Chronic rhinosinusitis in nasopharyngeal carcinoma patients post-IMRT: a meta-analysis

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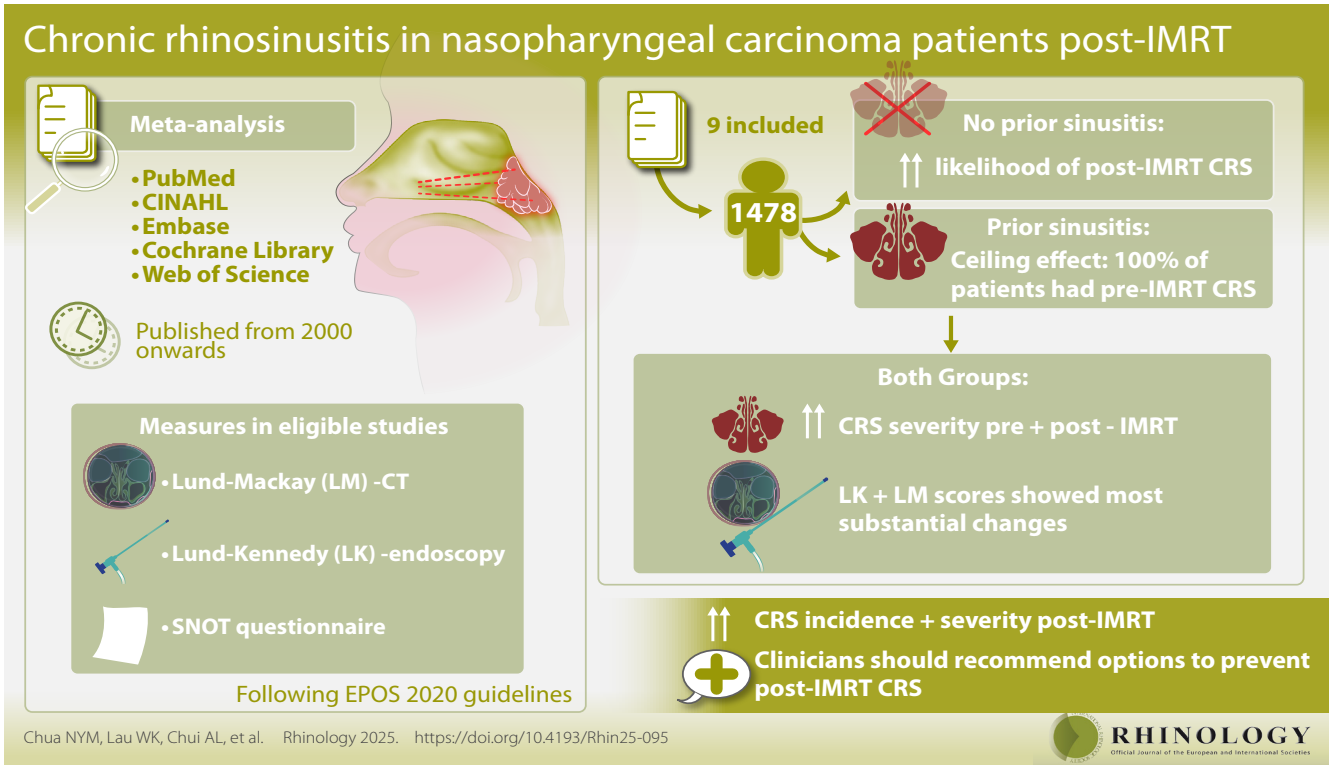

Abstract

Background: Intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma (NPC) can cause chronic rhinosinusitis (CRS), an underexplored side effect. This review aimed to determine the incidence and severity of CRS in NPC patients post-IMRT.

Methods: Electronic databases (PubMed, CINAHL, Embase, Cochrane Library, Web of Science) were searched for studies published from 2000 onwards. Eligible studies assessed CRS in NPC patients post-IMRT, using validated methods per EPOS 2020 (Lund-Mackay (LM) CT scoring, Lund-Kennedy (LK) endoscopic scoring, SNOT questionnaire). Meta-analysis was conducted using SPSS and R to quantify pooled CRS incidence and severity.

Results: Nine studies (n=1,478) were included, revealing distinct patterns in CRS development and severity. Patients without prior sinusitis showed significantly increased likelihood of developing CRS post-IMRT, while those with prior sinusitis had reduced odds due to a ceiling effect, as CRS was already present in 100% of these patients before IMRT. Both groups showed significant increases in CRS severity pre- and post-IMRT, with the LK and LM scoring methods showing the most substantial changes.

Conclusions: This review underscores the significant increases in both the incidence and severity of CRS in NPC patients post-IMRT. Clinicians should recognise the risk of CRS post-IMRT and recommend options to reduce the likelihood of CRS development.

Key words: nasopharyngeal carcinoma, intensity-modulated radiotherapy, VMAT, proton therapy, helical tomotherapy, chronic rhinosinusitis

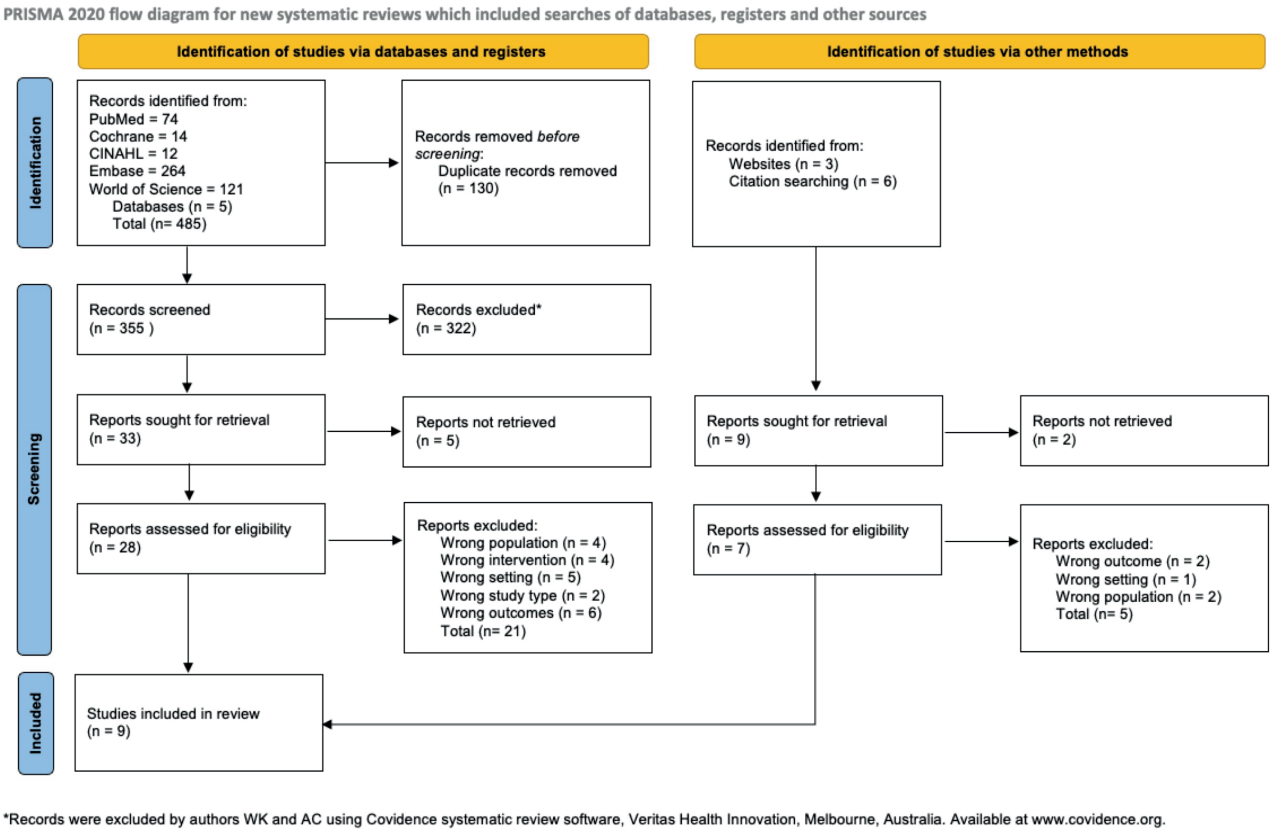

Figure 1. PRISMA chart showing database search conducted.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant head and neck cancer arising from the epithelial lining of the nasopharynx [1], primarily caused by genetic factors and Epstein-Barr Virus, along with influences such as diet, lifestyle, and environmental exposures [2]. Classified by the WHO into four subtypes (Type 1, 2a, 2b, C), the keratinizing subtype (Type 1) has the poorest prognosis [3]. NPC is rare globally (<1 in 100,000) but exceeds 20 in 100,000 in endemic East Asia [4]. Recent declines in NPC incidence and mortality are attributed to Intensity-Modulated Radiotherapy [5,6] (IMRT), which improves target conformity [7] while reducing toxicities like xerostomia (23%-45%), grade 3 dysphagia (15%-30%), and mucositis (30%-70%), compared to conventional radiotherapy [8]. IMRT, with an overall survival (OS) of 87.4% [9,10], can cause acute toxicities like mucositis and late effects such as xerostomia and hearing loss [11]. IMRT, including its subtypes like Volumetric-Modulated Arc Therapy (VMAT) and Tomotherapy, have become the gold standard for NPC treatment due to its precision and adaptability [12]. However, despite its advantages, one side effect – rhinosinusitis - remains poorly studied and underexplored, particularly in relation to its incidence and severity following IMRT. This paper focuses on investigating rhinosinusitis as a side effect of IMRT, addressing a critical gap in the literature.

Numerous studies establish IMRT toxicities, but sinus toxicities remain underexplored. Existing studies [13] investigating 3D conformal radiotherapy and its effect on head and neck cancers found that up to 40% of patients presented with Chronic Rhinosinusitis (CRS) 3 months after treatment, with marked impairment of olfactory functions [14]. With such a high incidence of sinusitis in 3D conformal radiotherapy, it stands to reason that IMRT would also have its own associated risks of developing CRS. To our knowledge, we are the first systematic review to specifically focus on the incidence and severity of rhinosinusitis post IMRT in NPC patients. Other systematic reviews [15,16] have been conducted on the side effects of radiotherapy of NPC patients but these either focused on radiotherapy as a whole and not on IMRT or on general head and neck cancers. In our review, we have included a stricter definition for CRS and assessed only papers published after 2000. The incidence of CRS post IMRT and its extent were investigated in depth. Although there is much evidence to support radiation as a cause of CRS, it is not discussed in detail in the landmark papers the 'European Position Paper on Rhinosinusitis and Nasal Polyps 2020' [17] (EPOS 2020) or the 'International consensus statement on allergy and rhinology: rhinosinusitis 2021' [18] (ICAR-RS-2021) and currently is not well-established as a cause of CRS. This paper aims to address that by highlighting the high likelihood of patients developing/worsening CRS after using advanced radiotherapy modalities and to highlight any possible adjunct therapies.

Methods

Outcomes measured

The following outcomes were assessed in the study but were not used as a basis to include or exclude any studies.

