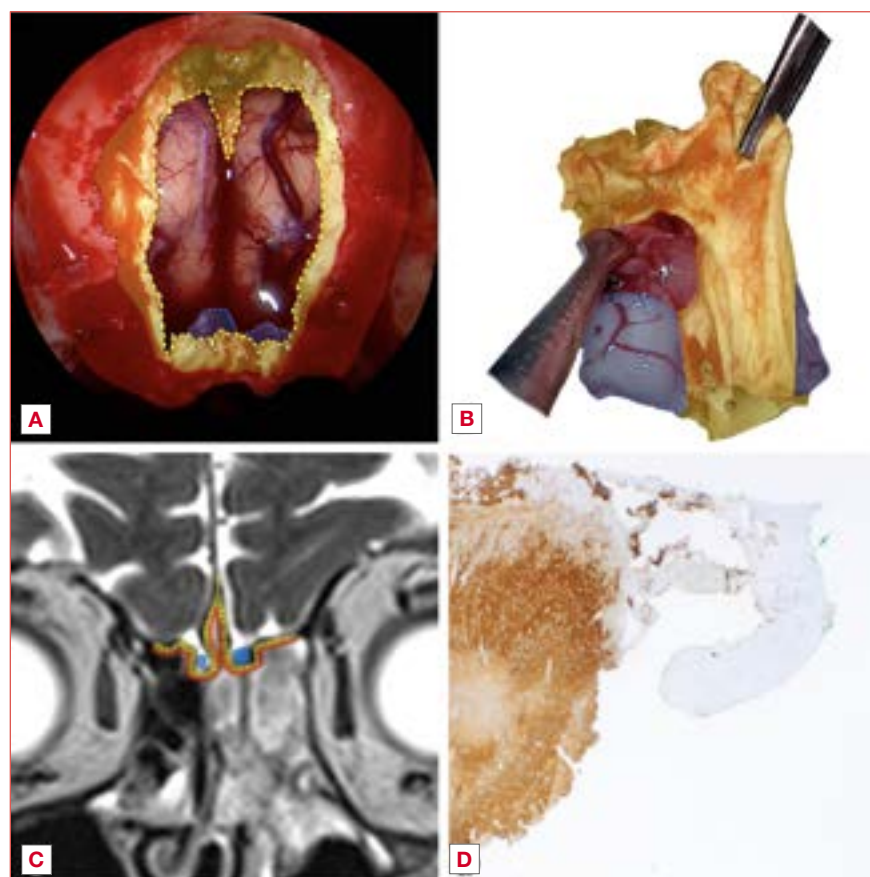


# Surgical margin assessment and prognostic impact in sinonasal cancers: a systematic review and meta-analysis



**Cover figure.** Comprehensive assessment of resection margins in endoscopic skull base surgery. (A) Endoscopic view of the defect following a bilateral endoscopic transnasal craniectomy with en bloc resection of the olfactory bulbs for olfactory neuroblastoma Kadish Stage C. Colour-coded layers denote bone (red), dura (yellow), and olfactory bulbs (blue), with dashed lines indicating the corresponding resection margins; (B) Resected surgical specimen with matching colour codes, illustrating the anatomical layers included in the en bloc resection; (C) Coronal T2-weighted MRI demonstrating the tumour with colour-enhanced delineation of key surgical planes at the skull base; (D) Histopathological examination of the specimen, highlighting the dural margin on the right (marked with ink) and synaptophysin-positive immunohistochemical staining of the olfactory bulb on the left.

## Summary

**Objective.** Surgery remains a cornerstone in treatment of sinonasal malignancies, but the prognostic role of margin status is controversial. This systematic review and meta-analysis

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evaluated the prognostic significance of surgical margins in sinonasal cancer and their impact on survival, alongside key challenges in its evaluation.

**Methods.** A systematic search in PubMed, Scopus, and Web of Science identified 64 studies (34,120 patients).

**Results.** The overall margin infiltration rate was 33.2%, varying widely across studies (4.5-88.2%) and histotypes, and was the highest in adenoid cystic carcinoma (ACC, 61.5%). Meta-analysis of 31 studies showed positive margins were associated with worse survival (overall survival, odds ratio [OR] 2.61; disease-specific survival, OR 5.89; disease-free survival, OR 4.40). Squamous cell carcinoma, olfactory neuroblastoma, and mucosal melanoma had the strongest correlation with margin status, while for ACC and adenocarcinomas statistical significance was not reached. High heterogeneity was noted across studies, alongside inconsistent margin classification, distance thresholds, and use of frozen sections, limiting cross-study comparability.

**Conclusions.** This study confirms the prognostic value of surgical margins, but underscores the urgent need for standardised definitions to improve prediction of oncologic outcomes and clinical decision-making.

**Key words:** cancer, paranasal sinus neoplasms, margins of excision, survival analysis, meta-analysis

## Introduction

Sinonasal tumours are a rare and heterogeneous group of malignancies with multiple histopathological subtypes. Over the past decades, treatment strategies have significantly evolved, driven by advances in multimodal protocols tailored to tumour histology<sup>1</sup>. However, no universally accepted treatment guidelines exist, as therapeutic approaches continue to adapt alongside an evolving understanding of tumour biology<sup>2</sup>. While non-surgical strategies, including neoadjuvant chemotherapy and immunotherapy, hold promise for expanding future treatment options, surgery remains the cornerstone for most resectable tumours and has been the primary therapeutic approach in recent decades<sup>3</sup>. Surgical margin status is a key determinant of oncologic outcomes, influencing local control, recurrence rates, overall survival, and the need for adjuvant treatment. Achieving clear margins in sinonasal tumours is particularly challenging due to the complex anatomy and proximity to critical structures, such as the skull base, orbit, major vessels, and cranial nerves. Over the past two decades, endoscopic techniques have transformed the surgical landscape, providing superior visualisation, reduced morbidity, and improved functional outcomes compared to open approaches<sup>3-6</sup>. However, these techniques have also complicated the definition of complete resection. Since en-bloc tumour removal is often unfeasible, oriented multi-bloc resection has emerged as an oncologically-safe alternative, requiring meticulous technique to preserve tumour orientation and spatial relationships and ensure accurate margin evaluation (Cover figure)<sup>2,7</sup>.

Despite the recognised importance of surgical margins, no universally accepted definition of a clear margin exists for sinonasal tumours<sup>4</sup>. This lack of consensus complicates the interpretation of surgical outcomes and hinders cross-study comparisons. Additionally, heterogeneity in the literature – with variations in sample size, histological subtypes, and study design – further limits the ability to establish a solid prognostic role for margin involvement. Given these challenges, a com-

prehensive evaluation of existing evidence is warranted to clarify the impact of surgical margins on survival outcomes and to assess the methodologies used for margin evaluation.

