonasal malignances (SNM) account for approximately 3%-5% of cancers in the head and neck region.[1] Due to the inconspicuous anatomic location, SNM are usually asymptomatic at early stages and diagnosed

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with extensive direct invasion to adjacent vital organs at risk (OARs). Surgery with negative margin is usually not feasible except for a minority of patients with early T-disease, and a multimodality strategy with surgery and radiotherapy with or without chemotherapy is often needed to achieve long-term local control (LC) for locally advanced SNM. Radiotherapy is also the mainstay treatment for unresectable and inoperable diseases. Nevertheless, like in surgery, radiation dose is also limited by the presence of critical OARs adjacent to or tethered with the tumor. As such, treatment outcomes historically reported in the literature for unresected SNM have been suboptimal.

The prevailing use of three-dimensional conformal radiotherapy (3D-CRT) has shed light to patients with SNM. The 5-year overall survival (OS) rate improved from less than 30% in the two-dimensional radiotherapy (2DRT) era to 50%-60% with the use of 3D-CRT.[2-4] Nevertheless, whether the more advanced intensity-modulated radiotherapy (IMRT) could further improve OS is controversial, although it significantly reduces radiation-induced toxicities.[3,5-7]

The unique physical properties of accelerated charged particle (such as proton and carbon ion) beams including small lateral scattering and a dose-focusing Bragg peak followed by a rapid fall-off thereby promise a more conformal dose distribution than photon-based IMRT.[8,9] The higher linear energy transfer (LET) and greater relative biological effectiveness (RBE) of carbon ion as compared with photon or proton may further improve disease control and OS especially for radio-resistant histologies such as mucosal melanoma (MM), sarcoma, and adenoid cystic carcinoma (ACC). In 2014, a meta-analysis[10] that included a few observational studies using proton therapy (10 studies with 218 patients) or heavy-ion radiotherapy (3 studies with 68 patients) revealed that charged-particle therapy significantly improved the 5-year and/or long-term OS, disease-free survival (DFS), and potentially LC rates as compared with photon radiotherapy (30 studies including IMRT, 3D-CRT, 2DRT, or brachytherapy in 1186 patients). However, there were not enough carbon ion studies to compare the survival outcomes sufficiently, and direct comparison among IMRT, carbon ion radiation therapy (CIRT), and proton radiation therapy (PRT) has not been attempted in view of the rarity of SNM and the scarce particle beam radiotherapy facilities. During the past 5 years, the prevailing use of advanced radiotherapy worldwide has made conventional 2DRT and 3D-CRT obsolete in the treatment of tumors with complex anatomy such as SNM. In addition, the clinical efficacy of CIRT or PRT has been suggested by the results of a few more recently published[11-16] retrospective studies, although many of them had a limited sample size.[15,17,18] However, it is highly improbable to initiate and complete a randomized clinical trial to confirm superior outcomes of CIRT and PRT over IMRT. Therefore, we conducted this study to estimate the worldwide survival status and compare the treatment outcomes of SNM patients who received CIRT or PRT versus photon-based IMRT.

2 | MATERIALS AND METHODS

2.1 | Study design

We conducted a meta-analysis of SNM patients who received CIRT (including an unpublished online cohort from our institute), PRT, and photon-based IMRT. In addition, we compared the survival difference among combined cohorts and identified potential prognostic factors of SNM using Chi^2 (χ^2) test. The meta-analysis was performed according to a defined protocol (Appendix S1) and reported adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) (Appendix S2).[19] The unpublished online cohort from Shanghai Proton and Heavy Ion Center (SPHIC) has signed a patient consent form and has been approved by the ethics committee of SPHIC. This cohort study has been accepted by the Journal of Cancer Medicine[20] but has not been published online yet. The rest of the cohorts were from published studies online; thus, no patient consent or ethical approval was required.

2.2 | Search strategy and selection criteria

We conducted systematic literature searches to identify studies of interest with two search queries in PubMed, Web of Science, and the Cochrane library (last search updated in November 2019). The first search query was for identification of studies with CIRT or PRT in SNM, and the second one was for studies using IMRT. We used the PICO (patient, intervention, comparison, and outcome) framework[21] to structure the search queries in PubMed with MeSH (Medical Subject Headings) terms if possible. The full search strategy is classified and reported in Appendix S3.

We included studies after 1990 that met all of the following criteria: (a) patients with primary SNM (ie, the maxillary, ethmoid, sphenoid, and frontal sinus or the nasal cavity); (b) treatment by radiotherapy technology of IMRT, PRT, or CIRT; (c) reported outcomes of interest including survival, LC, and complications. CIRT has been an emerging radiation technology in the past 10 years. Many patients were treated using CIRT in combination with proton or photon to explore the toxicity, efficacy as well as the optimal dose through dose escalation. Because of the potential additional biologic effects of the beam with higher LET and RBE, patients who received combined CIRT + PRT, CIRT + photon, and CIRT alone were defined as a single group (CIRT group) to be compared with other cohorts. For the same reasons, we grouped patients who received PRT and those who received PRT + photon together as "PRT group." Patients who received only photon-based IMRT were defined as "IMRT group" to get relatively accurate estimate rates.

We excluded studies if they met one of the following criteria: (a) review, comment, or other nonoriginal study; (b) sample size less than five patients; (c) patient sample only included lymphoma; (d) survival data of interest not extractable (note[22]: Mohr et al reported inconsistent and illogical survival data in the abstract and different parts of the result section in 2015 and thus were excluded due to

unreliable data); (e) median follow-up time <6 months; (f) overlapped population (note: Dagan et al published two articles[23,24] and one poster[25] with overlapped study population between 2016 and 2019; we display their basic information in Table 1 but only included the article published in 2019 and the survival data not reported in the article published in 2019; we dealt with the other three articles published by Zenda et al [26-28] between 2010 and 2014 in the same way). When patients in the study received IMRT and other conventional radiotherapy such as 2DRT or 3D-CRT, we excluded the study if the survival of the IMRT part was not extractable. We did not limit our study by language, country, or other conditions.

2.3 | Data collection

Data of eligible studies were extracted by two independent reviewers, and in case of discrepancies, consensus was reached involving a third reviewer. We recorded general characteristics: the first author, year of publication, radiotherapy type, country, study period, sample size, follow-up time, treatment phase, treatment strategy, radiation dose, age, sex, lymph node status, T4, histological type, tumor location, grade 3-5 adverse event rate (AER) and outcomes of interest. Primary outcomes of interest were defined as OS and LC. Secondary outcomes of interest were defined as distant metastasis–free survival (DMFS) and progression-free survival (PFS). We also divided and reported the histological types in detail: squamous cell carcinoma (SCC), adenocarcinoma (AC), MM, ACC, undifferentiated carcinoma (UC), mucoepidermoid carcinoma (MEC), olfactory neuroblastoma/esthesioneuroblastoma (ONB), neuroendocrine carcinoma (NEC), and other patterns except lymphoma. Tumor locations were displayed as follows: nasal cavity, maxillary sinus, ethmoid sinus, sphenoid sinus, frontal sinus, and other or mixed locations.

2.4 | Data analysis

We performed the meta-analysis with STATA 15.0 (Stata Corp). Survival rate available or calculated through individual data with Statistical Package for the Social Science version 19.0 (SPSS) were pooled with a random-effects model. We calculated the mean follow-up time, mean age, and variance according to the methods detailed by Hozo et al.[29] We also did meta-analysis of the follow-up time, toxicities, and age with a random-effects model. Heterogeneity across cohorts was evaluated by χ^2 test and expressed as I^2 statistic (<50% indicating obvious heterogeneity). In addition, we performed subgroup analysis and metaregression to test the heterogeneity. Potential publication bias was inspected with the symmetry of a funnel plot. Sensitivity analysis was performed to detect the reliability and stability of our results. We compared the survival difference among cohorts using χ^2 test. P value <.05 was defined as statistically significant and <.01 when doing repeated analysis.

3 | RESULTS

3.1 | Eligible studies

Forty-four (44) eligible studies (7 carbon ion,[11-16] 16 proton,[17,18,24,28,30-41] and 21 IMRT[5-7,42-59]) including the unpublished online data from our hospital[20] were identified from the database (see Figure 1). A representative sample of 2282 real-world patients from 49 cohorts (8 CIRT cohorts, 20 PRT cohorts, and 21 IMRT cohorts) was included. Characteristics of the included studies are shown in Table 1.