Primary outcome

Incidence and severity/extent of chronic rhinosinusitis post IMRT as reported by the studies with more than ≥12 weeks of rhinosinusitis as defined through EPOS 2020 [19] and ICAR-RS-2021 [18] specified methods such as endoscopic scoring (Lund-Kennedy scoring), CT changes (Lund-Mackay scoring) or clinical assessment of ≥2 symptoms of: 1) Nasal blockage/obstruction/congestion or nasal discharge, 2) Facial pain/pressure, 3) Reduction or loss of smell.

Secondary outcomes [20]

Additional secondary outcomes such as: 1) Other objective physiological [21] measurements such as dosimetric predictors, nasal volume, nasal peak flow etc., 2) Therapies for post-IMRT CRS were also assessed

Database search

Five databases (PubMed, CINAHL, Embase, Cochrane, Web of Science) yielded 355 studies after removing duplicates. The PICO Table and exclusion criteria are included in the supplementary (Table S1, Table S2). The search criteria only included studies from the year 2000 onwards to match the definitions of CRS as mentioned in ICAR-RS-2021 and EPOS 2020.

Study selection

The search results were exported to a Zotero library, and duplicates were removed using the Covidence duplicate removal function. Remaining articles were imported into Covidence, where two reviewers, WK and AC, independently screened titles and abstracts using inclusion and exclusion criteria in an independent, blinded process. Articles were appraised using the University of Oxford Centre for Evidence-Based Medicine tool [22] to assess reliability and applicability. Full texts were reviewed by WK and AC, with NC resolving disagreements. Exclusion reasons were documented, and most extracted papers were expected to be retrospective due to the study population.

Data extraction

Data from each study was extracted into a standardised extraction template and tabled in Microsoft Excel under pre-determined headers (Table S3).

Risk of Bias assessment in included studies

Bias in any RCTs were assessed using Cochrane's Risk of Bias (RoB) tool 2.0 (Table S4) as specified in the Cochrane Handbook for systematic reviews of interventions, version 6.4 [23]. Retrospective studies were assessed using the ROBINS-I tool as it was more appropriate to the intents and purposes of the study (Table S4). Two review authors independently used the criteria above to assess bias and resolved any differences by discussion along with a third reviewer.

Measurement of treatment effect

Peto's log odds ratio (OR) was used for binary outcomes due to cases of no sinusitis at all prior to IMRT, which made log odds inappropriate. Standardised mean difference (SMD) or Cohen's d was used for continuous outcomes, assuming normal data distribution. Without control groups, SMD indicates only the magnitude of change (extent of sinusitis) and not causation. Missing data for effect size calculation prompted attempts to contact authors; if unsuccessful, alternative methods, such as using P-values, were employed.

Unit of analysis issues

Due to the retrospective nature of most studies, cohort-level data were used instead of individual-level analysis. Many studies lacked control groups, so mean pre- and post-intervention scores were used for continuous outcomes. For studies with multiple follow-ups, data ≥3 months closest to peak CRS incidence or severity were used. Subgroups were analysed independently, and attempts were made to contact authors of studies with missing data; unresponsive studies were excluded.

Statistical analysis and meta-analysis

Studies were assessed for clinical and methodological heterogeneity. Meta-analysis was performed if protocols and outcomes were comparable. Heterogeneity was assessed using I^2, Cochran's Q, and meta-regression if possible. Publication bias was evaluated with a funnel plot and Egger's test, applying the trim-and-fill method if needed. Fixed-effect models were used for low heterogeneity, and random-effects models for high heterogeneity. If meta-analysis was not possible, outcomes were summarized with tables and forest plots. Statistical analyses were conducted using R (v2024.09.1+394) and SPSS (v29). Subgroup analyses explored scoring methods, concurrent chemotherapy, geographical location, prior sinusitis, and follow-up duration, with sensitivity analyses addressing bias, outliers, and extreme weights.

Results

Search strategy results

Using the outlined search strategy (Table S5), 485 studies were identified. After removing duplicates and screening titles and abstracts, 33 studies underwent full-text review. Of these, 26 were excluded for not meeting the PICO framework. 2 additional studies were included from citation searches, resulting in 9 studies for analysis. The study selection process is shown in the PRISMA chart (Figure 1).

Table 1. Characteristics of studies assessing CRS incidence post IMRT.

S/N	First author, year	Country	Study design	Incidence of sinusitis in NPC based on study	Final sample size	IMRT dosage/ GTV	Concurrent chemotherapy (%)	Sinusitis diagnosis criteria	Incidence of sinusitis before RT	Incidence of sinusitis after RT	Peto's Odds ratio (OR)	Effect size	Follow-up duration
1	Bao Xiaomin et al., 2023	China	Retrospective study	37.50%	196	68-76 Gys	87.2	CT scoring (Non-LM)	0 (0%)	93 (47.7%)	10.04, (95% CI: 5.78 – 17.45, P= 0.00)	2.307, (95% CI: -1.754 – 2.859, P<0.001)	12 months
2	Chih-Jen Huang et al., 2019	Taiwan	Retrospective study	54.30%	125 (Prior sinusitis)	70 Gys	83.5	LM ≥ 4	125 (100%)	91 (72.8%)	0.11, (95% CI: 0.05 – 0.22, P= 0.00)	-2.247, (95% CI: -2.960 – -1.535, P<0.001)	6 months
		Taiwan			105 (No prior sinusitis)				0 (0%)	17 (16.2%)	7.80, (95% CI: 2.98 – 20.45, P= 0.00)	2.054, (95% CI: 1.091 – 3.018, P<0.001)	
3	Hsin Chung-Han et al., 2016	Taiwan	Longitudinal study	12.70%	102	70 Gys	91.2	LM ≥ 3 on same paranasal side	13 (12.7%)	17 (16.7%)	1.36, (95% CI: 0.63 – 2.96, P= 0.43)	0.311, (95% CI: -0.462 – 1.084, P=0.430)	60 months
4	Su Yan-Xia et al., 2014	Taiwan	Retrospective study	45.20%	128 (Prior sinusitis)	70 Gys	66.4	CT/MRI (scoring system not mentioned)	128 (100%)	115 (89.8%)	0.14, (95% CI: 0.05 – 0.41, P= 0.00)	-1.956, (95% CI: -3.031 – 0.881, P<0.001)	9 months
		Taiwan			155 (No prior sinusitis)				CT/MRI (scoring system not mentioned)	0 (0%)	114 (73.5%)	22.87, (95% CI: 14.45 – 36.20, P= 0.00)	
5	Wei-Chieh Lin et al., 2022	Taiwan	Retrospective study	34.40%	90	60 Gys	86.7	LM ≥ 4	31 (34.4%)	33 (36.7%)	1.10, (95% CI: 0.60 – 2.02, P= 0.76)	0.096, (95% CI: -0.512 – 0.705, P=0.756)	45 months
6	Zheng Wenya et al., 2023	China	Retrospective study	48.80%	98 (prior sinusitis)	60 – 70 Gys	93	LM ≥ 4	98 (100%)	97 (99%)	0.22, (95% CI: 0.03 – 1.58, P= 0.13)	-1.515, (95% CI: -3.484 – 0.455, P=0.132)	24 months
		China			103 (no prior sinusitis)			LM ≥ 4	0 (0%)	94 (91.2%)	31.26, (95% CI: 20.84 – 46.88, P= 0.00)	3.442, (95% CI: -3.037 – 3.848, P<0.001)	24 months

Characteristics of included studies

Nine studies involving 1,478 NPC patients (75.6% male; mean age 48.9 years) were included. Six studies assessed CRS incidence, and six evaluated CRS severity post-IMRT. Only one study each reported secondary outcomes, including olfactory tests, physiological measures, or adjunct therapies. Seven studies were retrospective [24–30], with one longitudinal [31] and one randomised controlled trial [32]. Study characteristics are detailed in Tables 1 and 2, and risk of bias assessments are provided in the supplementary (Table S6, Table S7). Sensitivity analyses were performed to assess study impacts on overall findings.

Absolute incidence and severity of CRS

Nine datasets from six studies assessed CRS incidence, three with distinct populations with and without prior CRS [25,26,30]. Of these, six data sets [24–26,28,30,31] showed an absolute increase

Table 2. Characteristics of studies assessing the severity and extent of CRS post IMRT

S/N	First author, year	Study design	Incidence of sinusitis in NPC based on study	Final sample size	IMRT dosage/ GTV	Concurrent chemotherapy (%)	Method of assessing CRS severity	Mean LM score before RT	Mean LM score after RT	SMD	Follow up duration
1	Hsin Chung-han et al, 2016	Longitudinal study	12.70%	102	70 Gys	91.2	Lund-Mackay Scoring (LM)	0.77	1.14	0.39, (95% CI: 0.11 – 0.66, P= 0.01)	60 months
2	Liang Kai Li et al, 2008	Randomised controlled trial	Not stated	63 (non-irrigation) 44 (Irrigation)	70 Gys	73.8		0.24 0.7	2.95 3.14	7.08, (95% CI: 6.13 – 8.03, P= 0.00) 3.89, (95% CI: 3.18 – 4.61, P= 0.00)	3 months 3 months
3	Wang Jing-Jie et al., 2015	Retrospective study	Not stated	41	70 Gys	90.2		1.7	3.2	0.52, (95% CI: 0.13 – 0.91, P= 0.01)	12 months
4	Wei-Chieh Lin et al., 2022	Retrospective study	34.40%	90	60 Gys	86.7		7.7	8.1	0.08, (95% CI: -0.21 – 0.38, P= 0.58)	45 months
5	Wu Pei-Wen et al, 2021	Retrospective study	Not stated	54	70 Gys	Majority (number unstated)		0.33	4.02	1.85, (95% CI: -1.39 – 2.30, P= 0.00)	3 months
6	Zheng Wenya et al., 2023	Retrospective study	48.80%	98 (Prior sinusitis) 103 (No prior sinusitis)	60 – 70 Gys	93		7.03 2.08	11.15 8.49	1.23, (95% CI: 0.98 – 1.47, P= 0.00) 2.78, (95% CI: 2.50 – 3.06, P= 0.00)	24 months 24 months
S/N	**First author, year**	**Study design**	**Incidence of sinusitis in NPC based on study**	**Final sample size**	**IMRT dosage/ GTV**	**Concurrent chemotherapy (%)**	**Method of assessing CRS severity**	**Mean LK score before RT**	**Mean LK score after RT**	**SMD**	**Follow up duration**
1	Liang Kai Li et al, 2008	Randomised controlled trial	Not stated	63 (non-irrigation)	70 Gys	73.8	Lund-Kennedy Endoscopic scoring (LK)	1.39	2.80	3.87, (95% CI: 3.20 – 4.54, P= 0.00)	3 months
S/N	**First author, year**	**Study design**	**Incidence of sinusitis in NPC based on study**	**Final sample size**	**IMRT dosage/ GTV**	**Concurrent chemotherapy (%)**	**Method of assessing CRS severity**	**Mean questionnaire score before RT**	**Mean questionnaire score after RT**	**SMD**	**Follow up duration**
1	Liang Kai Li et al, 2008	Randomised controlled trial	Not stated	63 (non-irrigation) 44 (Irrigation)	70 Gys	73.8	SNOT	8.71 6.77	11.43 7.38	2.33, (95% CI: 1.82 – 2.84, P= 0.00) 0.48, (95% CI: 0.04 – 0.92, P= 0.03)	3 months 3 months
2	Wang Jing-Jie et al., 2015	Retrospective study	Not stated	41	70 Gys	90.2	TWSNOT-22	32.1 (SNOT)	28.8 (SNOT)	0.87, (95% CI: -0.61 – 2.34, P= 0.33)	12 months

in CRS incidence post-IMRT, four of which had no prior CRS [24–26,31]. Conversely, three data sets [25,26,30] showed decreased CRS incidence post-IMRT, as these included only patients with pre-existing sinusitis (Table 1).