This systematic review and meta-analysis aims to summarise the available evidence on the definition and prognostic significance of surgical margins in sinonasal cancer, evaluating their impact on survival outcomes and the methodologies used for margin assessment.

## Materials and methods

### *Protocol registration*

The protocol of this systematic review and meta-analysis was registered on PROSPERO, an international database of prospectively registered systematic reviews in health and social care (Center for Reviews and Dissemination, University of York, York, UK), on November 24, 2024, under the registry number CRD42024618259.

### *Search strategy*

A systematic literature review was performed in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>8</sup>. The inclusion criteria for study selection were defined according to the PICOS framework: patients (P), adults diagnosed with sinonasal malignancies; intervention (I), surgical treatment performed via open or endoscopic approaches; comparator (C), none; outcomes (O), overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), local recurrence-free survival (LRFS); study design (S), retrospective and prospective cohort studies.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, using predefined search strings tailored for each database, from database inception to 21 November 2024. The search strategy included terms related to sinonasal and paranasal anatomical region, neoplasms, surgical margins, and prognostic outcomes. The

full search queries are available in Supplementary Table SI. No filters or language restrictions were applied. The reference lists of all included articles were thoroughly screened to identify additional relevant studies.

References were exported to Zotero (v6.0.10, Center for History and New Media, George Mason University, Fairfax, VA, USA) for bibliography management. After duplicate removal, a team of 3 reviewers (ADA, EC, GM) independently screened all titles and abstracts, followed by a full-text evaluation of eligible articles based on the inclusion criteria. Any disagreements were resolved through discussion among all authors to reach a consensus.

No ethical approval or informed consent were required for this study, as all reported data were obtained from publicly available published literature.

### *Eligibility criteria*

The inclusion criteria for the studies were: (a) histopathological diagnosis of sinonasal malignancy; (b) treated with an open or endoscopic surgical approach; (c) surgical margin status clearly reported, using any defined classification, including clinical or pathological assessment, microscopic or macroscopic infiltration, or close margins; (d) availability of at least one survival outcome, including OS, DSS, DFS, LRFS, regional recurrence-free survival (RRFS), or distant recurrence-free survival (DRFS); (e) correlation between survival outcome and margin status, requiring studies to either provide survival data stratified by margin status or analyse the impact of margin status on survival using univariate or multivariate analysis.

The exclusion criteria were: (a) unavailability of the full text; (b) overlapping cohorts or data redundancy, in which case the most recent and comprehensive eligible publication was selected; (c) absence of relevant clinicopathological data regarding margin status and survival outcomes; (d) studies reporting fewer than 10 cases of interest; (e) inability to segregate data between surgical and non-surgical cohorts; (f) articles including survival data on sarcomas, tumours of uncertain malignant potential, haematolymphoid malignancies, or tumours originating from extra-nasal sites, unless survival data for sinonasal malignancies of interest were separately analysable; (g) non-original studies, such as letters, editorials, and book chapters; (h) animal studies; (i) non-English publications.

In cases where eligible articles did not provide the necessary data within the text, the corresponding authors were contacted to request raw data. Articles were included if the requested data were provided; otherwise, they were excluded from the analysis. All papers were thoroughly screened for duplicates.

### *Data extraction*

Two independent reviewers (EC and GS) extracted data from the included studies using a standardised data collection form. Discrepancies were resolved through discussion or, if necessary, by consulting a third reviewer (ADA). The data extracted included study characteristics (author, year of publication, country, enrollment period), patient demographics (total number of patients, age, gender, histopathological diagnosis, primary tumour site, tumour staging), treatment strategies (patients treated surgically, type of surgery performed, prior treatments and use of adjuvant therapy in the surgical cohort), surgical margin status, survival outcomes, and follow-up duration.

Surgical margin status was extracted as reported by the authors. Additionally, an analysis of the methods used to define margins was conducted, including any threshold distance in millimetres, the use of frozen sections, and the distinction between close margins, microscopic infiltration, or macroscopic involvement. Furthermore, any other qualitative descriptions of how margins were assessed and managed by the authors were also examined.

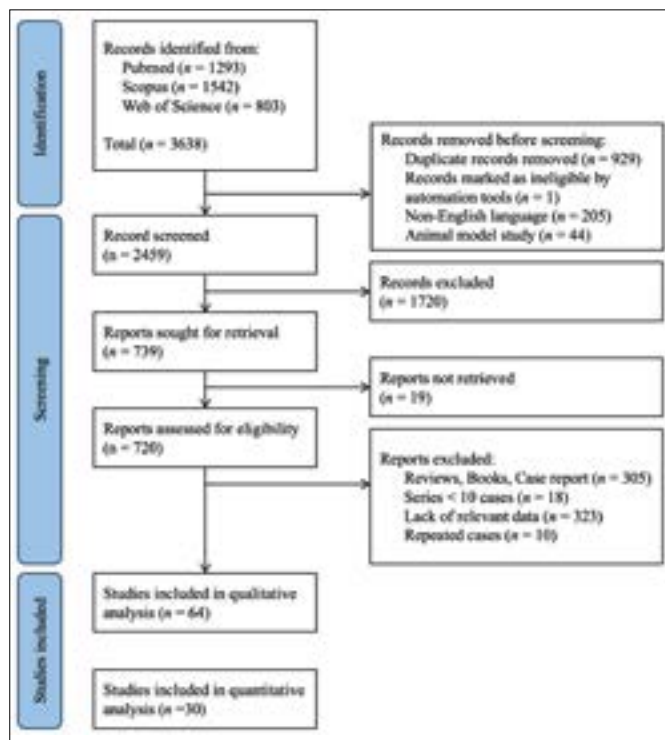
### *Quality assessment*

The quality of the studies eligible for inclusion was categorised as poor, fair or good, in agreement with the National Institutes of Health quality assessment tool for Observational Cohorts and Cross-Sectional Studies (NHLBI NIH). Study quality assessment tools. July 2021. Available at: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>. Accessed December 10, 2024). Three reviewers (ADA, AL and GD) independently evaluated the papers, and any disagreements were resolved by discussion.

### *Data synthesis*

Data analysis was conducted using both quantitative and qualitative synthesis, depending on the availability and structure of the reported outcomes. Studies were eligible for quantitative analysis (meta-analysis) if they provided 5-year survival data stratified by positive and negative margins, explicitly reporting the number of patients alive at 5 years in relation to OS, DSS, and DFS. These studies were included in the pooled statistical analysis to estimate the impact of margin status on survival. Where feasible, subgroup analyses were performed based on histology.