We pooled baseline information from the eligible studies and displayed it in Table 2. Overall, there were 911 patients in the CIRT group, 599 patients in the PRT group, and 772 patients in the IMRT group. The ratios of male patients in the CIRT, PRT, and IMRT group were 50.3%, 56.4%, and 63.1%, respectively. The mean age for the CIRT group was 58.1 (range 53.4-62.9) years, for the PRT group 54.8 (range 48.4-61.2) years, and for the IMRT group 58.2 (range 55.7-60.7) years. Most patients presented with T4 and N0 disease. The majority of the patients were treatment-naive, but there were 104 (11.4%), 46 (7.7%), and 84 (10.9%) recurrent patients in each group, respectively. We also calculated the distribution of different histological types and primary sites. In the CIRT group, MM (28.9%) and ACC (42.7%) were the main constituents. In the PRT group, the top three pathological types were SCC (31.7%), ONB (26.7%), and MM (16.7%). SCC (31.3%), AC (23.0%), UC (15.0%), and ACC (10.6%) covered two-third of the IMRT group.

3.2 | Data synthesis and comparison

We calculated the mean follow-up time of different survival outcomes and compared the pooled survival (Table 3). For all the cohorts, the mean follow-up time was 36.8 (range 32.5-41.0) months for OS, 37.3 (range 32.1-42.5) months for LC, 38.9 (range 27.5-50.4) months for DMFS, and 40.4 (range 34.0-46.8) months for PFS. The pooled 3-year OS was 67% (95% CI: 62.0%-71.9%), 3-year LC was 72.8% (95% CI: 68.0%-77.5%), 3-year DMFS was 69.4% (95% CI: 60.8%-78.0%), and 3-year PFS was 52.8% (95% CI: 47.1%-58.5%) for all the SNM patients included, regardless of radiotherapy technology or histological types. The corresponding funnel plots of OS and LC are shown in Figure S1. We did not perform further quantitative tests such as Begg's test or Egger's test in view of the very high heterogeneity (I^2 > 80%).

All the eight cohorts in the CIRT group reported OS and LC, but only three cohorts reported DMFS, and five cohorts reported PFS. The mean follow-up time was 34.6 (range 24.4-44.8) months for OS and LC, 39.5 (range 15.3-63.6) months for DMFS and 25.1 (range 19.2-30.9) months for PFS. The pooled 3-year OS was 75.1% (95% CI: 67.1%-83.2%), 3-year LC was 80.2% (95% CI: 73.9%-86.5%), 3-year DMFS was 76.1% (95% CI: 65.2%-86.9%), and 2-year PFS was 54.8% (95% CI: 46.3%-63.2%) for SNM patients who received CIRT.

TABLE 1 Characteristics of the eligible studies

Study	Country	No.	Inclusion period	Naive/ recurrent no.	Median age (y)	Median follow-up time (mo)	Pathology (no.)							Survival outcome				
							MM	ACC	SCC	ONB	AC	UC	Other	OS	LC	DMFS	PFS/ DFS	Year
CIRT																		
Demizu 2013-C	Japan	29	2003-2011	Naive	72 (33-89)	14.2 (6.3-28.9)	29	–	–	–	–	–	–	75.0%	57.1%	28.6%	–	1
Koto 2014	Japan	22	1997-2010	18/4	61 (26-73)	43 (4-126)	–	–	–	–	22	–	–	59.1%	76.9%	–	45.5%	3
Ohkubo 2016	Japan	5	2006-2015	Naive	56 (43-78)	27 (9-91)	2	1	–	1	–	–	1	60.0%	80.0%	–	–	2
Koto 2018	Japan	458	2003-2014	393/65	63 (21-91)	25.2 (1.4-132.3)	221	122	31	30	21	6	27	79.6%	84.1%	–	52.8%	2
Toyomasu 2018	Japan	59	2001-2012	Naive	60 (35-92)	30 (8-127)	–	–	59	–	–	–	–	56.2%	54.0%	–	42.9%	3
Akbaba 2019- Cohort1	Germany	90	2009-2019	Naive	56 (21-80)	50 (3-109)	–	90	–	–	–	–	–	64.0%	79.0%	67.0%	–	3
Akbaba 2019- Cohort2	Germany	137	2009-2019	Naive	53 (17-77)	50 (3-109)	–	137	–	–	–	–	–	79.0%	82.0%	74.0%	–	3
SPHIC-unpublished	China	111	2015-2019	76/35 (30re-RT)	49 (14-85)	18.5 (2.7-49)	11	39	19	9	3		30	82.0%	[b]80.5%	85.9%	66.0%	2
PRT																		
Fitzek 2002	USA	19	1992-1998	Naive	44 (26-67)	45 (20-92)	–	–	–	9	–	–	10	74.0%	88.0%	–	–	5
Trong 2009	USA	20	1991-2005	Naive	53 (17-78)	21	–	7	10	–	1	–	2	53.0%	86.0%	50.0%	31.0%	2
Okano 2012	Japan	13	2006-2012	Naive	47 (28-60)	56.5 (0.6-63.5)	–	–	3	7	1	1	1	75.5%	75.5%	–	33.8%	5
Fukumitsu 2012	Japan	17	2001-2007	15/2	62 (30-83)	23	–	2	11	–	2	1	1	47.1%	35.0%	–	–	2
Demizu 2013-P	Japan	33	2003-2011	Naive	70 (39-86)	25.9 (5.2-82.7)	33	–	–	–	–	–	–	58.0%	83.0%	–	30.0%	2
Herr 2013	USA	22	1997-2013	Naive	45.5 (11-77)	73 (24-183)	–	–	–	22	–	–	–	95.2%	–	–	86.4%	5
Fuji 2014	Japan	20	2006-2012	11/9	74 (55-81)	35 (6-77)	20	–	–	–	–	–	–	54.0%	62.0%	–	38.0%	5
Zenda 2014	Japan	90	1999-2008	Naive	57 (17-84)	57.5 (12.4-162.7)	14	15	22	27	–	–	12	64.2%	–	–	44.5%	5
Zenda 2010-study1	Japan	39	1999-2006	Naive	57 (22-84)	45.4 (1.3-90.9)	6	5	11	9	–	3	5	59.3%	–	–	49.1%	3
Zenda 2010-study2	Japan	14	2004-2007	Naive	73 (56-79)	36.7	14	–	–	–	–	–	–	58.0%	–	–	-	3
Zenda 2015	Japan	32	2008-2012	Naive	73 (36-89)	36.2	32	–	–	–	–	–	–	46.1%	–	–	36.4%	3
Saito 2015	Japan	7	1997-2012	Naive	63 (46-79)	43 (12-62)	–	–	7	–	–	–	–	28.6%	38.1%	–	14.3%	4
Lucas 2015	USA	8	2000-2013	7/1	10 (4-21)	55.2 (9.6-112.8)	–	–	–	8	–	–	–	87.5%	100%	75.0%	75.0%	5
Russo 2016	USA	54	1991-2008	Naive	56 (18-82)	82 (36-219)	–	–	54	–	–	–	–	47.0%	80.0%	78.0%	48.0%	5
Nakamura 2016	Japan	26	2009-2011	Naive	66 (26-85)	-	1	6	15	–	1		3	57.0%	74.0%	–	74.0%	3
Nakamura 2017- Cohort1	Japan	5	1999-2012	Naive	51 (20-87)	69 (7-186)	–	–	–	5	–	–	–	100%	–	–	80.0%	5

(Continues)