Six studies [27–32] evaluated CRS severity, primarily using Lund-Mackay (LM) scores, with all studies reporting increased LM scores post-IMRT (Table 2). Only one study reported Lund-Kennedy (LK) scores [32], and two studies included questionnaire scores [27,32]. Liang [32] showed increased LK and questionnaire scores in both irrigation and non-irrigation groups, while Wang [27] reported a questionnaire score decrease.

Meta-synthesis assessing CRS incidence

Ultimately, a random-effects model with the generic inverse-variance weighting method and Knapp-Hartung adjustments was used. A common estimate of between-study heterogeneity was used for subgroup analyses with ≤5 studies. 95% confidence intervals (95% CI) were calculated, and P-value ≤0.05 was taken for statistical significance.

The incidence of CRS post-IMRT was assessed with subgroup analysis for populations with and without prior sinusitis. The overall Peto's OR was 1.98 (95% CI: 0.47–8.36; P = 0.26>0.05), though a small number of studies limited statistical power and increased random variation (Figure 2, Table S8). In the "No prior sinusitis" subgroup, Peto's OR was 16.60 (95% CI: 8.87–31.07; P < 0.05), while the "Prior sinusitis" subgroup showed no significant reduction in CRS odds (Peto's OR: 0.37; 95% CI: 0.12–1.12; P = 0.08>0.05) likely due to a ceiling effect as CRS was already present in all the patients. I^2 values were 81% and 87.6%, with significant OR differences between subgroups (Q = 33.95, P < 0.05), emphasizing the importance of establishing prior sinusitis in the analysis.

Further subgroup analysis was conducted (Figure S1) using the follow-up duration of >12 months and patient's nationalities as the subgroups. Analysis was not conducted for presence of concurrent chemotherapy or scoring method used as these were largely homogenous across all the studies assessed. Subgroup analysis based on follow-up duration showed that both the "No" groups (<12 months) and "Yes" groups (>12 months) had P>0.05 with high I^2 values. A Q-value = 0.0001, P = 0.989>0.05 indicated no significance difference in odds ratios between subgroups (Table S10). For geographic location, the "Mainland China" and "Taiwan" subgroups also reported P >0.05 with high I^2 values, and a Q-value = 0.617, P = 0.432>0.05 further confirmed no significant differences in odds ratios between these subgroups.

Meta-synthesis assessing CRS severity

CRS severity post-IMRT was assessed using SMD for LK, LM, and SNOT scoring methods, compiled into a forest plot with method subgroups. The overall SMD was 2.09 (95% CI: 0.99–3.19; P < 0.05), indicating a significant effect of IMRT on CRS severity (Figure 3, Table S10). Subgroup analysis revealed the "LK" subgroup had a SMD of 3.55 (95% CI: 2.92–4.18; P < 0.05, I^2 = 44.1%), indicating low heterogeneity. The "LM" subgroup had a significant SMD value of 2.20 (95% CI: 0.60–3.80; P < 0.05, I^2 = 99.4%) while the "SNOT" subgroup had a SMD value of 0.87 (95% CI: -0.61–2.34; P > 0.05, I^2 = 97.0%), respectively. Significant differences between scoring methods were observed (Q = 11.887, P < 0.05).

Further subgroup analysis was done using LM scoring as the representative data set (Figure S2). More details on the subgroup analysis are in the appendix (Table S11). The presence of prior sinusitis, follow-up duration >12 months and patient nationalities were used as subgroups. Subgroup analysis based on prior sinusitis showed both "No" and "Yes" groups had P<0.05 and high I^2 values, indicating heterogeneity within subgroups. A Q-value = 8.237, P = 0.001<0.05 indicated significant differences between subgroups. For follow-up duration, the "No" group (<12 months) had P<0.05, while the "Yes" group (>12 months) had P>0.05, both with high I^2 values. A Q-value = 2.015, P = 0.156>0.05 showed no significant difference. For geographic location, the "Mainland China" and "Taiwan" subgroups reported P<0.05 with high I^2 values, but Q = 0.041, P = 0.839>0.05 indicated no significant differences in odds ratios.

Heterogeneity

Heterogeneity was assessed for CRS incidence and severity post-IMRT, with both showing high variability. CRS incidence had an I^2 of 98%, Q = 324.64, P < 0.05, and T^2 = 4.66, while CRS severity showed an I^2 of 99%, Q = 602.32, P < 0.05, and T^2 = 4.05. The high heterogeneity was expected due to the small number of studies and the predominantly retrospective designs.

Small sample effect and publication bias

Funnel plots were plotted for both CRS incidence and severity in the supplementary (Figure S3, Figure S4). Visual inspection suggested potential small study effects or publication bias but once again should be interpreted cautiously due to fewer than 10 studies. Trim-and-Fill analyses (Table S12, Table S13) found no missing studies, with the observed effect size unchanged, suggesting publication bias likely did not influence the effect size estimate. Egger's regression test was not performed as there were fewer than 10 studies.

Sensitivity analysis

Excluding studies with moderate or high bias showed consistent effect sizes, though Bao [24] and Huang [25] had the largest impacts (Table S14). Bao [24] used non-standardised CRS diagnostic methods and excluded patients with prior sinusitis, while Huang

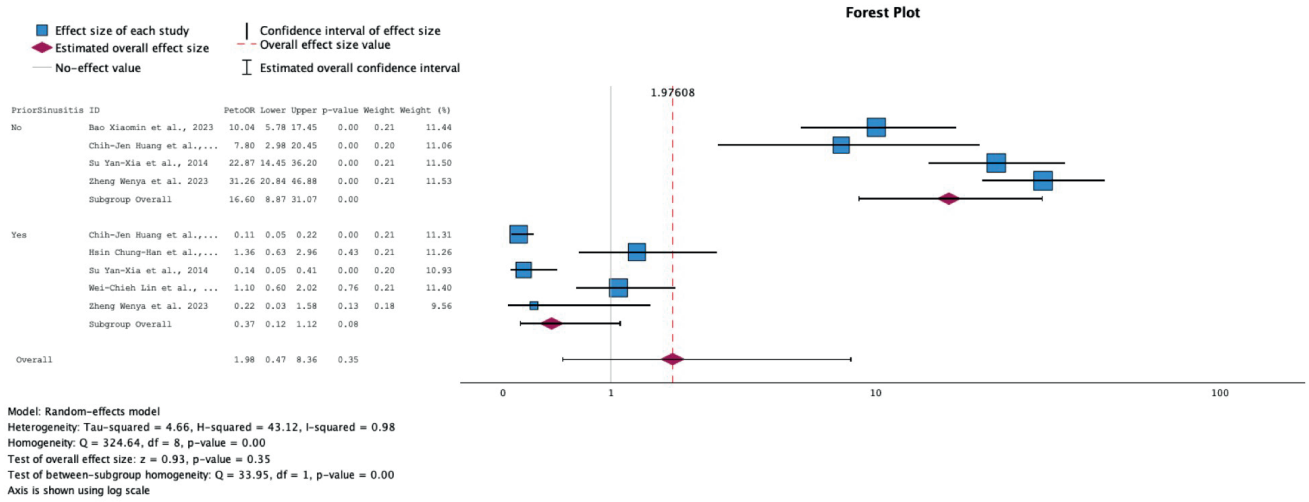

Figure 2. Forest plot of CRS incidence using Peto's OR.

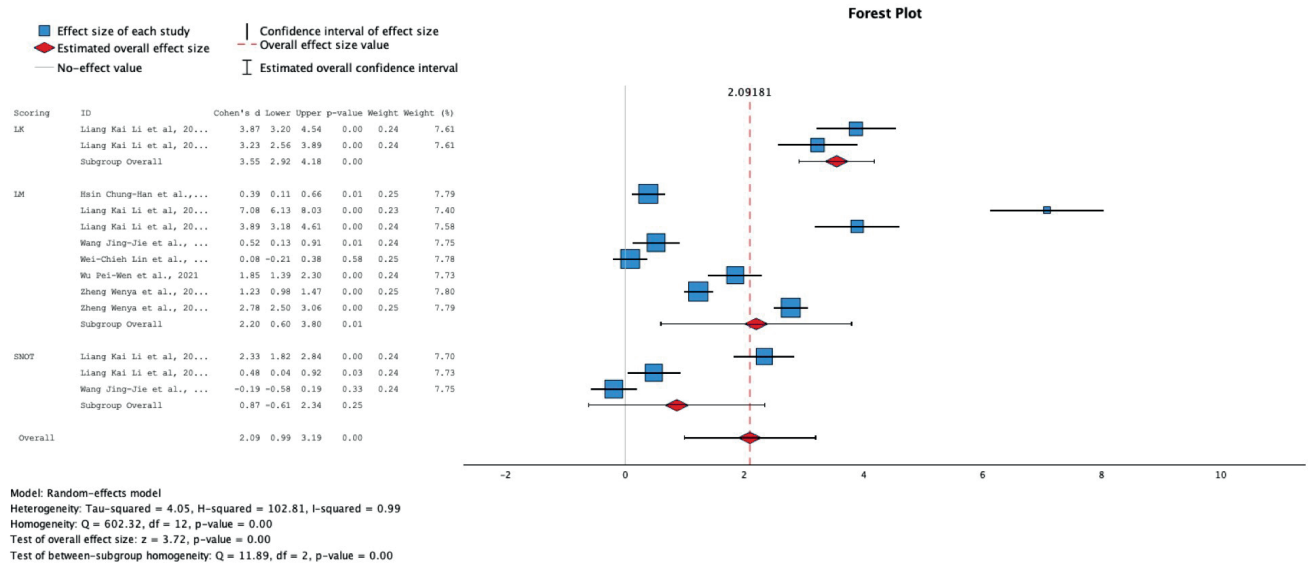

Figure 3. Forest plot of CRS severity using SMD.

[25] had the highest proportion of prior sinusitis cases and the shortest follow-up time. Sensitivity analyses on CRS severity also showed consistent results, except for Liang [32] and Wang [27] (Table S15). Wang [27] introduced variability due to high heterogeneity and patient loss to follow-up, while Liang [32], the only RCT, had the most significant effect size and was further analysed individually. High heterogeneity likely amplified these effects.

Additional analysis on RCT

Additional analysis was conducted on Liang [32] as it was the only RCT among the studies extracted. The study had an overall Cohen's d of 3.46 (95% CI: 1.73-5.18; P=0.00<0.05) which suggested that the data was statistically significant and IMRT did worsen CRS severity (Figure S5). Out of the 3 scoring modalities for Liang [32], the SNOT score was statistically insignificant with a P-value= 0.13>0.05. Overall heterogeneity was still high, but the data sets assessed using the LK score was the least heterogeneous.