As a secondary outcome, studies were included in the qualitative synthesis if they assessed the impact of margin status on any survival endpoint (OS, DSS, DFS, LRFS, RRFS, and DRFS) through uni- or multivariate analysis but did not provide exact survival percentages for each group. While



**Figure 1.** PRISMA flow diagram illustrating the study selection process. The diagram details the number of records identified, screened, excluded, and included in the qualitative and quantitative analyses, following PRISMA guidelines.

these studies were not eligible for meta-analysis, they were considered in the overall evaluation of the prognostic role of surgical margins and analysed descriptively.

### Statistical analysis

The meta-analysis was conducted using RStudio (version 2024.12.0+467, Posit Software, PBC). Event rates were calculated for the following 5-year outcomes: OS, considering death from any cause as an event; DSS, considering disease-specific death as an event; and DFS, considering disease recurrence or death from any cause as an event.

To assess the association between margin status and survival outcomes, the odds ratio (OR) of event rates was calculated, comparing positive and negative margin groups. A pooled OR with a 95% confidence interval (CI) was estimated using the DerSimonian and Laird random-effects model. The p value was derived using a Z-test based on the pooled OR and its standard error. Heterogeneity among studies was evaluated using Cochran's Q test and the  $I^2$  statistic. A p value < 0.05 in the Q test or an  $I^2 > 50%$  was considered indicative of substantial heterogeneity. Potential publica-

tion bias was assessed using funnel plots and Egger's linear regression test, with a p value < 0.05 indicating statistically significant asymmetry.

## Results

### Literature search and study identification

A total of 3,638 records were initially identified through the combined database search. After duplicate removal and initial screening, 2,459 titles were assessed for eligibility. Following the application of inclusion and exclusion criteria, 64 studies<sup>9-72</sup> were included in the qualitative synthesis, of which 31 were deemed eligible for the quantitative analysis<sup>11,12,14,19,21,22,24,27,30,31,33-39,41,44,46-48,50,51,55-57,64,68,71,72</sup>. A detailed PRISMA flowchart illustrating the search process is presented in Figure 1.

### Quality assessment

According to the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, 38 (59.4%) studies<sup>10,12,13,15,16,20,22-24,27-40,42,44-47,53,54,57,59,60,62,67,69-71</sup> were classified as good quality, while 26 (40.6%)<sup>9,11,14,17-19,21,25,26,41,43,48-52,55,56,58,61,63-66,68,72</sup> were rated as fair. No studies were deemed poor, as none exhibited a significant lack of clinical details (Tab. I).

### Characteristics of the studies included

Among the 64 studies included, 46 were retrospective case series (RCS) and 18 were National Cancer Database (NCDB) analyses. These studies were published over a 25-year period (1999-2024), with patient recruitment spanning from 1956 to 2022. The majority of the studies were from Northern America, Europe, and Asia, with a few contributions from Australia.

The total number of patients reported across all studies was 34,120, with individual sample sizes ranging from 12 to 7,808 patients. The mean patient age varied between 44 and 71 years, with a male predominance reported in most studies.

Regarding histological distribution, squamous cell carcinoma (SCC) was the most frequent histotype, accounting for 18,859 cases (64.6%). Olfactory neuroblastoma (ONB) followed with 3,437 cases (11.8%), while sinonasal mucosal melanoma (SNMM) was reported in 3,527 cases (12.1%). Sinonasal adenocarcinoma (SNAC) accounted for 1,137 cases (3.9%), and sinonasal undifferentiated carcinoma (SNUC) for 740 cases (2.5%). Adenoid cystic carcinoma (ACC) was identified in 817 cases (2.8%), whereas minor salivary glands tumours (MSGT) were observed in 458

**Table I. Quality assessment of studies included.**

Study	Year	C1	C2	C3	C4	C5	C6	C7	C8	C9	Quality
Agarwal <sup>9</sup>	2023	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Fair
Al-Qurayshi <sup>10</sup>	2021	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Amit <sup>11</sup>	2017	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Fair
Auger <sup>12</sup>	2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bahig <sup>13</sup>	2023	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bristol <sup>14</sup>	2007	Yes	Yes	CD	Yes	Yes	Yes	No	No	Yes	Fair
Chao <sup>15</sup>	2001	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Good
Choby <sup>16</sup>	2023	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Good
Cracchiolo <sup>17</sup>	2018	Yes	Yes	CD	Yes	Yes	Yes	No	Yes	Yes	Fair
Crawford <sup>18</sup>	2020	Yes	Yes	CD	Yes	Yes	Yes	No	Yes	Yes	Fair
Duru Birgi <sup>19</sup>	2024	Yes	Yes	CD	Yes	Yes	Yes	No	Yes	Yes	Fair
Eide <sup>20</sup>	2023	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Good
Elamna <sup>21</sup>	2021	Yes	Yes	CD	Yes	No	Yes	Yes	Yes	Yes	Fair
Ferrari <sup>22</sup>	2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Ganti <sup>23</sup>	2019	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Good
Guazzo <sup>24</sup>	2019	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Good
Guo <sup>25</sup>	2022	Yes	Yes	CD	Yes	Yes	Yes	No	Yes	Yes	Fair
Harvey <sup>26</sup>	2016	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Herr <sup>27</sup>	2013	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Good
Hirakawa <sup>28</sup>	2016	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Issa <sup>29</sup>	2023	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jafari <sup>30</sup>	2019	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Khan <sup>31</sup>	2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kilic <sup>32</sup>	2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kim <sup>33</sup>	1999	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Konig <sup>34</sup>	2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Konig <sup>35</sup>	2019	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Konig <sup>36</sup>	2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Konuthula <sup>37</sup>	2016	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Konuthula <sup>38</sup>	2017	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Lehrich <sup>39</sup>	2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Li <sup>40</sup>	2020	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Li <sup>41</sup>	2021	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Li <sup>42</sup>	2023	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lian <sup>43</sup>	2024	Yes	Yes	No	CD	Yes	Yes	No	Yes	No	Fair
Malouf <sup>44</sup>	2012	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Good
McMillan <sup>45</sup>	2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Nakagawa <sup>46</sup>	2017	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Nakamaru <sup>47</sup>	2020	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Nakaya <sup>48</sup>	2004	Yes	Yes	No	CD	Yes	Yes	No	Yes	No	Fair
Nalavenkata <sup>49</sup>	2015	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Nishio <sup>50</sup>	2015	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Ogawa <sup>51</sup>	2000	Yes	Yes	No	CD	Yes	Yes	Yes	Yes	Yes	Fair
Ono <sup>52</sup>	2018	Yes	Yes	No	CD	Yes	Yes	Yes	Yes	Yes	Fair