Study	Country	No.	Inclusion period	Naive/ recurrent no.	Median age (y)	Median follow-up time (mo)	Pathology (no.)							Survival outcome				
							MM	ACC	SCC	ONB	AC	UC	Other	OS	LC	DMFS	PFS/ DFS	Year
Nakamura 2017- Cohort2		9					–	–	–	9	–	–	–	86.0%	–	–	65.0%	5
Nakamura 2017- Cohort3		28					–	–	–	28	–	–	–	76.0%	–	–	39.0%	5
Yu 2019- Cohort1	USA	42	2010-2016	Naive	53.1 (15.7-82.1)	26.4 (3.5-220.5)	–	8	15	10	5	2	2	100%	[b]92.9%	84.0%	77.3%	3
Yu 2019- Cohort2		27		re-RT	57.4 (31.3-88)		–	6	11	4	4	1	1	76.2%	[b]33.8%	47.4%	32.1%	3
Mimica 2019	USA	7	2000-2018	Naive	66 (38-86)	11.6 (3.3-33.4)	–	–	7	–	–	–	–	100%	75.0%	100%	75.0%	1
Dagan 2019	USA	120	2007-2016	113/7	58 (21-82)	38.4	–	20	35	31	9	9	16	–	80.0%	73.0%	63.0%	3
Dagan 2016-study1	USA	24	-	22/2	-	28.8 (4.8-80.4)	–	8	9	2	1	1	2	71.0%	65.0%	96.0%	61.0%	2
Dagan 2016-study2	USA	84	2007-2013	77/7	59 (28-71)	28.8 (4.8-86.4)	–	14	22	23	8	7	7	68.0%	83.0%	73.0%	63.0%	3
IMRT																		
Uchida 2004	Japan	25	1976-2002	Naive	58 (35-78)	16.8 (7.2-171.6)	–	–	20	–	–	5	–	34.0%	48.9%	–	–	3
Daly 2006	USA	36	1998-2004	Naive	57 (27-84)	39 (6-82)	–	5	12	7	5	5	2	45.0%	58.0%	–	55.0%	5
Combs 2007	Germany	8	1999-2004	2/6	44.5 (18-74)	27 (12-71)	8	–	–	–	–	–	–	75.0%	57.1%	28.6%	–	3
Hoppe 2008	USA	37	2000-2006	Naive	55 (15-88)	28 (11-57)	–	4	17	3	3	3	7	80.0%	[b]75.0%	–	–	2
Dirix 2009	Belgium	40	2003-2008	Naive	66 (37-84)	30 (4-74)	–	–	2	2	31	1	4	89.0%	76.0%	89.0%	72.0%	2
Duprez 2011	Belgium	130	1998-2009	113/17	62 (24-80)	52 (15-121)	–	6	23	10	82	8	1	52.0%	59.0%	–	39.0%	5
Luo 2011[a]	China	52	2006-2008	Naive	50 (17-72)	32 (6-48)	6	–	31	8	19	-	20	46.7%	–	–	–	3
Al-mamgani 2012[a]	Netherland	57	1999-2010	Naive	62 (28-86)	51 (4-132)	–	12	40	–	10	19	1	–	80.0%	–	–	5
Wiegner 2012	USA	52	2000-2009	Naive	63 (11-87)	26.6 (2.9-118.4)	–	5	28	7	1	7	4	66.0%	[b]64.0%	71.0%	–	2
Kaur 2013	USA	6	1995-2009	Naive	56 (40-63)	53.4 (12.3-68.2)	–	–	–	6	–	–	–	80.0%	100%	–	–	3
Suh 2015[a]	Korea	19	2001-2012	Naive	61 (29-73)	34	–	4	9	–	–	–	6	75.3%	[b]89.2%	94.7%	–	3
Burt 2015	USA	11	1998-2010	Naive	61 (28-75)	41 (2-114)	–	–	3	2	–	1	5	–	72.7%	–	45.5%	2
Mukai 2016	Switzerland	36	2008-2015	26/8	66 (34-94)	33 (5-92)	1	–	25	–	3	–	7	88.0%	91.0%	–	–	3
Askoxylakis 2016	Germany	122	1999-2009	82/40	56 (21-79)	36 (1-124)	6	47	26	–	17	4	22	70.0%	60.0%	–	57.0%	3
Chopra 2017[a]	USA	17	1998-2009	Naive	31-88	50.9	–	6	10	–	1	4	2	73.0%	–	–	41.2%	3
Gamez 2017[a]	USA	24	1990-2014	Naive	56.7 (29-82)	82.8 (13.2-204)	–	–	–	–	–	24	–	59.0%	–	–	–	5

(Continues)

TABLE 1 (Continued)

Study	Country	No.	Inclusion period	Naive/recurrent no.	Median age (y)	Median follow-up time (mo)	Pathology (no.)							Survival outcome				
							MM	ACC	SCC	ONB	AC	UC	Other	OS	LC	DMFS	PFS/DFS	Year
Debonnecaze 2018[a]	France	31	2007-2014	Naive	54 (27-81)	43 (29-48)	–	–	–	–	–	31	–	–	73.8%	–	–	2
Debacker 2018	Belgium	20	1998-2016	Naive	64.5 (36-78)	13.2 (2.5-128.9)	–	–	–	–	20	–	–	55.0%	–	–	45.0%	1
Sas-Korczynska 2018	Poland	6	2008-2016	Naive	65.5 (56-72)	20 (8-60)	6	–	–	–	–	–	–	33.3%	–	–	–	2
Thierauf 2018[a]	Germany	9	1993-2014	8/13	63	51 (2-202)	9	–	–	–	–	–	–	74.2%	–	–	–	4
Ferella 2019	Italy	34	2007-2015	Naive	53 (34-81)	73	–	–	16	–	–	13	5	42.9%	[b]33.3%	29.4%	37.3%	5

Abbreviations: AC, adenocarcinoma; ACC, adenoid cystic carcinoma; CIRT, carbon ion radiation therapy; DFS, disease-free survival; DMFS, distant-metastasis–free survival; IMRT, intensity-modulated radiation therapy; LC, local control; MM, mucosal melanoma; ONB, olfactory neuroblastoma; OS, overall survival; PFS, progress-free survival; PRT, proton radiation therapy; Re-RT, reirradiation radiotherapy; SCC, squamous cell carcinoma; SPHIC, Shanghai Proton and Heavy Ion Center; UC, undifferentiated carcinoma.

[a]The sample size of these studies we displayed were those who received IMRT.

[b]Local-regional control survival.

The forest plots of OS and LC for the CIRT group are displayed in Figure 2.

All the 20 cohorts in the PRT group reported OS, and 14 cohorts reported LC. There were 7 cohorts that reported DMFS, and 18 cohorts reported PFS. The mean follow-up time was 41.6 (range 35.5-47.7) months for OS, 36.0 (range 29.8-42.2) months for LC, 37.0 (range 23.9-50.1) months for DMFS, and 42.6 (range 36.0-49.1) months for PFS. The pooled 3-year OS was 66.2% (95% CI: 57.7%-74.6%), 3-year LC was 72.9% (95% CI: 63.7%-82.0%), 3-year DMFS was 67.6% (95% CI: 56.2%-79.1%), and 3-year PFS was 53.7% (95% CI: 43.7%-63.8%) for SNM patients who received PRT.

There were 18 cohorts of the IMRT group that reported OS, and 15 cohorts reported LC. The mean follow-up time was 39.2 (range 31.1-47.4) months for OS and 39.7 (range 29.9-49.5) months for LC. The pooled 3-year OS was 63.8% (95% CI: 55.3%-72.3%), and 3-year LC was 67.8% (95% CI: 59.4%-76.2%) for SNM patients receiving photon-based IMRT.

Through cross-group analysis, the OS was significantly higher for CIRT than for PRT ($\chi^2 = 13.374$, $P < .0001$) or IMRT ($\chi^2 = 23.814$, $P < .0001$), but there was no significant difference between PRT and IMRT ($\chi^2 = 0.846$, $P = .358$). LC was significantly higher for CIRT than for PRT ($\chi^2 = 8.955$, $P = .003$) or IMRT ($\chi^2 = 30.955$, $P < .0001$), but there was no significant difference between PRT and IMRT ($\chi^2 = 3.014$, $P = .083$). There was improved DMFS for CIRT compared with IMRT ($\chi^2 = 6.782$, $P = .009$), but there was no significant difference between CIRT and PRT or between PRT and IMRT. There was also no significant difference among the groups for PFS.

3.3 | Subgroup analysis

We also performed a subgroup analysis based on the following aspects: treatment-naive or recurrent, reirradiated, surgically resected or not, chemotherapy or not, pathological types, primary sites, T4, and N0 if possible (Table 4). Compared with different subgroups in the table, the pooled OS ($\chi^2 = 14.028$, $P < .0001$) and LC ($\chi^2 = 10.14$, $P = .001$) rates of the studies in which all patients underwent surgical resection (regardless of extent) appeared to be better than those without surgery. Similarly, the pooled LC rate of the studies in which all patients received chemotherapy was better than those without chemotherapy ($\chi^2 = 5.688$, $P = .017$), although there was no significant difference for OS ($\chi^2 = 0.614$, $P = .433$). Moreover, ACC and ONB patients had relatively good prognosis. The 3-year OS for ACC (mean follow-up time: 34.9 months) was 83.3%, and 4-year OS for ONB (mean follow-up time: 48.1 months) was 88.6%. The 3-year LC for ACC and ONB was 84.1% and 90.3%, respectively. Though the 2-year OS for MM was 66.6%, the 2-year LC could be as good as 81.4%. SCC patients had both poor OS and poor LC. As for the primary site, tumors originating from the nasal cavity and maxillary sinus had relatively good 3-year OS (nasal cavity: 79.3%; maxillary sinus: 73.2%) and 3-year LC (nasal cavity:

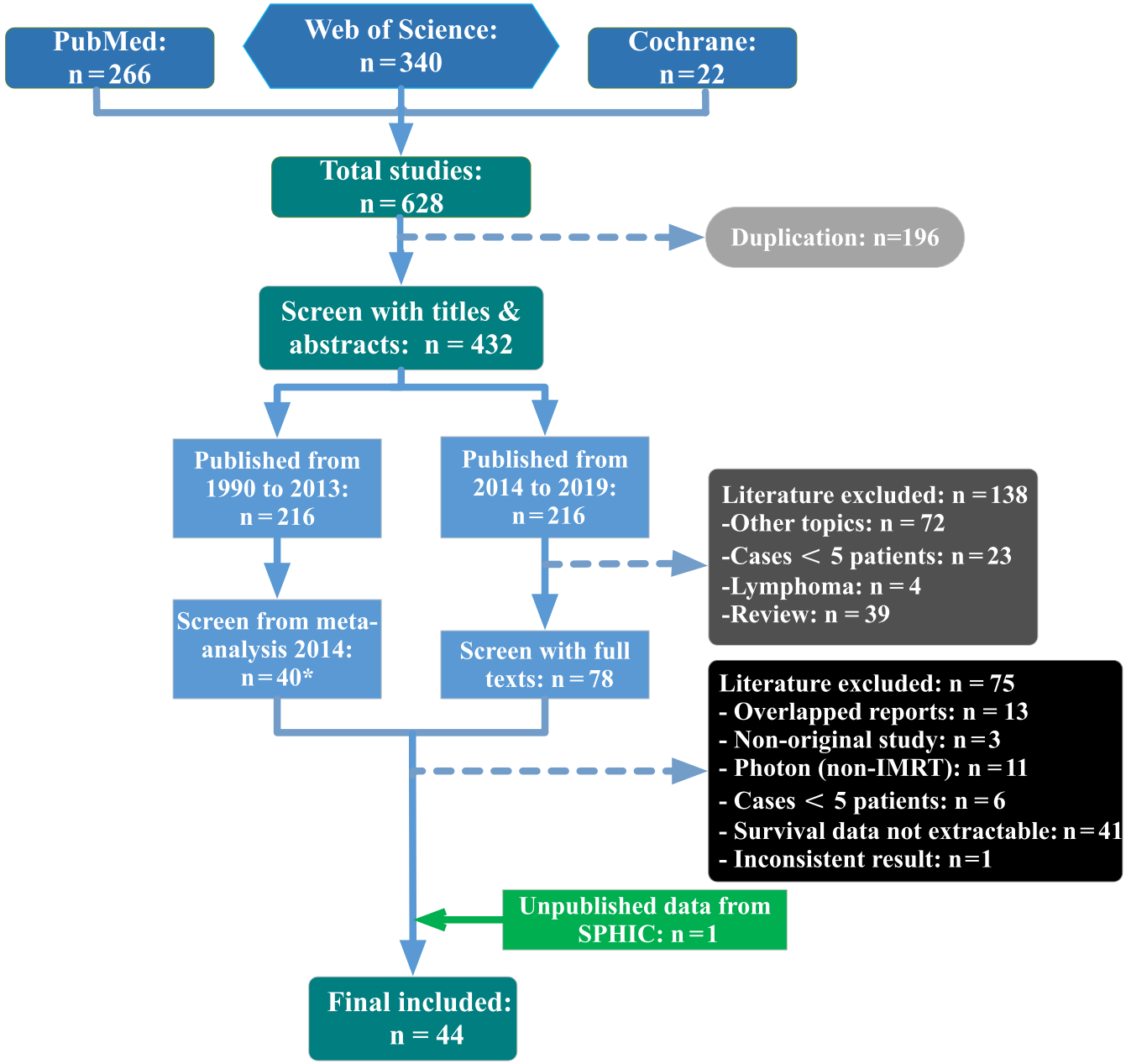

FIGURE 1 Flow chart. *One study published before 1990 which met the exclusion criteria was excluded and meta-analysis 2014 referred to the article published in lancet oncology in 2014 by Patel, S. H. et al

86.1%; maxillary sinus: 81.7%). However, tumors originating from the ethmoid sinus may have relatively poor prognosis. Although we could not collect the entire T- and N-category–related survival, we extracted and pooled the survival of T4 and N0 subgroup patients, who covered 51.6%-90.2% of the entire population. The 3-year OS and LC of T4 patients was 60.3% and 65.2%, respectively. The 3-year OS and LC of N0 patients was 67.0% and 78.1%, respectively. For the recurrent patients, the 2-year OS (n = 132) was 71.2% and the 2-year LC (n = 92) was 66.5%. When treated with reirradiation (n = 57), the OS was 77.9%, and the LC was 55.2% with a mean follow-up time of 18.6 (range 16.0-21.4) months.

3.4 | Metaregression

We performed a metaregression analysis of the overall OS and LC based on the sample size, year of publication, and technology of radiotherapy, respectively. We found that the sample size and year of publication had no obvious effect on the heterogeneity of the OS or LC. Although the technology of radiotherapy had no significant relationship with the heterogeneity of OS (P = .16) or LC (P = .106) either, it might contribute to 4.84% and 7.7% heterogeneity, respectively. We display the metaregression results of the OS based on the year of publication and radiotherapy technology in Figure S2.

TABLE 2 Pooled baseline information of the eligible studies

	CIRT group	PRT group	IMRT group
Cohorts (n)	8	20	21
Total patients (n)	911	599	772[a]
Sex (n, %)			
Male	458 (50.3%)	338 (56.4%)	559 (63.1%)[b]
Female	453 (49.7%)	261 (43.6%)	327 (36.9%)[b]
Mean age (range) (year)	58.1 (53.4-62.9)	54.8 (48.4-61.2)	58.2 (55.7-60.7)
T4 (n, %)	625 (68.6%)	309 (51.6%)	538 (60.7%)[b]
N status (n, %)			
N0	822 (90.2%)	370 (61.8%)	572 (64.6%)[b]
N+	54 (5.9%)	85 (14.2%)	72 (8.1%)[b]
NA	35 (3.9%)	144 (24.0%)	242 (27.3%)[b]
Treatment status (n, %)			
Naive	807 (88.6%)	553 (92.3%)	688 (89.1%)
Recurrent	104 (11.4%)	46 (7.7%)	84 (10.9%)
Dose range (cGy/GyE)	57.6-80.0	12.0-89.6	50.4-79.0
Pathology (n, %)			
MM	263 (28.9%)	100 (16.7%)	36 (4.3%)
ACC	389 (42.7%)	64 (10.7%)	89 (10.6%)
SCC	109 (12.0%)	190 (31.7%)	262 (31.3%)
NEC	1 (0.1%)	22 (3.7%)	13 (1.6%)
ONB	40 (4.4%)	160 (26.7%)	45 (5.4%)
AC	46 (5.0%)	23 (3.8%)	192 (23.0%)
UC	6 (0.6%)	14 (2.4%)	125 (15.0%)
MEC	6 (0.6%)	5 (0.8%)	5 (0.6%)
Sarcoma	24 (2.6%)	0	23 (2.8%)
NA	27 (3.0%)	21 (3.5%)	45 (5.4%)
Total	911 (100%)	599 (100%)	835 (100%)
Primary site (n, %)			
Nasal cavity	299 (32.8%)	186 (31.1%)	116 (15.0%)
Maxillary sinus	270 (29.6%)	108 (18.0%)	85 (11.0%)
Ethmoid sinus	108 (11.9%)	50 (8.3%)	190 (24.6%)
Sphenoid sinus	31 (3.4%)	20 (3.3%)	15 (2.0%)
Frontal sinus	9 (1.0%)	1 (0.2%)	1 (0.1%)
Mixed sites	81 (8.9%)	96 (16.0%)	22 (2.9%)
NA	113 (12.4%)	138 (23.1%)	343 (44.4%)

Abbreviations: AC, adenocarcinoma; ACC, adenoid cystic carcinoma; CIRT, carbon ion radiation therapy; IMRT, intensity-modulated radiation therapy; MEC, Mucoepidermoid carcinoma; MM, mucosal melanoma; NA, not available; NEC, neuroendocrine carcinoma; ONB, olfactory neuroblastoma; PRT, proton radiation therapy; SCC, squamous cell carcinoma; UC, undifferentiated carcinoma.

[a]This number only included patients who received IMRT.

[b]The total sample size was 886.

3.5 | Sensitivity analysis

We performed a sensitivity analysis of the overall OS (46 cohorts), LC (37 cohorts), and DMFS (15 cohorts) including the cohorts with 100% survival (Figure S3). The combined survival rates were 67.0% (95% CI: 62.0%-71.9%), 72.8% (95% CI: 68.0%-77.5%), and 69.4% (95% CI: 60.8%-78.0%) for the OS, LC, and DMFS, respectively. The results were in concordance with our previous data listed in Table 3. When taking out of each cohort from the population to analyze the rest cohorts, the remaining studies had similar combined results of OS, LC, and DMFS (Appendix S4). As such, we considered the results in this study reliable and stable.