Temporal development of symptom scores

Longitudinal analyses demonstrate peak CRS symptom severity within 3 months post-IMRT. Liang, 2008 [32] observed maximal nasal obstruction (Lund-Kennedy score: 3.67 ± 0.78) at 2–3 months in non-irrigation cohorts, with earlier resolution (1.47 ± 0.29 by 3 months) in irrigation groups. Huang [25] reported acute mucosal oedema in 78% of patients at 3 months (Lund-Mackay CT >8), persisting in 42% at 6 months. Lin [28] linked worsening Lund-Mackay scores post-IMRT to poor survival, reflecting acute-phase inflammatory burden. These findings underscore the critical 3-month window for monitoring CRS progression.

Relationship between T-staging and CRS

Advanced T-stage tumours (T3–T4) were also associated with significantly greater CRS severity. Patients [25] with T4 tumours exhibited 2.3-fold higher mucosal thickening on MRI (LM scores: 8.4 vs. 3.7, P = 0.01) and 58% higher CRS incidence at 12 months post-IMRT compared to T1–T2 cases. This disparity correlated [26] with larger irradiated sinus volumes (mean maxillary sinus dose: 54 Gy for T4 vs. 42 Gy for T1; P < 0.01), as broader radiation fields [24] for advanced tumours encompassed ethmoid and sphenoid sinuses. Prolonged mucosal oedema [25] (Lund-Mackay >8 in 63% of T4 vs. 28% of T1–T2 at 6 months) further underscored the dose-dependent mucosal toxicity in advanced T-stage disease.

Alternative physiological measurements

Bao [24] was the only paper to assess alternative physiological measurements of CRS. In the study, dose-volume histogram parameters of the sinuses were used to predict the outcome of sinusitis after being exposed to certain amounts of irradiation. The results demonstrated that there was a statistically significant relationship when more than 70 Gys were used between IMRT and sinusitis.

Post IMRT CRS therapies

Liang [32] assessed the effectiveness of nasal irrigation on post-IMRT CRS. It was found that patients who underwent concurrent nasal irrigation had fewer nasal complaints and less severe endoscopic findings when compared to those who did not receive any nasal irrigation. Patients in the non-irrigation group had significantly higher SNOT and endoscopic scores compared to the irrigation group from pre-RT to 6 months after. There was no significant difference in the CT scores between the two groups.

Discussion

NPC, one of the most common head and neck cancers in Asia, is closely associated with the EBV virus and presents with a range of symptoms, from nasal to neurological [33]. Notably, NPC itself increases the risk of CRS, with patients being 1.8 times more likely to develop chronic sinonasal inflammation compared to the general population [34]. Chee et al. [35] reported CRS incidence in East Asia to be 8-14.2%, much lower than the 38.8% observed in NPC patients in this study, indicating that NPC alone accounts for a 24% increase in CRS incidence. This study further found that IMRT raises CRS incidence by an additional 8.2%, with 47% of patients without prior sinusitis developing CRS. Additionally, IMRT significantly worsened CRS severity, increasing Lund-Mackay scores from a baseline of 2.57 to 5.28, surpassing the threshold for clinically significant CRS per ICAR-RS-2021 [18] and EPOS 2020 [19]. These findings highlight the heightened risk and severity of CRS in NPC patients post-IMRT.

The mechanism linking NPC and CRS remains unclear, with two main theories: inflammation and sinus drainage obstruction. NPC was shown to have substantial leukocyte infiltration and elevated inflammatory markers [36], including CCL3, CCL4, CCL20, IL-1α, IL-1β, IL-6, IL-8, and IL-10 [37], many of which are key in CRS development [38–41]. Overexpression of these markers via the NF-κB and STAT3 pathways [42], promotes neutrophil and eosinophil activity [43,44], causing inflammation and symptoms like nasal congestion and loss of smell. Additionally, sinus drainage obstruction from tumour invasion or altered microbiota predisposes patients to secondary bacterial infections [45,46]), further contributing to CRS development.

Radiation has also been established as a major cause of CRS, with studies [47–50] demonstrating that radiotherapy increases rhinosinusitis incidence by up to 86.1% [15]. This is supported by our results which shows that the average incidence of NPC patients developing CRS post IMRT is 60.4%, a 21.2% increase from patients developing CRS due to NPC alone. The results obtained show that NPC patients are 1.98 times more likely to develop CRS after IMRT and have a marked increase in the extent and severity of CRS. Patients without prior sinusitis were 16.6 times more likely to develop CRS post-IMRT, while those with prior CRS showed increased severity. Interestingly, Su et al. [24] and Yuan et al. [51] reported that sinusitis might have resolved in patients who had sinusitis prior to IMRT due to decreased tumour size, smoother sinus drainage, or gradually decreased sinus effusion. Further subgroup analysis showed that the incidence of sinusitis is not affected much by the geographical location of the patient or follow-up duration.

The pathophysiology linking CRS and radiotherapy primarily involves ionizing radiation damaging the nasal epithelial barrier, making it more susceptible to infections [52,53], altering the sinonasal microbiome toward *Staphylococcus* dominance and *Fusobacterium* depletion, which exacerbates susceptibility to pathogenic colonization [54]. Microbial translocation into deeper epithelial layers stimulates the immune system [55], triggering a cycle of inflammation and further epithelial damage [56,57]. Radiation was also found to significantly reduce both the quantity and functionality of ciliated cells in the nasal cavity, impairing mucociliary clearance [58–60] - a critical defence mechanism against CRS [61]. Concurrently, irreversible epithelial damage [62] including goblet and basal cell depletion [63,64] (evidenced by decreased levels of p63, Ki67, MUC5AC, and Tap73) creates a niche for dysbiosis-perpetuated chronic inflammation.

The peak in CRS severity at 2–3 months post-IMRT reflects acute-phase mucosal injury driven by radiation-induced epithelial necrosis, ciliary loss, and pro-inflammatory cascades (IL-6, TNF-α) that amplify oedema and crust formation [65]. Direct DNA damage to rapidly dividing mucosal cells triggers apoptosis,

while secondary oxidative stress generates reactive oxygen species (ROS), destabilizing mucosal integrity. These acute-phase changes are exacerbated in advanced T-stage tumors (T3–T4), where broader radiation fields increase integral sinus doses (>45 Gy), amplifying stromal ROS and TGF-β1 signalling [66]. Beyond 3 months, fibroblast activation and squamous metaplasia dominate, driven by sustained TGF-β1 and IL-6 [67].

Various treatment modalities have been proposed to manage radiation-induced CRS. Nasal irrigation, supported by Liang et al. [32] in an RCT showed reduced LM and LK scores post-IMRT in patients using irrigation during treatment. Similarly, Luo et al. [68] demonstrated a decrease in sinusitis incidence at one year for patients using disposable nasal irrigators compared to those who did not. Endoscopic sinus surgery (ESS) is another effective option; Ayoub et al. [69] and Hu et al. [70] reported improved nasal function, reduced SNOT scores (15-point decrease), and shorter saccharin transit times in post-IMRT CRS patients undergoing ESS. ESS also enhances sinus drainage and facilitates better access for topical therapies like nasal irrigation, aiding mucosal recovery. Additionally, studies [49,71] found that combining oral traditional Chinese medicine and intranasal steroids with nasal irrigation significantly improved quality of life and CRS symptoms. These adjunct treatments show promise but require further research to better define their role in managing radiation-induced CRS.

Limitations

Due to the nature of our question, most studies were retrospective with diverse methodologies contributing to high heterogeneity. While multiple CRS severity assessment modalities were accounted for, there was a lack of studies using the LK staging system or SNOT QOL score, both having strong correlations with LM scores and crucial for data robustness [72]. Standardising CRS severity assessment methods could enable more meaningful comparisons between pre- and post-IMRT CRS severity. Additionally, petro-clival osteoradionecrosis, a rare but severe late complication, was not assessed in included studies. Recent case reports highlight its incidence in 3–5% of NPC patients receiving >70 Gys to the skull base [73], warranting future studies.

Conclusion

This is the first study of its kind to assess the incidence burden of CRS from NPC and from IMRT separately. It highlights the distinct link between IMRT and the subsequent development of Chronic Rhinosinusitis. Despite IMRT being more precise and effective for head and neck cancers such as NPC, it not only increases the odds of NPC patients developing CRS after IMRT but also worsens the extent and severity of CRS. Thus, clinicians should recognise the risks of CRS associated with IMRT and consider evidence-based treatments post-IMRT such as ESS.

Further research

Future prospective studies and randomised controlled trials are needed to better evaluate the extent of IMRT-related damage and its relationship with CRS. The lack of data from western populations limits generalizability, as all studies were based in Asia. Additionally, the effects of CRS on individual sinuses remain unexplored and warrant further investigation.

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Authorship contribution

Conception and design of study: DYW, NYMC; Acquisition of data: NYMC, LWK, ACL; Analysis and/or interpretation of data: NYMC, LWK, ACL; Drafting of manuscript: NYMC; Revising of manuscript: NYMC, LWK, ACL, CLG, DYW. All listed authors participated meaningfully in the study and have seen and approved the final manuscript.

Conflict of interest

The authors have no conflicts of interests to declare.