**Table I. continues.**

Study	Year	C1	C2	C3	C4	C5	C6	C7	C8	C9	Quality
Paré <sup>53</sup>	2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Parikh <sup>54</sup>	2021	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Patel <sup>55</sup>	2012	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Patel <sup>56</sup>	2024	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Petruzzelli <sup>57</sup>	2015	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Qatanani <sup>58</sup>	2023	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Resto <sup>59</sup>	2000	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Rojas Lechuga <sup>60</sup>	2022	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Sayed <sup>61</sup>	2017	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Sun <sup>62</sup>	2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Tajudeen <sup>63</sup>	2014	Yes	Yes	No	CD	Yes	Yes	No	Yes	Yes	Fair
Torabi <sup>64</sup>	2019	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Tsutsumi <sup>65</sup>	2023	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Tsutsumi <sup>66</sup>	2024	Yes	Yes	Yes	CD	Yes	Yes	No	Yes	Yes	Fair
Ungar <sup>67</sup>	2024	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Vedula <sup>68</sup>	2023	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair
Vermassen <sup>69</sup>	2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Wang <sup>70</sup>	2024	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Zafereo <sup>71</sup>	2008	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Zhou <sup>72</sup>	2024	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Fair

Quality assessment of the included studies according to the National Heart, Lung and Blood Institute (NHLBI), Study Quality Assessment Tools: C1: "Was the study question or objective clearly stated?"; C2: "Was the study population clearly and fully described, including a case definition?"; C3: "Were the cases consecutive?"; C4: "Were the subjects comparable?"; C5: "Was the intervention clearly described?"; C6: "Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?"; C7: "Was the length of follow-up adequate?"; C8: "Were the statistical methods well-described?"; C9: "Were the results well-described?".  
CD: cannot determine.

cases (1.6%). Less frequent histotypes included sinonasal neuroendocrine carcinoma (SNEC) with 95 cases (0.3%). Other rare histotypes were reported in 118 cases (0.4%). The surgical approach was detailed in 43 of 68 studies, while in 21 the type of surgery was not specified. Among the reported cases, 2,662 patients underwent endoscopic surgery, whereas 3,483 patients were treated with an open or combined approach. The follow-up period varied significantly among studies, ranging from 0 to 288 months. Patient and tumour characteristics of the studies included are summarised in Table II.

Regarding margin definition, most studies lacked a specific description of their assessment (Tab. III). Margin status was reported in all studies but not for all patients, covering a total of 17,758 patients. Among them, 11,806 patients had negative margins, 5,899 patients had positive margins, and 53 patients were classified as having close margins. The pooled global rate of margin infiltration was 33.2% with a wide range, spanning from 4.5% to 88.2%. Notably, me-

dian rates of margin infiltration varied considerably across histotypes. Focusing on 54 articles analysing single histological groups, SCC showed a median infiltration rate of 31.4% (17.2-65.9%), while ONB had a median rate of 29% (4.5-56.8%). SNAC presented a higher median infiltration rate of 42.9% (21.1-45.5%), whereas SNMM exhibited a median rate of 31.3% (13.9-50%). Among salivary-type malignancies, ACC displayed a notably high infiltration rate, with a median of 61.5% (61.1-88.2%), while other salivary tumour had a median of 27.4% (22.2-32.5%). Lastly, SNUC demonstrated a median infiltration rate of 43.4% (37.3-49.5%).

### Qualitative analysis

The studies were evaluated for any reported associations between margin status and survival, based on uni- and multivariate analyses of the previously mentioned survival outcomes in each study. Among the 64 included papers, 10 (15.6%) evaluated multiple histotypes, of which 8 (80%) identified at least one significant association between mar-

gin status and survival. The remaining 54 studies (84.4%) focused on a single histology, of which 36 (66.7%) reported a significant association, while 18 (33.3%) did not find a significant correlation. When considering SNMM, a total of 3,145 patients were analysed across 6 studies identifying at least one significant association. For ONB, 2,906 patients were included across 13 studies with significant findings. Regarding SCC, 17,921 patients were analysed in 12 studies showing a significant association. In the case of SNAC, 123 patients were evaluated across 3 studies, while for SNUC, 173 patients were analysed in one study with significant results. Lastly, one study on MSGT, including 239 patients, identified a significant association. Details regarding specific survival outcomes and statistical models used are shown in Table II.

### Meta-analysis

Clinical and methodological heterogeneity precluded further statistical analysis and meta-analysis of LRFS. A total of 35 studies reported outcomes stratified by margin status for OS, DSS, or DFS (Fig. 2). After excluding 5 studies<sup>25,40,42,52,61</sup> due to the absence of data on 5-year outcomes, 28 were eligible for quantitative analysis of the association between margin status and OS<sup>11,12,14,19,21,22,24,27,30,31,33,34,37-39,41,44,46-48,50,55-57,64,68,71,72</sup>, 5 for DSS<sup>22,35,36,47,48</sup>, and 6 for DFS<sup>14,22,24,27,44,48</sup>.

The meta-analysis of 28 studies assessing the impact of surgical margin status on OS irrespective of histotype revealed a significant association between positive margins (R1) and poorer survival outcomes. The pooled OR for 5-year OS was 2.61 (95% CI: 1.98-3.44,  $p < 0.001$ ), indicating that patients with R1 resections had a significantly higher risk of mortality compared to those with negative margins. A uniform direction of effect was found across all studies, although only 10 studies individually reached statistical significance. Heterogeneity was substantial ( $I^2 = 69%$ ,  $\tau^2 = 0.2263$ ,  $p < 0.01$ ), suggesting variability across studies. The meta-analysis of studies assessing the impact of surgical margin status on DSS, irrespective of histotype, demonstrated a significant association between positive margins (R1) and worse survival outcomes. The pooled OR for 5-year DSS was 5.89 (95% CI: 4.22-8.22,  $p < 0.001$ ), indicating that patients with R1 resections had a significantly higher risk of disease-related mortality compared to those with negative margins. Unlike OS, heterogeneity was low ( $I^2 = 0%$ ,  $p = 0.64$ ), suggesting a high degree of consistency across studies. A uniform direction of effect was observed, although only 2 studies individually reached statistical significance.