TABLE 3 Summary of meta-analysis results

Outcome	Cohorts no.	Sample size	Mean follow-up time (mo)	Survival, 95% CI	I^2, %	χ^2 (comparison)	*P* value*
OS							
CIRT	8	911	34.6 (24.4-44.8)	75.1% (67.1%-83.2%)	85.4%	13.374 (CIRT vs PRT)	<.0001
PRT	20	563	41.6 (35.5-47.7)	66.2% (57.7%-74.6%)	77.8%	0.846 (PRT vs IMRT)	.358
IMRT	18	673	39.2 (31.1-47.4)	63.8% (55.3%-72.3%)	81.9%	23.814 (CIRT vs IMRT)	<.0001
Total	46	2183	36.8 (32.5-41.0)	67.0% (62.0%-71.9%)	83.6%	26.489 (among groups)	<.0001
LC							
CIRT	8	911	34.6 (24.4-44.8)	80.2% (73.9%-86.5%)	77.4%	8.955 (CIRT vs PRT)	.003
PRT	14	413	36.0 (29.8-42.2)	72.9% (63.7%-82.0%)	80.1%	3.014 (PRT vs IMRT)	.083
IMRT	15	644	39.7 (29.9-49.5)	67.8% (59.4%-76.2%)	81.9%	30.955 (CIRT vs IMRT)	<.0001
Total	37	1968	37.3 (32.1-42.5)	72.8% (68.0%-77.5%)	83.3%	31.432 (among groups)	<.0001
DMFS							
CIRT	3	338	39.5 (15.3-63.6)	76.1% (65.2%-86.9%)	83.0%	5.379 (CIRT vs PRT)	.02
PRT	7	278	37.0 (23.9-50.1)	67.6% (56.2%-79.1%)	73.5%	0.378 (PRT vs IMRT)	.539
IMRT	5	153	41.0 (13.0-69.0)	64.7% (40.9%-88.4%)	93.8%	6.782 (CIRT vs IMRT)	.009
Total	15	769	38.9 (27.5-50.4)	69.4% (60.8%-78.0%)	87.2%	8.573 (Among groups)	.014
PFS[a]							
CIRT	5	679	25.1 (19.2-30.9)	54.8% (46.3%-63.2%)	66.5%	0.163 (CIRT vs PRT)	.687
PRT	18	563	42.6 (36.0-49.1)	53.7% (43.7%-63.8%)	84.0%	1.435 (PRT vs IMRT)	.231
IMRT	8	410	43.3 (29.1-57.6)	49.8% (40.4%-59.2%)	68.4%	2.596 (CIRT vs IMRT)	.107
Total	31	1652	40.4 (34.0-46.8)	52.8% (47.1%-58.5%)	79.5%	2.681 (Among groups)	.262

Abbreviations: CI, confidence interval; CIRT, carbon ion radiation therapy; DMFS, distant-metastasis–free survival; IMRT, intensity-modulated radiation therapy; LC, local control; OS, overall survival; PFS, progress-free survival; PRT, proton radiation therapy.

[a]We pooled PFS and disease-free survival together as PFS.

*$P < .05$ has statistical significance for comparison among groups and $P < .01$ has statistical significance for repeating analysis between groups.

3.6 | Toxicities

We recorded the occurrence of grade 3-5 adverse effects and calculated the corresponding AER. Seven of the eight CIRT cohorts covering 99.4% of the CIRT-treated population reported acute grade 3-5 AER. Only one case series of five patients did not report AER.[12] The rates were substantially lower in the PRT group (11/20 cohorts, 45.6% of the population) and the IMRT group (12/21 cohorts, 75.8% of the population). The overall acute AER of the CIRT group was 31.1% (95% CI: 22.9%-39.3%), which was higher than the IMRT group (23.9%, 95% CI: 10.8%-36.9%). In the CIRT group, the percentages of the severe acute AER (ie, grade 3-5) ranged from 0% to 41.6%, including three cohorts[14,16] reporting > 40% severe acute AER. Two[16] of these three cohorts divided from one article studied IMRT followed-by CIRT

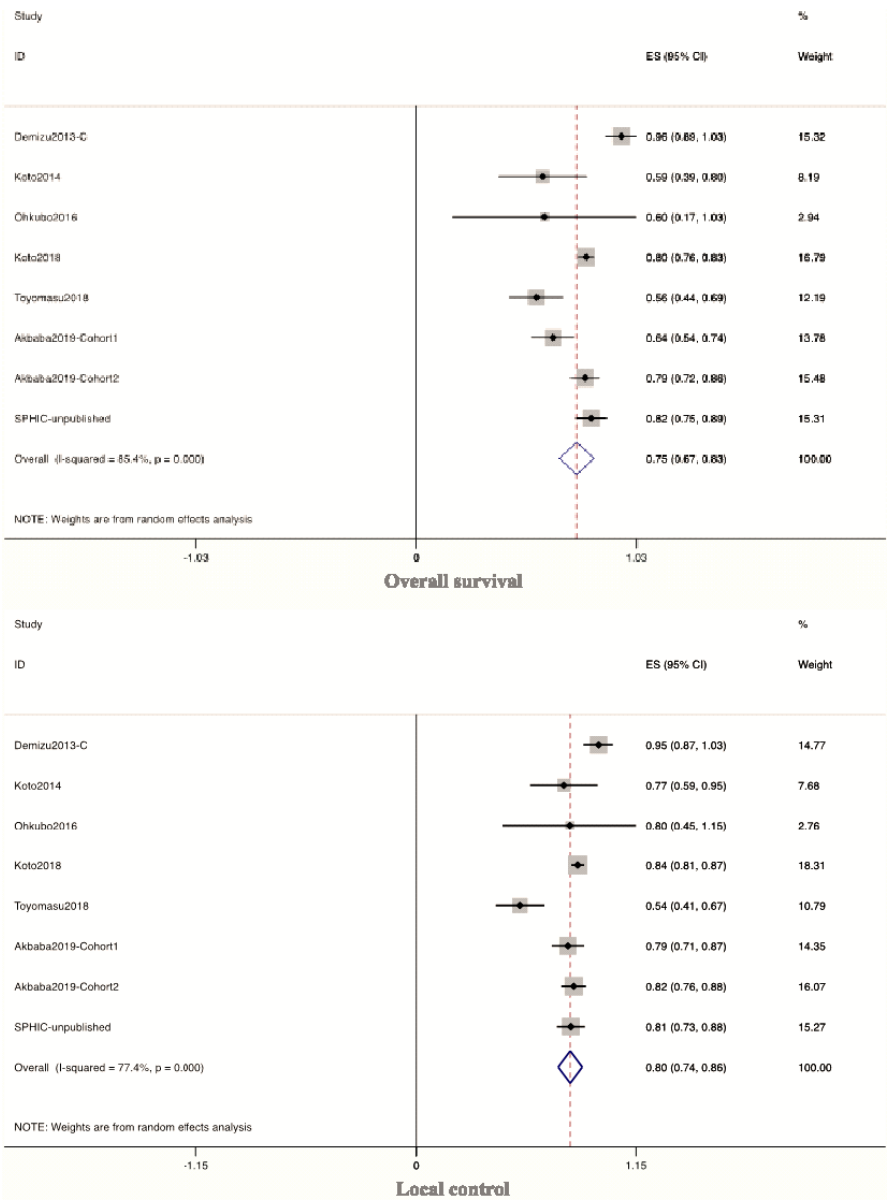

FIGURE 2 Forest plots of overall survival and local control for the CIRT group. CIRT, carbon ion radiation therapy; IMRT, intensity-modulated radiotherapy; SPHIC, Shanghai Proton and Heavy Ion Center

boost to treat patients, and another cohort[14] focused on malignant melanoma originated from the nasal cavity treated with CIRT alone. The PRT group had the slightest acute toxic reaction (14.4%, 95% CI: 10.0%-18.7%) with reported percentages ranging from 0% to 40%. The reported severe acute AER of the IMRT group ranged from 0% to 52% across different cohorts. The late toxic reactions were similar among the three groups, ranging from 10.8% to 13.4%.

4 | DISCUSSION

Our study of 2282 patients from the real world revealed that CIRT might be the optimal radiotherapy technology for malignancies of the nasal cavity and paranasal sinus. This was the first direct and effective comparison among CIRT, PRT, and photon-based IMRT with sufficient available population. Our analysis indicated improved 3-year OS and LC rates for patients who received CIRT as compared with those treated with PRT or IMRT. CIRT might also have improved effects on DMFS, which warrants further investigation for its mechanism.