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SUPPLEMENTARY MATERIAL

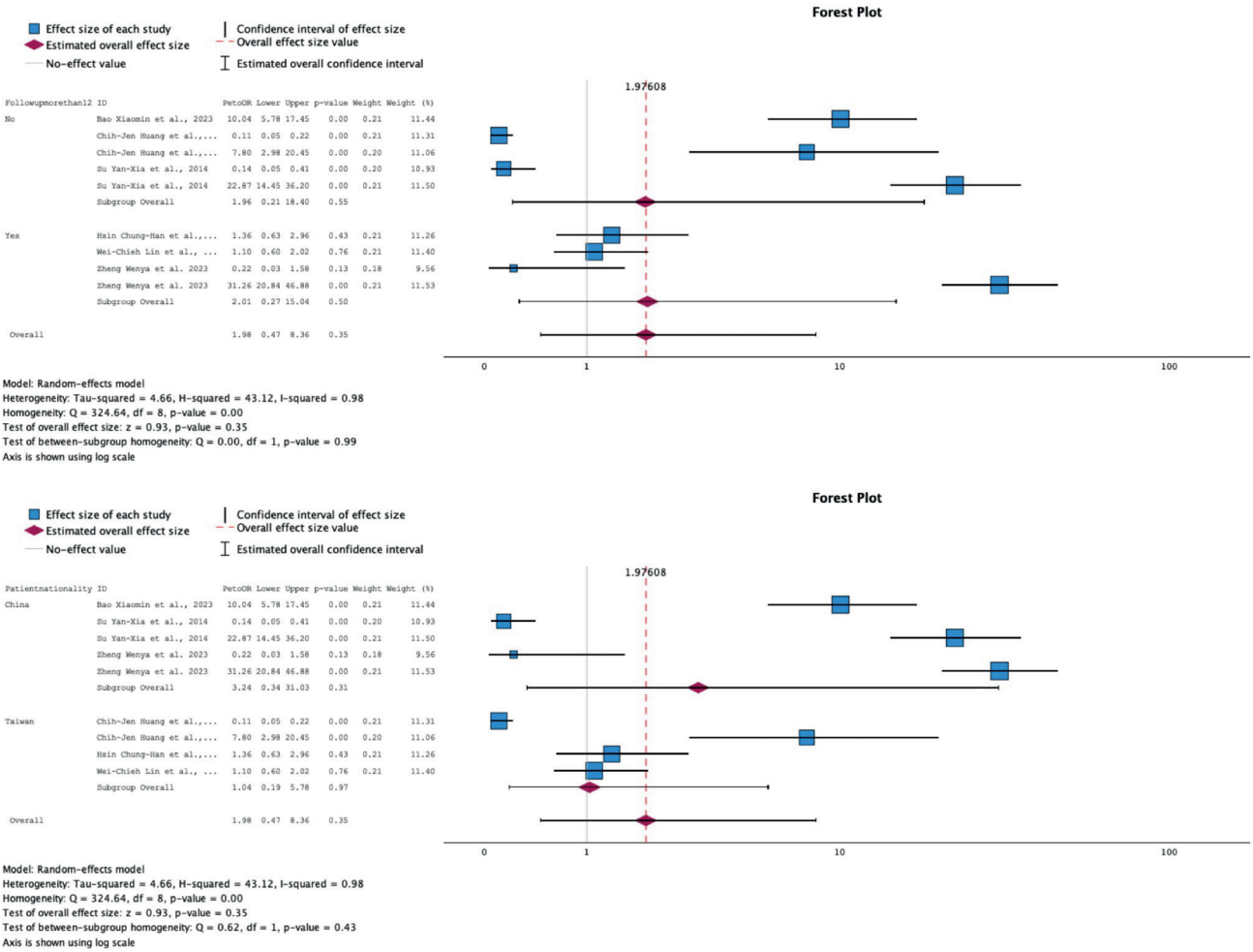
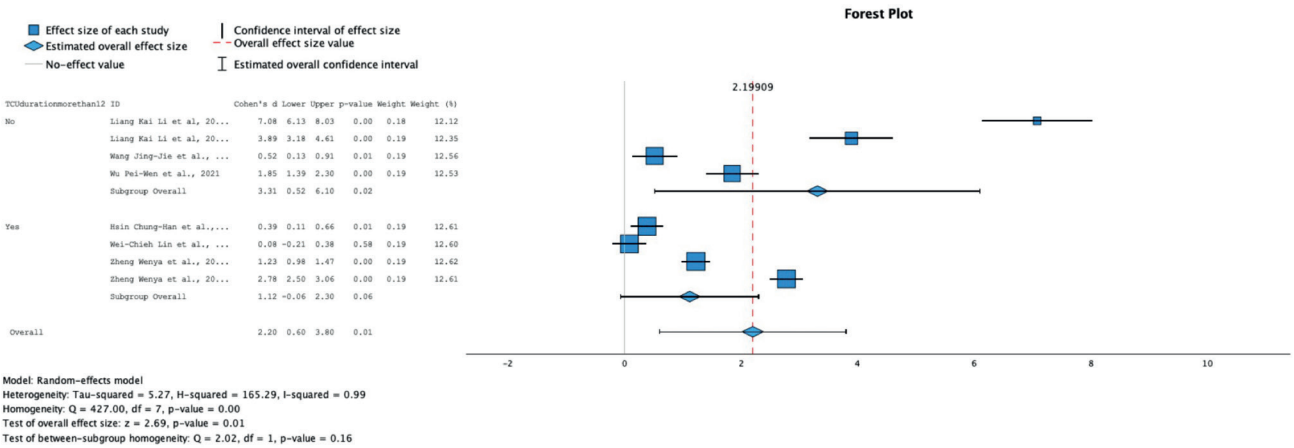
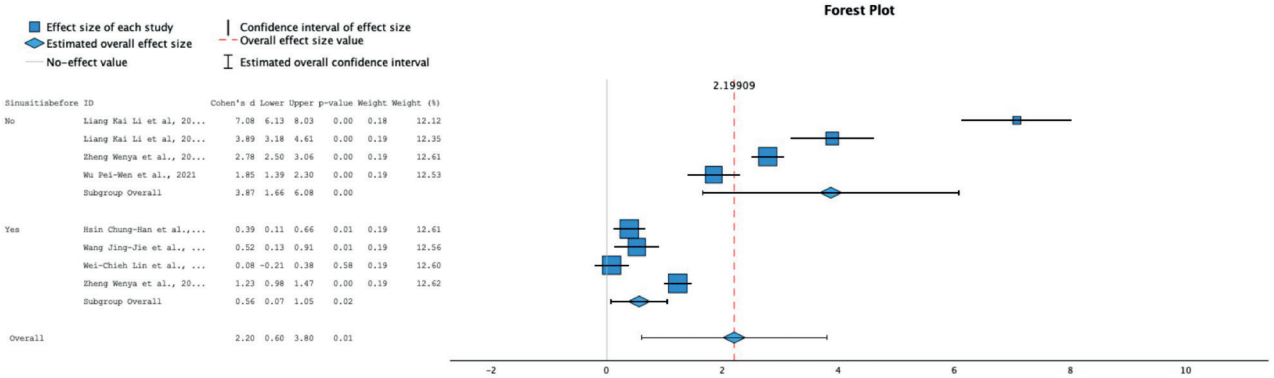


Figure S1. Forest plots of further subgroup analyses conducted for CRS incidence post IMRT.



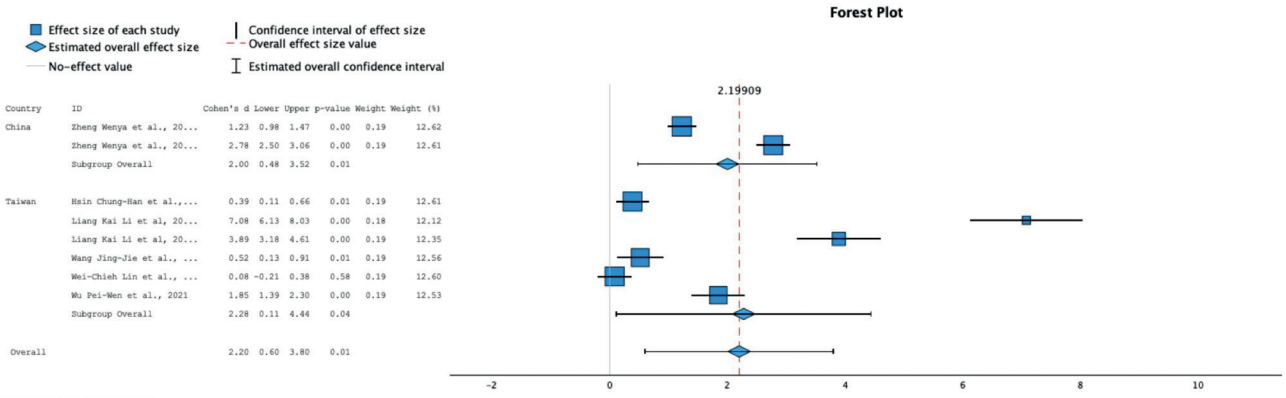
TCUdurationmorethan12	ID	Cohen's d	Lower	Upper	p-value	Weight	Weight (%)
No	Liang Kai Li et al, 20...	7.08	6.13	8.03	0.00	0.18	12.12
	Liang Kai Li et al, 20...	3.89	3.18	4.61	0.00	0.19	12.35
	Wang Jing-Jie et al., ...	0.52	0.13	0.91	0.01	0.19	12.56
	Wu Pei-Wen et al., 2021	1.85	1.39	2.30	0.00	0.19	12.53
	Subgroup Overall	3.31	0.52	6.10	0.02		
Yes	Hsin Chung-Han et al.,...	0.39	0.11	0.66	0.01	0.19	12.61
	Wei-Chieh Lin et al., ...	0.08	-0.21	0.38	0.58	0.19	12.60
	Zheng Wenya et al., 20...	1.23	0.98	1.47	0.00	0.19	12.62
	Zheng Wenya et al., 20...	2.78	2.50	3.06	0.00	0.19	12.61
	Subgroup Overall	1.12	-0.06	2.30	0.06		
Overall		2.20	0.60	3.80	0.01		

Model: Random-effects model
Heterogeneity: Tau-squared = 5.27, H-squared = 165.29, I-squared = 0.99
Homogeneity: Q = 427.00, df = 7, p-value = 0.00
Test of overall effect size: z = 2.69, p-value = 0.01
Test of between-subgroup homogeneity: Q = 2.02, df = 1, p-value = 0.16



Sinusitisbefore	ID	Cohen's d	Lower	Upper	p-value	Weight	Weight (%)
No	Liang Kai Li et al, 20...	7.08	6.13	8.03	0.00	0.18	12.12
	Liang Kai Li et al, 20...	3.89	3.18	4.61	0.00	0.19	12.35
	Zheng Wenya et al., 20...	2.78	2.50	3.06	0.00	0.19	12.61
	Wu Pei-Wen et al., 2021	1.85	1.39	2.30	0.00	0.19	12.53
	Subgroup Overall	3.87	1.66	6.08	0.00		
Yes	Hsin Chung-Han et al.,...	0.39	0.11	0.66	0.01	0.19	12.61
	Wang Jing-Jie et al., ...	0.52	0.13	0.91	0.01	0.19	12.56
	Wei-Chieh Lin et al., ...	0.08	-0.21	0.38	0.58	0.19	12.60
	Zheng Wenya et al., 20...	1.23	0.98	1.47	0.00	0.19	12.62
	Subgroup Overall	0.56	0.07	1.05	0.02		
Overall		2.20	0.60	3.80	0.01		

Model: Random-effects model
Heterogeneity: Tau-squared = 5.27, H-squared = 165.29, I-squared = 0.99
Homogeneity: Q = 427.00, df = 7, p-value = 0.00
Test of overall effect size: z = 2.69, p-value = 0.01
Test of between-subgroup homogeneity: Q = 8.24, df = 1, p-value = 0.00



Country	ID	Cohen's d	Lower	Upper	p-value	Weight	Weight (%)
China	Zheng Wenya et al., 20...	1.23	0.98	1.47	0.00	0.19	12.62
	Zheng Wenya et al., 20...	2.78	2.50	3.06	0.00	0.19	12.61
	Subgroup Overall	2.00	0.48	3.52	0.01		
Taiwan	Hsin Chung-Han et al.,...	0.39	0.11	0.66	0.01	0.19	12.61
	Liang Kai Li et al, 20...	7.08	6.13	8.03	0.00	0.18	12.12
	Liang Kai Li et al, 20...	3.89	3.18	4.61	0.00	0.19	12.35
	Wang Jing-Jie et al., ...	0.52	0.13	0.91	0.01	0.19	12.56
	Wei-Chieh Lin et al., ...	0.08	-0.21	0.38	0.58	0.19	12.60
	Wu Pei-Wen et al., 2021	1.85	1.39	2.30	0.00	0.19	12.53
	Subgroup Overall	2.28	0.11	4.44	0.04		
Overall		2.20	0.60	3.80	0.01		

Model: Random-effects model
Heterogeneity: Tau-squared = 5.27, H-squared = 165.29, I-squared = 0.99
Homogeneity: Q = 427.00, df = 7, p-value = 0.00
Test of overall effect size: z = 2.69, p-value = 0.01
Test of between-subgroup homogeneity: Q = 0.04, df = 1, p-value = 0.84

Figure S2. Forest plots of further subgroup analyses conducted for studies assessing the severity and extent of CRS post IMRT.