A similar result was found in the meta-analysis assessing DFS, with a pooled OR for 5-year DFS of 4.4 (95% CI: 2.12-9.11,  $p < 0.001$ ) and moderate heterogeneity across studies ( $I^2 = 47%$ ,  $p = 0.09$ ). Only 2 studies individually reached statistical significance.

When stratified by histology, a significant association between negative margins and 5-year OS was found in SNMM (OR 4.89, 95% CI: 1.41-17,  $p = 0.013$ ), SCC (OR 3.77, 95% CI: 1.52-9.4,  $p = 0.004$ ), and ONB (OR 6.85, 95% CI: 2.6-18.09,  $p < 0.001$ ). Conversely, statistical significance was not reached for ACC (OR 2.43, 95% CI: 0.53-11.19,  $p = 0.253$ ) and SNAC (OR 3.13, 95% CI: 0.97-10.09,  $p = 0.056$ ). Quantitative analysis for 5-year DFS was possible only for ONB, confirming a strong association between negative margins and better survival (OR 8.85, 95% CI: 3.55-22.11,  $p < 0.001$ ). Details of histology-specific meta-analysis are reported in Figure 3.

Funnel plot analysis and Egger's test (Supplementary Figure 1) revealed potential publication bias in the 5-year OS analysis across all studies ( $p = 0.008$ ), as well as in the SNMM ( $p = 0.031$ ), and ONB ( $p = 0.031$ ) subgroups. In contrast, no significant asymmetry was found for 5-year DSS ( $p = 0.712$ ), DFS ( $p = 0.423$ ), or for SCC ( $p = 0.113$ ), ACC ( $p = 0.275$ ), ONB ( $p = 0.559$ ), and SNAC ( $p = 0.974$ ).

## Discussion

### Impact of surgical margins on survival

The results of this systematic review and meta-analysis confirm the significant prognostic role of surgical margins in sinonasal malignancies. Across all studies included, positive margins were associated with poorer survival outcomes, reinforcing the importance of achieving negative margins whenever feasible. While not all studies demonstrated a significant association between margin status and survival, a consistent trend emerged, highlighting the negative prognostic impact of margin infiltration. More importantly, considering only studies eligible for quantitative analysis, the present analysis demonstrated that patients with R1 resections had a 2.61-fold increased risk of mortality (OS), a 5.89-fold higher risk of disease-related mortality (DSS), and a 4.4-fold higher risk of recurrence (DFS). Our findings are consistent with evidence from other head and neck malignancies, where the fundamental oncologic principle of achieving complete tumour resection has been widely recognised as essential for improving survival outcomes<sup>73</sup>. However, at present, the prognostic value of margin status in sinonasal cancer is far from being completely clarified<sup>74</sup>, even though multiple studies have demonstrated

**Table II.** Studies included in the qualitative analysis.

First author (year)	Study	Demographics			Tumour				
		No. of patients	Age (years) mean or #median (range, IQR or SD)	Gender (M/F)	Histology	Initial location	T Stage	N. Stage	
Agarwal 2023 <sup>9</sup>	RCS (USA 2012-2018)	50	#65.6 (IQR: 52.8-74.4)	32/18	SCC: 50	NC: 25 MS: 17 ES: 2 FS: 1 NR: 5	Tis-T2:14 T3: 27 unknown: 9	N0: 28 N+: 9 NR: 13	
Al-Qurayshi 2021 <sup>10</sup>	NCDB (USA 2004-2015)	574	61.7 (SD: 16.5)	320/254	SNAC: 213 ACC: 131 SNMM: 115 ONB: 68 SNUC: 47	NR	NR	NR	
Amit 2017 <sup>11</sup>	RCS (USA 1991-2016)	66	63 (34-85)	33/33	SNMM: 66	NC: 53 MS: 8 SS: 3 ES: 1 FS: 1	T3: 35 T4a: 23 T4b: 8	N0: 59 N+: 7	
Auger 2020 <sup>12</sup>	NCDB (USA 2004-2015)	239	< 50y: 56 50-60y: 62 60-70y: 60 > 70y: 61	125/114	MEC: 239	MS: 109 NC: 98 SS: 5 FS: 3 ES: 1 other: 10	NR	NR	
Bahig 2023 <sup>13</sup>	RCS (USA 2000-2016)	311	#57 (20-90)	193/118	SCC: 132 SNUC: 45 ACC: 45 ONB: 41 SNEC: 24 SNAC: 17 MEC: 3 other: 4	NC: 132 MS: 102 ES: 47 FS: 17 SS: 4 other: 9	T1: 15 T2: 38 T3: 39 T4: 219	N0: 263 N+: 48	
Bristol 2007 <sup>14</sup>	RCS (USA 1969-2002)	146	#59 (26-90)	86/60	SCC: 89 ACC: 33 SNAC: 6 SNUC: 11 other: 7	MS: 146	T1-T2: 22 T3: 47 T4: 77	N0:126 N+: 20	
Chao 2001 <sup>15</sup>	RCS (USA 1976-1996)	25	#57 (16-73)	11/14	ONB: 25	NR	Kadish A: 3 Kadish B: 13 Kadish C: 8 Kadish D: 1	NR	
Choby 2023 <sup>16</sup>	RCS (USA 2005-2021)	256	52 (43-63)	141/115	ONB: 256	NR	Kadish A: 26 Kadish B: 52 Kadish C: 136 Kadish D: 34 NR: 8	NR	
Cracchiolo 2018 <sup>17</sup>	NCDB (USA 2003-2012)	4770	< 50y: 583 50-64y: 1637 65-79y: 1775 > 80y: 775	3041/1729	SCC: 4770	NC: 2512 MS: 1961 ES: 297	T1: 1474 T2: 743 T3: 762 T4a: 1197 T4b: 594	N0: 4478 N+: 292	