The efficacy of particle beam radiotherapy (PBRT) versus photon-based radiotherapy has been previously addressed in a few retrospective studies and a well-conducted meta-analysis published in 2014.[10] However, the technology of radiotherapy used in many of the historical studies was conventional (eg, 2DRT and 3D-CRT). Its results[10] suggested an advantage of PBRT over conventional photon radiotherapy (including 2DRT, 3D-CRT, and IMRT), and the subgroup analysis indicated PRT (n = 191) had higher DFS at 5 years and locoregional control at longest follow-up than IMRT. However, the insufficient number of studies on CIRT limited further subgroup analysis that compared different PBRT technologies. In the past 5 years, several publications using more advanced and precision radiation technologies such as IMRT and PBRT have been published for SNM owing to the constantly updated radiotherapy equipment

TABLE 4 Summary of subgroup analysis results

Outcome/subgroup	CIRT cohort no.	PRT cohort no.	IMRT cohort no.	Total cohort no.	Sample size	Mean follow-up time (mo)	Survival, 95% CI	I^2, %
OS								
Naive	6	15	14	35	1570	40.3 (34.7-45.9)	65.9% (59.9%-75.4%)	85.2%
Recurrent	1	1	1	3	132	29.9 (21.2-38.6)	71.2% (52.4%-89.9%)	83.0%
Reirradiation	1	1	0	2	57	18.6 (16.0-21.4)	77.9% (67.1%-88.6%)	0%
Post operation	2	2	9	13	426	38.6 (28.8-48.4)	72.1% (62.2%-82.1%)	83.7%
Without operation	6	11	4	21	938	40.4 (32.3-48.5)	61.6% (53.7%-69.5%)	79.4%
Received chemo.	0	5	0	5	73	36.4 (21.3-51.6)	72.4% (59.8%-85.0%)	29.7%
Without chemo.	1	0	2	3	119	29.8 (25.6-34.0)	67.6% (42.6%-92.6%)	89.8%
T4	2	4	3	9	507	36.6 (21.8-51.3)	60.3% (48.4%-72.3%)	83.0%
N0	4	5	4	13	789	35.5 (29.4-41.8)	67.0% (58.0%-76.0%)	82.5%
MM	3	4	3	10	383	26.3 (19.0-33.5)	66.6% (53.7%-79.4%)	84.9%
SCC	3	5	3	11	277	34.3 (26.2-42.4)	56.8% (46.6%-66.9%)	66.4%
ACC	4	0	2	6	440	34.9 (21.1-48.6)	83.3% (71.9%-94.6%)	93.5%
ONB	2	6	2	10	143	48.1 (34.0-62.1)	88.6% (81.2%-96.1%)	43.6%
UC	1	0	3	4	42	37.3 (17.6-53.4)	64.4% (50.2%-78.6%)	0%
AC	2	0	1	3	63	35.4 (21.3-51.6)	69.2% (45.1%-93.2%)	80.8%
Nasal cavity	1	1	1	3	325	36.8 (22.9-50.7)	79.3% (70.6%-87.9%)	54.4%
Ethmoid sinus	1	1	1	3	103	31.9 (22.6-41.3)	51.6% (7.9%-95.4%)	94.4%
Maxillary sinus	1	1	1	3	154	31.4 (22.3-40.4)	73.2% (58.6%-87.8%)	65.2%
LC								
Naive	6	10	11	27	1314	36.9 (30.6-43.2)	75.4% (70.4%-80.4%)	77.1%
Recurrent	1	1	0	2	92	25.3 (20.1-30.4)	66.5% (3.7%-129.3%)	97.9%
Reirradiation	1	1	0	2	57	18.6 (16.0-21.4)	55.2% (13.8%-96.5%)	91.9%
Post operation	2	1	7	10	351	36.1 (25.1-47.1)	77.0% (68.6%-82.1%)	83.7%
Without operation	6	7	4	17	874	37.1 (28.4-45.9)	67.7% (68.6%-82.1%)	82.0%
Received chemo.	0	5	0	5	73	36.4 (21.3-51.6)	80.3% (70.8%-89.8%)	0%
Without chemo.	1	0	2	3	119	30.0 (25.6-34.4)	64.9% (43.4%-86.5%)	81.9%
T4	2	3	1	6	443	37.7 (18.9-56.6)	65.2% (48.7%-81.7%)	88.8%
N0	4	3	3	10	730	34.6 (28.3-41.0)	78.1% (71.7%-84.6%)	62.2%
MM	3	3	1	7	354	26.1 (18.4-33.7)	81.4% (73.8%-88.9%)	58.2%
SCC	3	4	1	8	220	32.6 (22.4-42.7)	61.9% (49.0%-74.7%)	74.9%
ACC	4	0	1	5	393	34.6 (18.6-50.6)	84.1% (80.1%-88.1%)	14.9%

(Continues)

TABLE 4 (Continued)

Outcome/subgroup	CIRT cohort no.	PRT cohort no.	IMRT cohort no.	Total cohort no.	Sample size	Mean follow-up time (mo)	Survival, 95% CI	I^2, %
ONB	2	2	2	6	79	35.3 (21.5-49.1)	90.3% (83.2%-97.5%)	0%
UC	1	0	2	3	44	24.0 (22.4-25.7)	73.5% (60.6%-86.4%)	0%
AC	2	0	0	2	43	39.2 (11.0-67.5)	77.4% (64.9%-89.9%)	0%
Nasal cavity	1	0	1	2	299	32.7 (17.3-48.2)	86.1% (79.1%-93.1%)	50.2%
Ethmoid sinus	1	1	1	3	103	31.9 (22.6-41.3)	61.1% (26.9%-95.4%)	89.9%
Maxillary sinus	1	1	1	3	154	31.4 (22.3-40.4)	81.7% (75.6%-87.8%)	0%

Abbreviations: AC, adenocarcinoma; ACC, adenoid cystic carcinoma; Chemo., Chemotherapy; CI, confidence interval; CIRT, carbon ion radiation therapy; IMRT, intensity-modulated radiation therapy; LC, local control; MM, mucosal melanoma; ONB, olfactory neuroblastoma; OS, overall survival; PRT, proton radiation therapy; SCC, squamous cell carcinoma; UC, undifferentiated carcinoma.

worldwide. In addition, IMRT has replaced 3D-CRT and 2DRT and became a standard technology of radiotherapy for SNM. After a stringent screening, seven studies on CIRT published after 2014 including 911 patients with SNM (along with 111 unpublished online cases from the authors' own institute) were analyzed[11-16,20]. Moreover, 12 studies on PRT (with 508 patients) and 11 studies on photon-based IMRT (with 329 patients) that have been published since 2014 were accrued to our analysis.[11-18,24,28,30-36] With this surge of publications on CIRT and PRT in the management of SNM in the past several years, we consider that an update that directly compares the effectiveness of CIRT, PRT, and photon-based IMRT is feasible and necessary.

In our study, we combined the reported year of survival adjacent to the median follow-up time of each included study and got the estimated month of pooled survival through meta-analysis of the median follow-up time and its variance instead of extracting outcomes at 5 years and at the longest follow-up as performed in the previously published meta-analysis. Through efficient analysis, we concluded that there were no significant differences between PRT and IMRT in OS, LC, DMFS, and PFS rates at 3 years but demonstrated the superiority of CIRT over both PRT and X-ray–based IMRT in detail. Most patients in our study were treatment-naive and presented with T4 or N0 disease. The overall 3-year OS, LC, DMFS, and PFS of SNM patients were 67%, 72.8%, 69.4%, and 52.8%, respectively. When treated with CIRT, the treatment-naive patients could achieve a 3-year OS of 75% and a 3-year LC of 79.6%. We also found that patients who received surgery followed by adjuvant radiotherapy appeared to have better OS and LC than those who had radiotherapy alone. However, as the majority of patients presented with inoperable T4 disease with extensive invasion, the data set is skewed, and the seemingly improved outcome of combined modality over radiotherapy alone is most likely due to the favorable presenting stage of the disease. Nevertheless, our finding may explain, at least in part, why patients with malignancies of nasal cavity had better prognosis than those with ethmoid sinus, as surgery is more feasible for nasal cavity tumors.