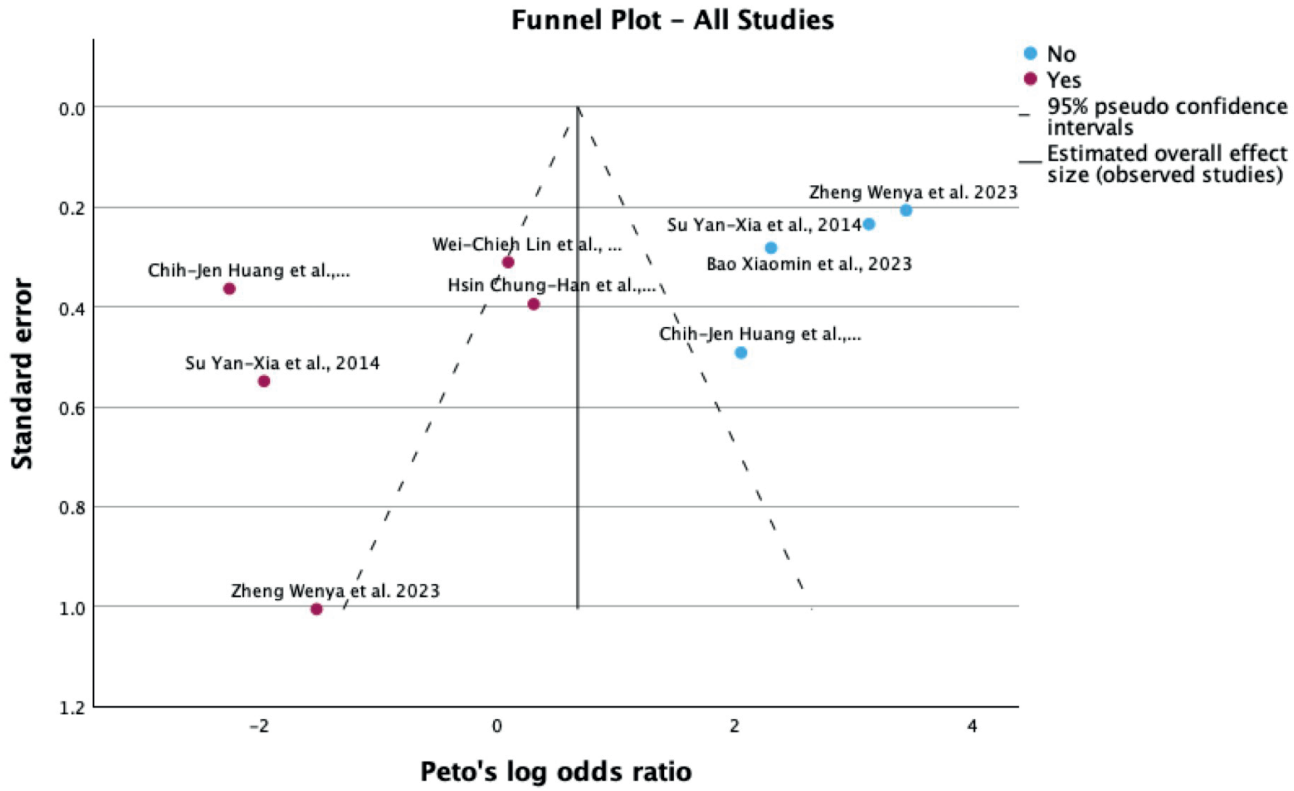


Figure S3. Funnel plot to assess publication bias of studies assessing the incidence of CRS post IMRT.

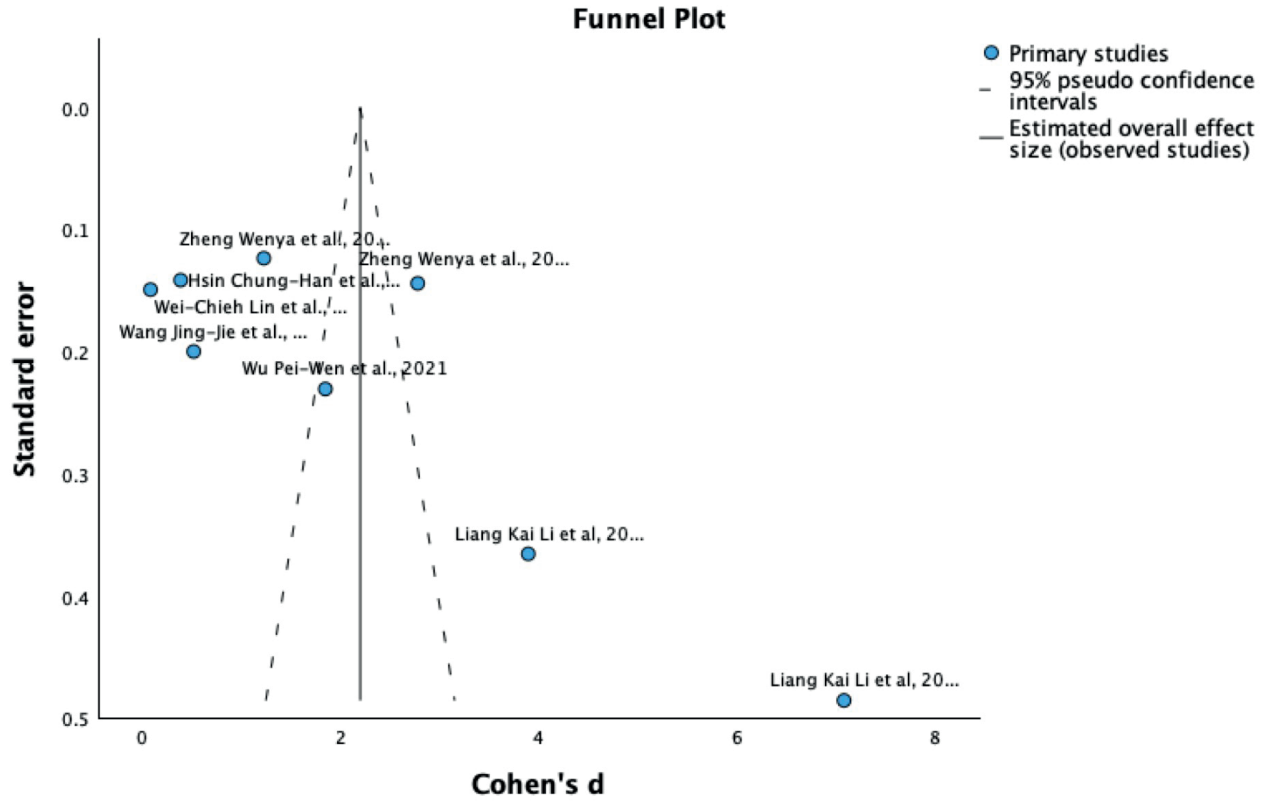
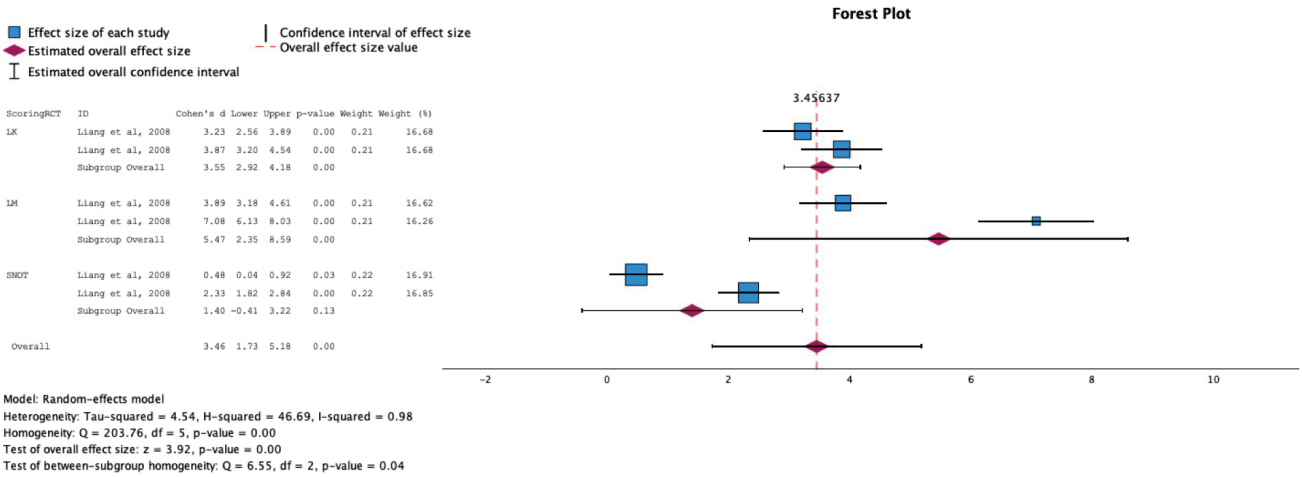


Figure S4. Funnel plot to assess publication bias of studies assessing the severity and extent of CRS post IMRT.



ScoringRCT	ID	Cohen's d	Lower	Upper	p-value	Weight	Weight (%)
LK	Liang et al, 2008	3.23	2.56	3.89	0.00	0.21	16.68
	Liang et al, 2008	3.87	3.20	4.54	0.00	0.21	16.68
	Subgroup Overall	3.55	2.92	4.18	0.00		
LM	Liang et al, 2008	3.89	3.18	4.61	0.00	0.21	16.62
	Liang et al, 2008	7.08	6.13	8.03	0.00	0.21	16.26
	Subgroup Overall	5.47	2.35	8.59	0.00		
SNOT	Liang et al, 2008	0.48	0.04	0.92	0.03	0.22	16.91
	Liang et al, 2008	2.33	1.82	2.84	0.00	0.22	16.85
	Subgroup Overall	1.40	-0.41	3.22	0.13		
Overall		3.46	1.73	5.18	0.00		

Model: Random-effects model
Heterogeneity: Tau-squared = 4.54, H-squared = 46.69, I-squared = 0.98
Homogeneity: Q = 203.76, df = 5, p-value = 0.00
Test of overall effect size: z = 3.92, p-value = 0.00
Test of between-subgroup homogeneity: Q = 6.55, df = 2, p-value = 0.04

Figure S5. Forest plot to assess Liang, 2008 [32] RCT.

PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5-6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Table S1. Table S2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7, 9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 9, Cover page
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8-9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8-9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8

PRISMA 2020 Checklist, *continued.*

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 10-11, Table 1, 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S6, Table S7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table S8, Table S10, Figure 2, 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 10-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 11-13; Figure 2, 3; Figure S1, Figure S2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 11-12, Figure S1, Figure S2, Table S9, Table S11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 12; Table S14, Table S15
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 12; Table S12, Table S13, Figure S3, Figure S4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 14-16
	23b	Discuss any limitations of the evidence included in the review.	Page 17
	23c	Discuss any limitations of the review processes used.	Page 17
	23d	Discuss implications of the results for practice, policy, and future research.	Page 17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Cover letter
Competing interests	26	Declare any competing interests of review authors.	Cover letter
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table S1. PICO table showing study scope.