	Treatment			Margin status		Follow-up	Outcome
	Surgery (approach)	Previous treatment	Adjuvant treatment	R0/R+/R close/unknown	Rate of positive margins (%)	F.U. (months) mean or #median (range, IQR or SD)	Investigated outcome (model)   association (* significant)
	47 (EEA: 25 Open: 22)	NR	RT: 26 RT-CHT: 7	R0: 34 R+: 8 unknown: 5	19	NR	DFS (u)   HR R+ 6.76 (CI 1.35-34.0), p = 0.020* DFS (m)   HR R+ 3.10 (CI 0.39-24.6), p = 0.285
	574 (NR)	RT: < 10° CHT: < 10° RT-CHT: 41	NR	R0: 311 R+: 263	45.8	#40.4 (IQR: 15.3-81.3)	OS (m)   HR R0 0.55 (CI 0.36-0.82), p = 0.004*
	66 (NR)	NR	RT: 30 RT-CHT: 6	R0: 44 R+: 22	33.3	40.1 (SD 5.6)	OS (u)   p = 0.009* OS (m)   HR R+ 5.43 (CI 1.44-21.85), p = 0.01* DSS (m)   HR R+ 21.9 (CI 3.71-180), p = 0.0004*
	198 (NR)	RT: 185; CHT: 38 (before or after surgery)		R0: 114 R+: 55 unknown: 29	32.5	NR	OS (u)   p = 0.048*
	211 (EEA: 91 Open: 120)	NR	211	R0: 170 R+: 41	19.4	#75 (1-186)	OS (u)   RR R+ 1.54 (CI 0.96-2.49), p = 0.07 PFS (u)   RR R+ 1.49 (CI 1-2.22), p = 0.05 OS (m)   RR R+ 1.54 (CI 0.96 2.49), p = 0.02*
	146 (NR)	CHT: 24	RT: 146	R0: 95 R+: 37 (R1: 33; R2: 4) R close: 12 unknown: 2	25.7	#46 (4-357)	OS (m)   HR R0 0.636 (CI 0.407-0.994), p = 0.047*
	19 (Open: 19)	NR	RT: 9 RT-CHT: 8	R0: 10 R+: 5 unknown: 4	33.3	#96 (24-288)	DFS (u)   p > 0.05
	243 NR: 2 (EEA: 161 Open: 82)	CHT: 12	RT: 137 RT-CHT: 57	R0: 154 R+: 60 unknown: 31	28	NR	OS(u)   HR R+ 2.09 (CI 1.13, 3.87)* OS(m)   HR R+ 3.78 (CI 1.82, 7.88)* DFS   HR R+ 2.06 (CI 1.22, 3.48)* DSS   HR R+ 2.25 (CI 0.71, 7.11)
	1717 (NR)	NR	RT: 670 RT-CHT: 395	R0: 1212 R+: 475 (R1: 273; R2: 202) unknown: 30	28.2	55 (0-128.5)	OS (u)   p < 0.001* OS (m)   R1 OR 1.74 (CI 1.4-2.16) p < 0.001* R2 OR 1.43 (CI 1.14-1.8) p = 0.002*



Table II. *continues.*

First author (year)	Study	Demographics			Tumour				
		No. of patients	Age (years) mean or #median (range, IQR or SD)	Gender (M/F)	Histology	Initial location	T Stage	N. Stage	
Crawford 2020 <sup>18</sup>	NCDB (USA 2004-2016)	1120	63.9 (NR)	747/373	SCC: 1120	MS: 589 NC: 421 ES: 110	T3-T4: 1120	NO: 1089 N+: 28 NR: 3	
Duru Birgi 2024 <sup>19</sup>	RCS (Turkey 2001-2021)	194	#58 (23-92)	136/58	SCC: 104 ACC: 36 SNAC: 14 other: 40	NC: 64 MS: 11 ES: 10	T1: 1 T2: 4 T3: 61 T4a: 100 T4b: 28	NO: 165 N+: 29	
Eide 2023 <sup>20</sup>	NCDB (USA 2004-2016)	38	60.7 (SD:18.1)	18/20	MEC: 38	NC: 19 MS: 16 ES: 2 other: 1	NR	NR	
Elsamna 2021 <sup>21</sup>	NCDB (USA 2010-2015)	446	≤ 65y: 146 ≥ 66y: 300	204/242	SNMM: 446	NC: 364 PNS: 82	T3: 244 T4: 163 NR: 39	NO: 403 N+: 24 NR: 19	
Ferrari 2022 <sup>22</sup>	RCS (Europe 1995-2021)	1360 [selected histology: 824]	62 (8-89)	574/250	SNAC: [348] SNC: [144] ONB: [112] SNMM: [87] SNUC: [54] MSGT: [79]	NC + ES: [741] MS: [62] SS: [11] FS: [4] NR: [6]	T1: [129] T2: [172] T3: [160]	NO: [804] N+: [20]	
Ganti 2019 <sup>23</sup>	NCDB (USA 2004-2015)	1874	71 (NR)	1000/874	SNMM: 1874	NC: 1312 MS: 252 ES: 114 FS: 7 SS: 4 other: 146	T3: 442 T4: 324 NR: 1126	NO: 718 N+: 65 NR: 1091	
Guazzo 2019 <sup>24</sup>	RCS (Australia 2005-2017)	32 [sinonasal: 17]	45.2 (26-73)	8/9	[ACC: 17]	NR	T3-T4b: [17]	NR	
Guo 2022 <sup>25</sup>	RCS (USA NR)	45	#71.8 (41.6-90.9)	17/28	SNMM: 45	NR	T3: 25 T4a: 11 T4b: 9	NR	
Harvey 2016 <sup>26</sup>	RCS (Australia NR)	109	49.2 (NR)	59/50	ONB: 109	NR	Kadish A: 11 Kadish B: 27 Kadish C: 71 Kadish D: 1	NR	
Herr 2013 <sup>27</sup>	RCS (USA 1997-2013)	22	#45.5 (11-77)	11/11	ONB: 22	NR	Kadish B: 10 Kadish C: 12	NO: 19 N+: 3	