The more commonly diagnosed histological types of SNM are of epithelial origin and include SCC (51.6%), AC (12.6%), ONB (6.3%), ACC (6.2%), MM (6.6%), and UC (3.1%).[10] Soft-tissue and bone sarcomas of the head and neck commonly originate from the nasal cavity as well as paranasal sinuses. Due to their inconspicuous anatomic location, SNM are usually asymptomatic at early stages and diagnosed with extensive direct invasion to adjacent vital OARs such as skull base, orbit, optic nerve/chiasm, brain, and/or brain stem. This reduces the opportunity of surgery and increases the difficulty of radiation dose distribution sufficient for disease control. Thus, the most common treatment failure pattern of SNM is local recurrence. The characteristics of carbon ion beams such as higher LET and greater RBE as well as their precise dosimetric distribution provide advantages for treating resistant histologies close to critical OARs. In the current analysis, patients with ACC and ONB achieved relatively good prognosis in terms of disease control. However, more acute grade 3-5 toxicities were observed after CIRT treatment (31.1%) in the literature as compared with proton and

photon therapy. This finding is highly different from what we had observed from our patients (0%).[20] Several cohorts exhibited particularly high probability of acute severe toxicity in our study. The following four reasons could be considered for such findings. First, seven out of eight studies on CIRT reported acute adverse effects. However, the studies on PRT and IMRT reported acute adverse effects for only 45.6% and 75.8%, respectively. Thus, the pooled rates of acute adverse effects from the PRT and IMRT groups could be underestimated and inaccurate. Second, the high rates of acute adverse events reported by Akbaba et al could be partly attributed to the high radiotherapy dose delivered.[16] Patients in that study received combined photon-based IMRT (48-56 Gy in 1.8 or 2 Gy fractions) followed by carbon ion radiation boost (18-24 Gy RBE in 3 Gy RBE fractions), with or without surgery, to a median combined dose of 80 Gy (range 71-80 Gy), whereas most photon-based IMRT cases reported in other studies used 70 Gy or less. Third, the use of surgery may complicate the analysis of adverse effects. For patients who received complete resection (eg, maxillectomy) before radiation, oral mucosa might be easily excluded from high-dose radiation field. On the other hand, surgery may affect the blood supply to the surgical bed which is usually encompassed by adjuvant radiation. In the study reported by Akbaba et al,[16] the acute and late grade 3-5 reactions were 34.4% and 6.2% after CIRT, and 41.6% and 17.2% after surgery followed by adjuvant CIRT. Fourth, most of the CIRT patients received treatment in Japan, and the biological model used for dose calculation (ie, the micro kinetic model [MKM]) is different from that used in Germany and our institution (ie, the local effect model [LEM]). The daily per fraction equivalent dose could be higher after conversion for patients treated using MKM.[60,61] In addition, hypofractioned CIRT is commonly practiced in Japan, and all patients treated at the Heidelberg Ion Therapy Center and our institute used 3.0 Gy (RBE) per fraction.

The present study has some limitations. First and most importantly, all the eligible studies were observation studies and 10 of them had less than 10 patients. Some variables and survival data might not be available or accurate. This may influence the reliability of our results to a limited extent. However, given the limited number of publications on the subject, these studies were of the highest quality available in the most updated literature search. With the prevailing application of proton and carbon ion radiotherapy worldwide, it is important to update the knowledge with the most recent available data to guide the clinical practice and decisions on public health endeavors. Second, three studies[17,18,36] that reported 100% survival rate in the PRT group (2 for OS, 1 for LC, and 1 for DMFS) and one study[59] that reported 100% LC rate in the IMRT group were excluded when pooled survival rate was calculated in Stata. However, these studies had quite small sample size and the influence could be ignored to some extent. We also performed sensitivity analysis including these four studies, which resulted in similar findings, as displayed in Appendix S4. Third, the results could have selection bias. SNM consists of many kinds of histological types and each radiotherapy group had a different pathological constituent ratio. However, the proportion of patients with high-risk pathologies such as MM in the CIRT group was much higher than in the PRT or IMRT group, which in turn confirmed the better tumor control and survival in the CIRT group. Fourth, the between-study heterogeneity should not be neglected. We performed subgroup analysis to test the heterogeneity and listed the results in detail. We also performed metaregression and sensitivity analysis to detect the heterogeneity and its influence on the results. However, metaregression, sample size, year of publication, and radiotherapy technology were not the main reasons for heterogeneity. In stead, the different histological types and primary sites should be considered. After sensitivity analysis, the heterogeneity among cohorts did not affect the stability and reliability of the results.

Despite the pitfalls mentioned above, the study was conducted to evaluate the effectiveness of conventional and novel radiation technologies head to head at the appropriate time. Our study firstly highlights promising treatment outcomes for SNM patients by CIRT in contrast to both PRT and photon-based IMRT. A prospective clinical trial is being evaluated at the SPHIC to confirm our results with much evidence of higher quality. As more and more particle therapy centers are expected to spring up all over the world in the following decade, prospective data on long-term effect, quality of life, and cost effectiveness of PBRT will be useful for effective utilization of the novel technology in SNM treatment.

ACKNOWLEDGEMENTS

This study was supported by grants from the National Key Research and Development Program of China (2018YFC0115700), Program of Shanghai Academic/Technology Research Leader (18XD1423000), and Science and Technology Commission of Shanghai Municipality (19411951000).

DISCLOSURE

The authors have declared no conflicts of interest.

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REFERENCES

1. Muir CS, Nectoux J. Descriptive epidemiology of malignant neoplasms of nose, nasal cavities, middle ear and accessory sinuses. *Clin Otolaryngol Allied Sci*. 1980;5:195-211.
2. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer*. 2001;92:3012-3029.
3. Siddiqui F, Smith RV, Yom SS, et al. ACR appropriateness criteria (R) nasal cavity and paranasal sinus cancers. *Head Neck*. 2017;39:407-418.
4. Turner JH, Reh DD. Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. *Head Neck*. 2012;34:877-885.
5. 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;67:151-157.
6. Duprez F, Madani I, Morbée L, et al. IMRT for sinonasal tumors minimizes severe late ocular toxicity and preserves disease control and survival. *Int J Radiat Oncol Biol Phys*. 2012;83:252-259.