Population	Adults (≥ 18Y/O) definitively diagnosed with NPC through validated means such as FNAC biopsy AND have undergone Intensity modulated Radiotherapy
Intervention	Studies assessing the relationship between Intensity modulated Radiotherapy (IMRT) and any possible sinus changes being validated through means such as Lund-Mackay or SNOT-22 Intensity-Modulated Radiotherapy with concurrent chemotherapy (cisplatin, platinum etc.) Intensity-Modulated Radiotherapy with any form of pharmacological management (Decongestants, corticosteroids, antihistamines etc.) Intensity-Modulated radiotherapy and its respective types: Conventional, Volumetric modulated arc therapy (VMAT), Helical tomotherapy, Hybrid
Control	NPC patients who underwent IMRT but did not develop sinus changes (CRS) persisting for ≥3 months validated through means such as the Lund-Mackay scoring system
Outcome	Primary Outcome: Patients who develop any sinus changes persisting for ≥3 months post IMRT validated through means such as the Lund-Mackay scoring system. Diagnosis and/or complaints of CRS were performed using subjective and objective measurements: questionnaires (e.g., Sino-Nasal Outcome Test–SNOT), mucociliary clearance (saccharine test, UPSIT-TC test), clinical examination by nasal endoscopy, cultures, nasal biopsy, nasal cytology, computed tomography and magnetic resonance imaging (MRI) Secondary Outcome: treatments used for sinus control and patient's subjective discomfort due to sinusitis
Study types	Case reports, case studies, clinical trials, Randomised Controlled Trials (RCTs)

Table S2. Exclusion criteria.

S/N	Criteria
1	Pediatric studies
2	Letters
3	Non-English studies
4	Editorials
5	Animal studies
6	Sinus changes < 3 months duration

Table S3. Data extracted from each study for analysis

- **First author**
- **Year published**
- **Study design**
- **Article title**
- **Country**
- **Recruited members**
- **Study population and baseline characteristics**
  - Final study population
  - M:F ratio
  - Mean/median age
  - NPC confirmatory diagnosis method
  - NPC type
  - CRS diagnostic criteria
  - Presence of baseline sinusitis
- **Intervention details**
  - Duration, dosage of IMRT
  - Neoadjuvant chemotherapy, agent, dosage
  - Concurrent chemo, agent, dosage
- **Risk of bias (see appendix)**
- **Study outcomes**
  - Follow-up duration
  - Sinus investigations
  - Incidence of sinusitis before intervention
  - Incidence of sinusitis after intervention
  - SNOT-22 baseline
  - SNOT-22 post IMRT
  - Lund-Mackay CT score baseline
  - Lund-Mackay CT post IMRT
  - Lund-Kennedy Endoscopy score baseline
  - Lund-Kennedy Endoscopy score post IMRT
  - Other investigations
  - Other findings
- **Statistical investigations used**

Table S4. Risk of bias tools used in the study.

Bias categories (Cochrane RoB 2.0 tool)	Risk of bias		
Random sequence generation	Low	High	Unclear
Deviation from intended intervention			
Measurement of the outcome			
Incomplete outcome data			
Selective reporting of the outcome data			
Reviewer judgement			
Bias categories (ROBINS-I tool)	Risk of bias		
Bias due to confounding	Low	High	Unclear
Bias in selection of participants into the study			
Bias in classification of interventions			
Bias due to deviations from intended interventions			
Bias due to missing data			
Bias in measurement of outcomes			
Bias in selection of the reported result			

Table S5. Search strategy adopted for the study.

Pubmed search (searched on October 2024).

#	Search terms	Results
1	Nasopharyngeal carcinoma[MeSH Terms]	6,872
2	NPC	22,703
3	nasopharyngeal neoplasms[MeSH Terms]	19,987
4	Nasopharynx[MeSH Terms]	15,018
5	nasophar* OR rhinophar* OR naso-phar* OR chonae	59,187
6	Neoplasms[MeSH Terms]	4,012,721
7	Cancer* OR Malignan* OR Malignant Neoplas* OR Neoplasia OR Tumor* OR Carcinom* OR Nasopharyn* disease	5,866,239
8	#6 OR #7	5,866,239
9	#4 OR #5	62,163
10	#8 AND #9	46,034
11	#1 OR #2 OR #3 OR #10	57,055
12	Radiotherapy, Intensity-Modulated [MeSH Terms]	14,286
13	Helical Tomotherap* OR Intensity-Modulated Arc Therap* OR Volumetric-Modulated Arc Therap*	5,610
14	Helical Tomotherapy OR Intensity-Modulated Arc Therapy OR Volumetric-Modulated Arc Therapy	21,924
15	#12 OR #13 OR #14	21,930
16	#15 AND #11	1,883
17	Sinusitis[MeSH Terms]	24,195
18	rhinosinusitis OR nasosinusitis OR sinusitis OR pansinusitis OR ethmoiditis OR ethmoiditis OR sphenoiditis	92,190
19	Rhinitis[MeSH Terms]	39,997
20	Rhinitis, atrophic[MeSH Terms]	1,336
21	Rhinitis, vasomotor[MeSH Terms]	616
22	Paranasal Sinus Diseases[MeSH Terms]	38,338
23	"inflammatory sinus"[Title/abstract:~5]	800
24	Rhinitis, allergic[MeSH Terms]	24,450
25	Sphenoid sinusitis[MeSH Terms] OR sphenoidal sinusitis	1,475
26	Ethmoid sinusitis[MeSH Terms] OR ethmoidal sinusitis	2,325
27	Transverse sinuses[MeSH Terms]	376
28	Lateral Sinus* OR Sinus Transversus	12,066
29	Paranasal sinuses[MeSH Terms]	28,850
30	Nasal Sinus* OR Osteomeatal Complex* OR Ostiomeatal Unit OR Sinonasal Tract OR Supraorbital Ethmoid Cell	54,575
31	Sinus	165,373
32	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	236,345
33	#16 AND #32	74

CINAHL search (searched on October 2024).

#	Search terms	Results
S1	MW Nasopharyngeal carcinoma OR NPC	2,808
S2	MW nasopharyngeal neoplasms	2,786
S3	MW Nasopharynx OR (nasophar* OR rhinophar* OR naso-phar* OR chonae)	9,635
S4	MW Neoplasms OR (Cancer* OR Malignan* OR Malignant Neoplas* OR Neoplasia OR Tumor* OR Carcinom*)	882,977
S5	S4 AND S3	5,229
S6	S5 OR S2 OR S1	5,826
S7	Intensity modulated radiation therapy	3,142
S8	Helical Tomotherap* OR Intensity-Modulated Arc Therap* OR Volumetric-Modulated Arc Therap*	1,522
S9	S7 OR S8	4,183
S10	S9 AND S6	365
S11	MW Sinusitis OR (rhinosinusitis OR nasosinusitis OR sinusitis OR pansinusitis OR ethmoiditis OR ethmoiditis OR sphenoiditis)	7,222
S12	MW Rhinitis	6,702
S13	MW Rhinitis, atrophic	24
S14	MW Rhinitis, vasomotor	43
S15	MW Paranasal Sinus Diseases	906
S16	inflammatory adj5 sinus	20
S17	MW Rhinitis, allergic	3,050
S18	MW Sphenoid sinusitis OR sphenoidal sinusitis	88
S19	MW Ethmoid sinusitis OR ethmoidal sinusitis	124
S20	MW Transverse sinuses OR (Lateral Sinus* OR Sinus Transversus)	1,413
S21	MW Paranasal sinuses OR (Nasal Sinus* OR Osteomeatal Complex* OR Ostiomeatal Unit OR Sinonasal Tract OR Supraorbital Ethmoid Cell)	4,837
S22	Sinus	28,494
S23	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22	38,263
S24	S23 AND S10	12

Web of Science search (searched on October 2024).

#	Search terms	Results
1	TS =(nasopharyngeal carcinoma OR NPC OR nasopharyngeal neoplasms)	38,918
2	TS =(nasophar* OR rhinophar* OR chonae)	57,119
3	TS =(Neoplasms OR Cancer* OR Malignan* OR Malignant Neoplas* OR Neoplasia OR Tumor* OR Carcinom* OR Nasopharyn* disease)	5,268,750
4	#2 AND #3	40,781
5	#4 OR #1	54,747
6	TS =(Radiotherapy, Intensity-Modulated OR Helical Tomotherap* OR Intensity-Modulated Arc Therap* OR Volumetric-Modulated Arc Therap*)	25,342
7	#5 AND #6	3,165
8	TS =(Sinusitis OR rhinosinusitis OR nasosinusitis OR sinusitis OR pansinusitis OR ethmoiditis OR ethmoiditis OR sphenoiditis)	31,066
9	TS =(Rhinitis OR Rhinitis, atrophic OR Rhinitis, vasomotor OR Paranasal Sinus Diseases OR inflammatory adj5 sinus OR Rhinitis, allergic)	46,363
10	TS =(Sphenoid sinusitis OR Ethmoid sinusitis OR transverse sinus OR Lateral Sinus* or Sinus Transversus OR Nasal Sinus* OR Osteomeatal Complex*OR Ostiomeatal Unit OR Sinonasal Tract OR Supraorbital Ethmoid Cell OR Sinus)	165,594
11	#8 OR #9 OR #10	218,168
12	#7 AND #11	121

Cochrane Search (searched on October 2024).

#	Search terms	Results
1	MeSH descriptor: [Nasopharyngeal Carcinoma] explode all trees	500
2	NPC	1210
3	MeSH descriptor: [Nasopharyngeal Neoplasms] explode all trees	836
4	MeSH descriptor: [Nasopharynx] explode all trees	595
5	nasophar* OR rhinophar* OR naso-phar* OR chonae	9872
6	MeSH descriptor: [Neoplasms] explode all trees	126379
7	Cancer* OR Malignan* OR Malignant Neoplas* OR Neoplasia OR Tumor* OR Carcinom* OR Nasopharyngeal diseases	288399
8	#6 OR #7	304695
9	#4 OR #5	9993
10	#8 AND #9	4052
11	#1 OR #2 OR #3 OR #10	4351
12	Radiotherapy, Intensity-Modulated	2444
13	Helical Tomotherap* OR Intensity-Modulated Arc Therap* OR Volumetric-Modulated Arc Therap*	2991
14	#12 OR #13	2991
15	#11 AND #14	419
16	MeSH descriptor: [Sinusitis] explode all trees	1546
17	rhinosinusitis OR nasosinusitis OR sinusitis OR pansinusitis OR ethmoiditis OR ethmoiditis OR sphenoiditis	4847
18	MeSH descriptor: [Rhinitis] explode all trees	5125
19	Nasal Catarrh	12
20	MeSH descriptor: [Rhinitis, Atrophic] explode all trees	8
21	MeSH descriptor: [Rhinitis, Vasomotor] explode all trees	49
22	MeSH descriptor: [Paranasal Sinus Diseases] explode all trees	1668
23	inflammatory adj5 sinus	48
24	MeSH descriptor: [Rhinitis, Allergic] explode all trees	3861
25	MeSH descriptor: [Sphenoid Sinus] explode all trees	17
26	MeSH descriptor: [Ethmoid Sinusitis] explode all trees	16
27	MeSH descriptor: [Transverse Sinuses] explode all trees	14
28	Lateral Sinus* OR Sinus Transversus	621
29	MeSH descriptor: [Paranasal Sinuses] explode all trees	802
30	Nasal Sinus* OR Osteomeatal Complex* OR Ostiomeatal Unit OR Sinonasal Tract OR Supraorbital Ethmoid Cell Sinus	2721
31	Sinus	11823
32	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	19468
33	#15 AND #32	14

Embase (1996 to 2024) (searched on October 2024).