	Treatment			Margin status		Follow-up	Outcome
	Surgery (approach)	Previous treatment	Adjuvant treatment	R0/R+/R close/unknown	Rate of positive margins (%)	F.U. (months) mean or #median (range, IQR or SD)	Investigated outcome (model)   association (* significant)
	1120 (NR)	NR	RT: 861 CHT: 373	R0: 376 R+: 618 unknown: 126	62.2	#54.5 (NR)	OS (u)   $p = 0.012^*$ OS (m)   HR R+ 1.309 (CI 1.078-1.590), $p = 0.007^*$
	155 (NR)	NR	RT: 155	R0: 67 R+: 74 R close: 6 unknown: 8	50.3	43 (6-158)	OS, PFS, LRFS, DMFS (u)   $p > 0.05$ DMFS (m)   HR R+ 4.409 (CI 1.369-14.19), $p = 0.013^*$
	35 (NR)	RT:16; CHT: 4 (before or after surgery)		R0: 21 R+: 6 unknown: 8	22.2	NR	OS (u)   $p > 0.05$
	383 (EEA: 90 Open: 160 NR: 133)	NR	RT: 207	R0: 263 R+: 120	31.3	NR	OS (u)   $p < 0.001^*$
	824 (EEA: [733] Open: [91])	NR	RT/RT-CHT: [535]	R0: [646] R+: [178 (R1:156; R2:22)]	21.6	[58 (1-213)]	SNAC (m)   OS*, CSS*, RFS*, LRFS*, RRFs*, DRFS* SCC (m)   OS*, CSS*, RFS*, LRFS*, RRFs*, DRFS* ONB (m)   OS, CSS, RFS*, LRFS*, RRFs, DRFS MM (m)   OS, CSS, RFS, LRFS, RRFs, DRFS Salivary (m)   OS, CSS*, RFS, LRFS, RRFs, DRFS
	1167 (EEA: 307 Open: 390 NR: 470)	RT: 1093; CHT: 223; IT: 158 (before or after surgery)		R0: 812 R+: 355	30.4	NR	OS (u)   $p < 0.001^*$ OS (m)   HR R0 0.44 (CI 0.30-0.65) $< 0.001^*$
	[17] (EEA: [7] Open: [10])	NR	[RT: 17]	R0: [2] R+: [15]	88.2	#82.1 (33.1-159.5)	NR
	45 (NR)	NR	RT: 43 CHT: 21 ICIs: 15	R0: 31 R+: 5 unknown: 9	13.9	38.7 (6.2-287)	OS (u)   HR R+ 1.96 (0.56, 5.43), $p = 0.26$ RFS (u)   HR R+ 1.58 (0.53, 3.88), $p = 0.38$
	109 (EEA: 67 Open: 42)	RT: 9	RT: 81	R0: 81 R+: 28	25.7	42 (6-421)	OS (u), $p = 0.004^*$
	22 (Open: 22)	CHT: 3	IMPT: 17 IMPT-CHT: 5	R0: 13 R+: 9	40.9	73 (NR)	OS (u) $p = 0.269$ DFS (u) $p = 0.015^*$



Table II. *continues.*

First author (year)	Study	Demographics			Tumour				
		No. of patients	Age (years) mean or #median (range, IQR or SD)	Gender (M/F)	Histology	Initial location	T Stage	N. Stage	
Hirakawa 2016 <sup>28</sup>	RCS (Japan 2000-2009)	58	60 (35-77)	51/7	SCC: 58	MS: 53 ES: 5	T2: 3 T3: 14 T4: 41	N0: 46 N+: 12	
Issa 2023 <sup>29</sup>	NCDB (USA 2004-2014)	1883	64.7 (20-90)	1233/650	SCC: 1883	NR	T1: 807 T2: 410 T3: 214 T4: 452	N0: 1673 N+: 210	
Jafari 2019 <sup>3</sup>	NCDB (USA 2004-2015)	7808	64.8 (SD:13.2)	5059/ 2749	SCC: 7808	PNS: 4298 NC: 3510	T1: 1255 T2: 946 T3: 1064 T4: 2640 NR: 1903	N0: 4824 N+: 1104 NR: 1880	
Khan 2017 <sup>31</sup>	NCDB (USA 2004-2010)	460 [late stage: 277]	55.8 (SD:15.3)	173/104	SNUC: 277	NR	NR	NR	
Kilic 2017 <sup>32</sup>	NCDB (USA 2010-2014)	1438	< 60y: 524 60-70y: 475 > 70y: 484	963/520	SCC: 1438	NC: 855 MS: 418 ES: 104 SS: 27 FS: 21 other: 58	NR	N0: 1438 N+: 0	
Kim 1999 <sup>33</sup>	RCS (Korea 1975-1993)	22	48 (26-68)	16/6	ACC:22	NR	T2: 4 T3: 9 T4a: 9	N0: 22	
Konig 2017 <sup>34</sup>	RCS (Norway 1998-2016)	20	58.1 (42-76)	12/8	ONB: 20	NR	T1: 3 T2: 8 T3: 6 T4: 3	NR	
Konig 2019 <sup>35</sup>	RCS (Norway 1988-2017)	72	67.1 (36-94)	51/21	SCC: 72	MS: 60 ES: 8 FS: 4	T1: 2 T2: 4 T3: 7 T4a: 20 T4b: 39	N0: 58 N+: 14	
Konig 2019 <sup>36</sup>	RCS (Norway 1995-2018)	20	57.5 (25-81)	15/5	SNAC: 20 (ITAC: 13; nITAC: 7)	ES: 17 MS: 3	T1: 2 T2: 3 T3: 4 T4: 11	N0: 20	
Konuthula 2016 <sup>37</sup>	NCDB (USA 2004-2010)	695	68.9 (SD: 13.4)	316/379	SNMM: 695	NC: 470 PNS: 225	NR	NR	
Konuthula 2017 <sup>38</sup>	NCDB (USA 2004-2013)	1167	54 (18-90)	706/461	ONB: 1167	NR	Kadish A: 173 Kadish B: 221 Kadish C: 621 Kadish D: 92 NR: 60	N0: 1015 N+: 92 NR: 60	

	Treatment			Margin status		Follow-up	Outcome
	Surgery (approach)	Previous treatment	Adjuvant treatment	R0/R+/R close/unknown	Rate of positive margins (%)	F.U. (months) mean or #median (range, IQR or SD)	Investigated outcome (model)   association (* significant)
	58 (NR)	CHT: 43 RT: 11	RT: 11	R0: 48 R+: 10	17.2	#40 (1-156)	LRC (u)   HR R+ 5.89 (1.92-17.14), p = 0.03* DMFS (u)   HR R+ 8.89 (2.96-26.84) 0.02* DFS (u)   HR R+ 8.63 (3.32-22.4) < 0.0001*
	994 (NR)	CHT: 9	RT: 408 RT-CHT: 117	R0: 781 R+: 213	21.4	NR	OS (m)   HR R+ 1.48 (CI 1.06-2.07); p = 0.02*
	3322 (NR)	166	2892	R0: 2289 R+: 1033 (R1: 511; R2: 521)	31.1	NR	OS HR R0 vs non-surg 0.54, p < 0.0001* OS HR R1 vs non-surg 0.78, p < 0.0001* OS HR R2 vs non-surg 0.92, p > 0.05
	[96] (NR)	NR	RT-CHT: [96]	R0: [37] R+: [22] unknown: [37]	37.3	NR	NR
	1438 (EEA: 353 Open: 1130)	0	RT/RT-CHT: 772	R0: 918 R+: 341 unknown: 179	27.1	NR	OS (u)   HR R+ 1.72 (CI 1.39-2-13), p < 0.001* OS (m)   HR R+ 1.51 (CI 1.19-1.91), p = 0.001*
	13 (Open: 13)	NR	RT: 10	R0: 5 R+: 8	61.5	96 (60-168)	p = 0.98
	17 (Open: 17)	RT: 2	RT: 11 RT-CHT: 4	R0: 10 R+: 7	41.2	86.2 (23.2-216)	p < 0.001*
	34 (EEA: 1 Open: 33)	RT: 5 CHT: 1	RT: 18 RT-CHT: 5	R0: 21 R+: 13	38.2	57 (1-314)	DSS (u)   p = 0.002* DSS (m)   p = 0.002*
	18 (EEA: 2 Open: 16)	NR	RT: 2	R0: 10 R+: 8	44.4	89 (1-239)	p = 0.005*
	555 (NR)	6	RT: 271 RT-CHT: 39 CHT: 29	R0: 300 R+: 127 unknown: 268	29.7	NR	OS (u)   p = 0.001* OS (m)   HR R0 0.74 (CI 0.56-0.97), p = 0.03*
	989 (NR)	25	RT: 404 RT-CHT: 300 CHT: 17	R0: 481 R+: 215 unknown: 293	30.9	NR	OS (u)   p = 0.0005* OS (m)   HR R0 0.62 (CI 0.40-0.96), p = 0.0302*