7. Dirix P, Vanstraelen B, Jorissen M, Vander Poorten V, Nuyts S. Intensity-modulated radiotherapy for sinonasal cancer: improved outcome compared to conventional radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;78:998-1004.
8. Mock U, Georg D, Bogner J, Auberger T, Pötter 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;58:147-154.
9. Mazeron J-J, Noel G, Feuvret L, Calugaru V, Racadot S. Clinical complementarities between proton and carbon therapies. *Radiother Oncol*. 2004;73:S50-S52.
10. Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lancet Oncology*. 2014;15:1027-1038.
11. Koto M, Hasegawa A, Takagi R, et al. Feasibility of carbon ion radiotherapy for locally advanced sinonasal adenocarcinoma. *Radiother Oncol*. 2014;113:60-65.
12. Ohkubo JI, Hohchi N, Takeuchi S, et al. Treatment outcome of ion beam therapy in eight patients with head and neck cancers. *Eur Arch Otorhinolaryngol*. 2016;273:4397-4402.
13. Koto M, Demizu Y, Saitoh JI, et al. Definitive carbon-ion radiation therapy for locally advanced sinonasal malignant tumors: subgroup analysis of a multicenter study by the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS). *Int J Radiat Oncol Biol Phys*. 2018;102:353-361.
14. Demizu Y, Fujii O, Terashima K, et al. Particle therapy for mucosal melanoma of the head and neck. A single-institution retrospective comparison of proton and carbon ion therapy. *Strahlenther Onkol*. 2014;190:186-191.
15. Toyomasu Y, Demizu Y, Matsuo Y, et al. Outcomes of patients with sinonasal squamous cell carcinoma treated with particle therapy using protons or carbon ions. *Int J Radiat Oncol Biol Phys*. 2018;101:1096-1103.
16. Akbaba S, Ahmed D, Mock A, et al. Treatment outcome of 227 patients with sinonasal adenoid cystic carcinoma (ACC) after intensity modulated radiotherapy and active raster-scanning carbon ion boost: a 10-year single-center experience. *Cancers*. 2019;11:E1705.
17. Mimica X, Yu Y, McGill M, et al. Organ preservation for patients with anterior mucosal squamous cell carcinoma of the nasal cavity: rhinectomy-free survival in those refusing surgery. *Head Neck*. 2019;41:2741-2747.
18. Nakamura N, Zenda S, Tahara M, et al. Proton beam therapy for olfactory neuroblastoma. *Radiother Oncol*. 2017;122:368-372.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Open Med*. 2009;3:e123-e130.
20. Hu W, Hu J, Huang Q, et al. Particle beam radiation therapy for sinonasal malignancies: single institutional experience at the Shanghai proton and heavy ion certer. *Cancer Med*. 2020.
21. 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-A13.
22. Mohr A, Chaudhri N, Hassel JC, et al. Raster-scanned intensity-controlled carbon ion therapy for mucosal melanoma of the paranasal sinus. *Head Neck*. 2016;38(Suppl 1):E1445-E1451.
23. Dagan R, Bryant C, Li Z, et al. Outcomes of sinonasal cancer treated with proton therapy. *Int J Radiat Oncol Biol Phys*. 2016;95:377-385.
24. Dagan R, Bryant CM, Mendenhall WM, et al. Isolated leptomeningeal progression from sinonasal carcinomas: Implications for staging workup and treatment. *Head Neck*. 2019.41(8):2647–2654.
25. Dagan R, Bryant CM, Mendenhall WM. Improving local control for unresectable/incompletely resected sinonasal cancer with hyperfractionated proton therapy and concurrent Chemotherapy. *Int J Radiat Oncol Biol Phys*. 2016;94:951.
26. Zenda S, Kawashima M, Nishio T, et al. Proton beam therapy as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study. *Int J Radiat Oncol Biol Phys*. 2011;81:135-139.
27. Zenda S, Kohno R, Kawashima M, et al. Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses. *Int J Radiat Oncol Biol Phys*. 2011;81:1473-1478.
28. Zenda S, Kawashima M, Arahira S, et al. Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up. *Int J Clin Oncol*. 2015;20:447-454.
29. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
30. Fuji H, Yoshikawa S, Kasami M, et al. High-dose proton beam therapy for sinonasal mucosal malignant melanoma. *Radiat Oncol*. 2014;9:162.
31. Lucas JT Jr, Ladra MM, MacDonald SM, et al. Proton therapy for pediatric and adolescent esthesioneuroblastoma. *Pediatr Blood Cancer*. 2015;62:1523-1528.
32. Saito T, Ishikawa H, Ohnishi K, et al. Proton beam therapy for locally advanced and unresectable (T4bN0M0) squamous cell carcinoma of the ethmoid sinus: a report of seven cases and a literature review. *Oncol Lett*. 2015;10:201-205.
33. Nakamura T, Azami Y, Ono T, et al. Preliminary results of proton beam therapy combined with weekly cisplatin intra-arterial infusion via a superficial temporal artery for treatment of maxillary sinus carcinoma. *Jpn J Clin Oncol*. 2016;46:46-50.
34. Russo AL, Adams JA, Weyman EA, et al. Long-term outcomes after proton beam therapy for sinonasal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2016;95:368-376.
35. Zenda S, Akimoto T, Mizumoto M, et al. Phase II study of proton beam therapy as a nonsurgical approach for mucosal melanoma of the nasal cavity or para-nasal sinuses. *Radiother Oncol*. 2016;118:267-271.
36. Yu NY, Gamez ME, Hartsell WF, et al. A multi-institutional experience of proton beam therapy for sinonasal tumors. *Adv Radiat Oncol*. 2019;4:689-698.
37. Truong MT, Kamat UR, Liebsch NJ, et al. Proton radiation therapy for primary sphenoid sinus malignancies: treatment outcome and prognostic factors. *Head Neck*. 2009;31:1297-1308.
38. Fukumitsu N, Okumura T, Mizumoto M, et al. Outcome of T4 (International Union Against Cancer Staging System, 7th edition) or recurrent nasal cavity and paranasal sinus carcinoma treated with proton beam. *Int J Radiat Oncol Biol Phys*. 2012;83(2):704-711.
39. Okano S, Tahara M, Zenda S, et al. Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin in patients with T4b nasal and sinonasal malignancies. *Jpn J Clin Oncol*. 2012;42:691-696.
40. Herr M, Lin A, Curry W, et al. Esthesioneuroblastoma: an update on the Massachusetts eye and ear infirmary and Massachusetts General Hospital Experience with craniofacial resection, proton beam radiation, and chemotherapy. *J Neurol Surg B Skull Base*. 2013;75(1):58–64.
41. Fitzek MM, Thornton AF, Varvares M, et al. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. *Cancer*. 2002;94:2623-2634.
42. Burt LM, Orlandi RR, Hunt JP, et al. Function preservation and optimal outcomes—definitive chemoradiotherapy with multi-phase treatment planning for locally advanced sinonasal cancer. *J Radiat Oncol*. 2015;5:47-54.
43. Askoxylakis V, Hegenbarth P, Timke C, et al. Intensity modulated radiation therapy (IMRT) for sinonasal tumors: a single center long-term clinical analysis. *Radiat Oncol*. 2016;11:17.
44. Suh YG, Lee CG, Kim H, et al. Treatment outcomes of intensity-modulated radiotherapy versus 3D conformal radiotherapy for

patients with maxillary sinus cancer in the postoperative setting. *Head Neck*. 2016;38(Suppl 1):E207-E213.
45. Chopra S, Kamdar DP, Cohen DS, et al. Outcomes of nonsurgical management of locally advanced carcinomas of the sinonasal cavity. *Laryngoscope*. 2017;127:855-861.
46. Gamez ME, Lal D, Halyard MY, et al. Outcomes and patterns of failure for sinonasal undifferentiated carcinoma (SNUC): the mayo clinic experience. *Head Neck*. 2017;39:1819-1824.
47. Mukai Y, Janssen S, Glanzmann C, Holzmann D, Studer G. Local control and intermediate-term cosmetic outcome following IMRT for nasal tumors: an update. *Strahlenther Onkol*. 2017;193:295-304.
48. de Bonnecaze G, Verillaud B, Chaltiel L, et al. Clinical characteristics and prognostic factors of sinonasal undifferentiated carcinoma: a multicenter study. *Int Forum Allergy Rhinol*. 2018;8:1065-1072.
49. Debacker J, Huvenne W, Bonte K, et al. Open surgery versus primary radiotherapy in T4b sinonasal carcinoma. *B-Ent*. 2018;14:93-99.
50. Sas-Korczynska B, Reinfuss M, Mitus JW, Pluta E, Patla A, Walasek T. Radiotherapy alone as a method of treatment for sinonasal mucosal melanoma: a report based on six cases and a review of current opinion. *Rep Pract Oncol Radiother*. 2018;23:402-406.
51. Ferella L, Cavallo A, Miceli R, et al. Prognostic role of primary tumor, nodal neck, and retropharyngeal GTVs for unresectable sinonasal cancers treated with IMRT and chemotherapy. *Tumori*. 2019;106(1):39-46.
52. Thierauf J, Gluck AM, Plinkert P, et al. Mucosal melanoma of the cranio-facial region: Surgical challenges and therapeutic options. *Auris Nasus Larynx*. 2019;46:252-259.
53. Uchida D, Shirato H, Onimaru R, et al. Long-term results of ethmoid squamous cell or undifferentiated carcinoma treated with radiotherapy with or without surgery. *Cancer J*. 2005;11:152-156.
54. Combs SE, Konkel S, Thilmann C, Debus J, Schulz-Ertner D. Local high-dose radiotherapy and sparing of normal tissue using intensity-modulated radiotherapy (IMRT) for mucosal melanoma of the nasal cavity and paranasal sinuses. *Strahlenther Onkol*. 2007;183:63-68.
55. Hoppe BS, Wolden SL, Zelefsky MJ, et al. Postoperative intensity-modulated radiation therapy for cancers of the paranasal sinuses, nasal cavity, and lacrimal glands: technique, early outcomes, and toxicity. *Head Neck*. 2008;30:925-932.
56. Prognostic analysis of patients with locally advanced nasal cavity and sino-nasal carcinoma treated by radiotherapy. 2011.
57. Al-Mamgani A, Monserez D, Rooij P, Verduijn GM, Hardillo JA, Levendag PC. Highly-conformal intensity-modulated radiotherapy reduced toxicity without jeopardizing outcome in patients with paranasal sinus cancer treated by surgery and radiotherapy or (chemo) radiation. *Oral Oncol*. 2012;48:905-911.
58. Wiegner EA, Daly ME, Murphy JD, et al. Intensity-modulated radiotherapy for tumors of the nasal cavity and paranasal sinuses: clinical outcomes and patterns of failure. *Int J Radiat Oncol Biol Phys*. 2012;83:243-251.
59. Kaur G, Kane AJ, Sughrue ME, et al. The prognostic implications of Hyam's subtype for patients with Kadish stage C esthesioneuroblastoma. *J Clin Neurosci*. 2013;20:281-286.
60. Fossati P, Molinelli S, Matsufuji N, et al. Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy. *Phys Med Biol*. 2012;57:7543-7554.
61. Wang W, Huang Z, Sheng Y, et al. RBE-weighted dose conversions for carbon ionradiotherapy between microdosimetric kinetic model and local effect model for the targets and organs at risk in prostate carcinoma. *Radiother Oncol*. 2019;144:30-36.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Zhang W, Hu W, Hu J, et al. Carbon ion radiation therapy for sinonasal malignancies: Promising results from 2282 cases from the real world. *Cancer Sci*. 2020;111:4465–4479. https://doi.org/10.1111/cas.14650