#	Search terms	Results
1	exp nasopharynx carcinoma/	21982
2	NPC.mp.	23089
3	nasopharyngeal neoplasms/	2966
4	Nasopharynx/	11773
5	(nasophar* or rhinophar* or chonae).mp.	92347
6	Neoplasms/	43279
7	(Cancer* or Malignan* or Malignant Neoplas* or Neoplasia or Tumor* or Carcinom* or Nasopharyn* disease).mp.	5933080
8	6 or 7	5939744
9	4 or 5	92347
10	8 and 9	42473
11	1 or 2 or 3 or 10	52967
12	Radiotherapy, Intensity-Modulated/	37194
13	(Helical Tomotherap* or Intensity-Modulated Arc Therap* or Volumetric-Modulated Arc Therap*).mp.	12999
14	12 or 13	44840
15	11 and 14	3821
16	Sinusitis/	217290
17	(rhinosinusitis or nasosinusitis or sinusitis or pansinusitis or ethmoiditis or ethmoiditis or sphenoiditis).mp.	53077
18	Rhinitis/	18737
19	Rhinitis, atrophic/	358
20	Rhinitis, vasomotor/	1066
21	Paranasal Sinus Diseases/	2431
22	(inflammatory adj5 sinus).mp.	732
23	Rhinitis, allergic/	26170
24	Sphenoid sinusitis/	19059
25	Sphenoidal sinusitis.mp.	58
26	Ethmoid sinusitis/	1139
27	ethmoidal sinusitis.mp.	70
28	transverse sinus/	2648
29	(Lateral Sinus* or Sinus Transversus).mp.	1415
30	Paranasal sinuses/	9047
31	(Nasal Sinus* or Osteomeatal Complex* or Ostiomeatal Unit or Sinonasal Tract or Supraorbital Ethmoid Cell).mp.	2632
32	Sinus.mp.	230985
33	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	304077
34	15 AND 33	264

Table S6. Risk of bias (ROBINS-I) assessment results of each study.

S/N	First author, year	Study design	Bias assessment tool	Confounding bias	Selection bias	Classification bias	Deviation bias	Missing data bias	Outcome measurement bias	Result selection bias	Overall
1	Bao Xiaomin et al., 2023	Retrospective cohort study	ROBINS- I	Serious	Moderate	Low	Serious	Moderate	Moderate	Serious	Serious
2	Chih-Jen Huang et al., 2019	Retrospective cohort study	ROBINS- I	Moderate	Serious	Low	Low	Low	Moderate	Low	Moderate
3	Hsin Chung-Han et al., 2016	Longitudinal cohort study	ROBINS- I	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
4	Su Yan-Xia et al., 2014	Retrospective cohort study	ROBINS- I	Moderate	Serious	Moderate	Serious	Moderate	Moderate	Serious	Serious
5	Wang et al., 2015	Retrospective cohort study	ROBINS- I	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
6	Wei-Chieh Lin et al., 2022	Retrospective cohort study	ROBINS- I	Moderate	Serious	Low	Low	Low	Moderate	Low	Moderate
7	Wu Pei-Wen et al., 2021	Retrospective cohort study	ROBINS- I	Moderate	Serious	Low	Moderate	Moderate	Low	Serious	Serious
8	Zheng Wenya et al., 2023	Retrospective cohort study	ROBINS- I	Moderate	Serious	Low	Low	Serious	Low	Low	Serious

Table S7. Risk of bias (RoB 2.0) assessment results of each study.

S/N	First author, year	Study design	Bias assessment tool	Bias arising from the randomization process	Bias due to deviations from the intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall	Result selection bias	Overall
1	Liang Kai Li, 2008	Randomised controlled trial	Cochrane RoB 2.0 tool	Unclear	High	Unclear	Unclear	High	High	Serious	Serious

Table S8. Individual effect sizes of studies assessing the incidence of CRS post IMRT.

Prior sinusitis	ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval		Exp. Effect Size	95% Confidence Interval		Weight	Weight (%)
						Lower	Upper		Lower	Upper		
No	Bao Xiaomin et al., 2023	2.307	.2820	8.179	<.001	1.754	2.859	10.039	5.776	17.448	.211	11.4
No	Chih-Jen Huang et al., 2019	2.054	.4916	4.179	<.001	1.091	3.018	7.802	2.977	20.450	.204	11.1
No	Su Yan-Xia et al., 2014	3.130	.2343	13.357	<.001	2.671	3.589	22.872	14.449	36.205	.212	11.5
No	Zheng Wenya et al. 2023	3.442	.2068	16.646	<.001	3.037	3.848	31.257	20.842	46.878	.213	11.5
Yes	Chih-Jen Huang et al., 2019	-2.247	.3636	-6.181	<.001	-2.960	-1.535	.106	.052	.216	.209	11.3
Yes	Hsin Chung-Han et al., 2016	.311	.3944	.789	.430	-.462	1.084	1.365	.630	2.957	.208	11.3
Yes	Su Yan-Xia et al., 2014	-1.956	.5486	-3.566	<.001	-3.031	-.881	.141	.048	.414	.202	10.9
Yes	Wei-Chieh Lin et al., 2022	.096	.3106	.311	.756	-.512	.705	1.101	.599	2.024	.210	11.4
Yes	Zheng Wenya et al. 2023	-1.515	1.0048	-1.507	.132	-3.484	.455	.220	.031	1.576	.176	9.6

Table S9. Further subgroup analyses of studies assessing the incidence of CRS post IMRT.

Subgroup analysed	Subgroup	Odds ratio	I^2 value	Q score
Follow-up duration of >12 months	No	1.96 (95% CI: 0.21-18.40; P=0.55>0.05)	98.1%	0.000; P=0.989>0.05
	Yes	2.01 (95% CI: 0.27-15.04; P=0.50>0.05)	97.0%	
Geographic location	Mainland China	3.24 (95% CI: 0.34-31.03; P=0.31>0.05)	98.5%	0.617; P=0.432>0.05
	Taiwan	1.04 (95% CI: 0.19-5.78; P=0.97>0.05)	95.3%	

Table S10. Individual effect sizes of each study assessing the severity and extent of CRS post IMRT.

Scoring type	ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval		Weight	Weight (%)
						Lower	Upper		
LK	Liang Kai Li et al, 2008 - Non irrigation	3.872	.3407	11.364	<.001	3.204	4.539	.220	8.3
LK	Liang Kai Li et al, 2008 - Irrigation	3.228	.3401	9.489	<.001	2.561	3.894	.220	8.3
LM	Hsin Chung-Han et al., 2016	.387	.1413	2.737	.006	.110	.664	.225	8.4
LM	Liang Kai Li et al, 2008 - Non irrigation	7.079	.4855	14.581	<.001	6.127	8.030	.214	8.0
LM	Liang Kai Li et al, 2008 - Irrigation	3.893	.3655	10.652	<.001	3.177	4.609	.219	8.2
LM	Wang Jing-Jie et al., 2015	.518	.1998	2.595	.009	.127	.910	.224	8.4
LM	Wei-Chieh Lin et al., 2022	.083	.1491	.559	.576	-.209	.376	.225	8.4
LM	Wu Pei-Wen et al., 2021	1.847	.2305	8.012	<.001	1.395	2.298	.244	7.7
LM	Zheng Wenya et al., 2023 - Sinusitis before IMRT	1.226	.1235	9.928	<.001	.984	1.468	.225	8.4
LM	Zheng Wenya et al., 2023 - No Sinusitis before IMRT	2.778	.1440	19.294	<.001	2.496	3.061	.225	8.4
SNOT	Liang Kai Li et al, 2008 - Non irrigation	2.334	.2604	8.960	<.001	1.823	2.844	.222	8.3
SNOT	Liang Kai Li et al, 2008 - Irrigation	.480	.2263	2.121	.034	.036	.924	.223	8.4
SNOT	Wang Jing-Jie et al., 2015	-.193	.1971	-.977	.328	-.579	.194	.224	8.4

Table S11. Further subgroup analyses of studies assessing the severity and extent of CRS post IMRT.

Subgroup analysed	Subgroup	Cohen's d	I^2 value	Q score
Prior sinusitis	No	3.87 (95% CI: 1.66-6.08; P=0.00<0.05	98.6%	8.237; P=0.004<0.05
	Yes	0.56 (95% CI: 0.07-1.05; P=0.02<0.05)	90.9%	
Follow-up duration >12 months	No	3.31 (95% CI: 0.52-6.10; P=0.02 <0.05)	99.0%	2.015; P=0.156>0.05
	Yes	1.12 (95% CI: -0.06-2.30; P=0.06>0.05)	98.7%	
Geographic location	Mainland China	2.00 (95% CI: 0.48-3.52; P=0.01<0.05)	98.5%	0.041; P=0.839>0.05
	Taiwan	2.28 (95% CI: 0.11-4.44; P=0.04<0.05)	99.4%	

Table S12. Trim-and-Fill analysis to assess publication bias of studies assessing the incidence of CRS post IMRT.

	Number	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval		Exp. Effect Size	Exp. 95% Confidence Interval	
						Lower	Upper		Lower	Upper
Observed	9	.681	.7361	.925	.355	-.762	2.124	1.976	.467	8.363
Observed + Imputed	9	.681	.7361	.925	.355	-.762	2.124	1.976	.467	8.363

a. Number of imputed studies: 0

Table S13. Trim-and-Fill analysis to assess publication bias of studies assessing the severity and extent of CRS post IMRT.

	Number	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval	
						Lower	Upper
Observed	8	2.199	.8167	2.693	.007	.598	3.800
Observed + Imputed	8	2.199	.8167	2.693	.007	.598	3.800

Table S14. Sensitivity analyses conducted for studies assessing the incidence of CRS post IMRT.

S/N	Study excluded	New Odds ratio	Change in Odds ratio
1	Bao Xiaomin et al., 2023	1.60 (95% CI: 0.33-7.73; P=0.56>0.05)	-0.38
2	Chih-Jen Huang et al., 2019	2.50 (95% CI: 0.51-12.29; P=0.26>0.05)	+0.52
3	Hsin Chung-Han et al., 2016	2.06 (95% CI: 0.40-10.54; P=0.39>0.05)	+0.08
4	Su Yan-Xia et al., 2014	2.01 (95% CI: 0.43-9.37; P=0.38>0.05)	+0.03
5	Wei-Chieh Lin et al., 2022	2.12 (95% CI: 0.41-10.80; P=0.37>0.05)	+0.14
6	Zheng Wenya et al., 2023	1.73 (95% CI: 0.37-8.15; P=0.49>0.05)	-0.25

Table S15. Sensitivity analyses conducted for studies assessing the severity and extent of CRS post IMRT

S/N	Study excluded	New Cohen's d	Change in Cohen's d
1	Hsin Chung-Han et al., 2016	2.24 (95% CI: 1.07-3.40; P=0.00<0.05)	+0.15
2	Liang Kai Li et al., 2008	0.95 (95% CI: 0.16-1.74; P=0.02<0.05)	-1.14
3	Wang Jing-Jie et al., 2015	2.45 (95% CI: 1.26-3.63; P=0.00<0.05)	+0.36
4	Wei-Chieh Lin et al., 2022	2.26 (95% CI: 1.12-3.41; P=0.00<0.05)	+0.17
5	Wu Pei-Wen et al., 2021	2.11 (95% CI: 0.91-3.32; P=0.00<0.05)	+0.02
6	Zheng Wenya et al., 2023	2.11 (95% CI: 0.81-3.42; P=0.00<0.05)	+0.02