Table II. *continues.*

First author (year)	Study	Demographics			Tumour				
		No. of patients	Age (years) mean or #median (range, IQR or SD)	Gender (M/F)	Histology	Initial location	T Stage	N. Stage	
Lehrich 2020 <sup>39</sup>	NCDB (USA 2004-2015)	3011 [salvage surgery: 207]	56.6 (SD:13.6)	140/67	SCC: [125] ONB: [38] SNUC:[25] SNAC: [19]	NC: [90] MS: [82 ] ES: [25] FS: [2] SS: [2] other: [6]	NR	NO: [130] N+: [26] NR: [51]	
Li 2023 <sup>40</sup>	RCS (China 2000-2020)	12	48 (33-65)	10/2	SNAC (nITAC): 12	NC: 11 ES: 1 MS: 2	T1-T3: 6 T4: 6	NO-N1: 8 N2: 4	
Li 2020 <sup>41</sup>	RCS (China 2007-2017)	21	59.2 (35-81)	18/3	SCC:21	MS: 11 NC/other: 10	T1: 2 T2: 1 T3: 10 T4: 8	NR	
Li 2021 <sup>42</sup>	RCS (China 2005-2018)	173	54.3 (NR)	128/45	SCC: 173	MS: 118 NC/ES: 41 FS+SS: 14	T2: 32 T3: 63 T4: 78	NO: 168 N+: 5	
Lian 2024 <sup>43</sup>	RCS (China 2004-2021)	219	#54 (16-82)	155/64	SCC: 219	MS: 111 NC: 66 ES: 26 other: 16	T1: 12 T2: 55 T3: 77 T4: 75	NO: 199 N+: 20	
Malouf 2012 <sup>44</sup>	RCS (France 1979-2009)	44	#43 (4-78)	23/21	ONB: 44	NR	Kadish B: 16 Kadish C: 15	NO: 27 N1: 4	
McMillan 2022 <sup>45</sup>	RCS (USA 1960-2020)	143	#50 (IQR 40-58)	80/58	ONB: 143	NR	Kadish A: 6 Kadish B: 26 Kadish C: 79 Kadish D: 16	NO: 124 N+: 19	
Nakagawa 2017 <sup>46</sup>	RCS (Japan 2008-2016)	22	49 (27-83)	10/12	ONB: 22	NR	Kadish A: 4 Kadish B: 5 Kadish: 13	NO: 22	
Nakamaru 2020 <sup>47</sup>	RCS (Japan 2005-2019)	15	#68 (47-81)	8/7	SCC: 15	NC: 6 MS: 5 ES: 4	T1:4 T2: 7 T3: 4	NO: 15 N+: 0	
Nakaya 2004 <sup>48</sup>	RCS (Japan 1980-2000)	16	65.5 (53-79)	11/5	SNMM: 16	NC: 16	NR	NO: 14 N+: 2	

	Treatment			Margin status		Follow-up	Outcome
	Surgery (approach)	Previous treatment	Adjuvant treatment	R0/R+/R close/unknown	Rate of positive margins (%)	F.U. (months) mean or #median (range, IQR or SD)	Investigated outcome (model)   association (* significant)
	[207] (EEA: [16] Open: [74] NR: [117])	CHT: [44] RT-CHT: [97] RT: [66]	NR	R0: 115 R+: 54 unknown: 38	32	NR	OS (u)   HR R+ 1.84 (CI 1.13-3), p = 0.02* OS (m)   HR R+ 2.31 (CI 1.29-4.13), p = 0.005*
	11 (EEA: 11)	NR	RT: 3 RT-CHT: 5 TT: 1	R0: 6 R+: 5	45.5	47 (17-106)	RR   p = 0.33 DSS   p < 0.01*
	21 (EEA: 16 Open: 5)	NR	RT: 7 RT-CHT: 7 CHT: 2 CHT + IT: 1	R0: 15 R+: 6	28.6	47.4 (3-123)	OS (u)   p < 0.001 OS (m)   HR R+ 1.931 (CI 1.082-3.447), p = 0.026*
	173 (EEA: 51 Open: 122)	NR	153	R0: 100 R+: 73	42.2	#65 (6-157)	OS (u)   p = 0.186
	219 (EEA: 88 Open: 131)	NR	NR	R0: 131 R+: 66 R close: 11 unknown: 11	31.7	43.9 (2-164)	OS (u)   HR R0/close vs R+ 0.137 (95% CI 0.0770-0.243), p < 0.0001* OS (u)   HR R0 vs Rclose 0.210 (95% CI 0.076-0.580), p < 0.01* RFS (u)   HR R0/close vs R+ 0.111 (95% CI 0.064-0.192), p < 0.0001* RFS (m)   HR R0 vs Rclose 0.263 (95% CI 0.088-0.780), p < 0.01*
	31 (NR)	CHT: 11	RT: 29 CHT: 6	R0: 22 R+: 9	29	11 (1-356)	OS (u)   p = 0.002* DFS (u)   p < 0.001* OS (m)   HR R+ 5.94 (95% CI 1.23-28.77) p = 0.03* DFS (m)   HR R+ 7.09 (95% CI 2.1-23.89) p = 0.002*
	135 (EEA: 31 Open: 104)	NR	RT: 111 CHT: 66	R0: 67 R+: 30 unknown: 38	30.9	#76.6 (IQR 25.5-153)	OS, DMFS (u)   n.s. PFS (u)   p < 0.05* OS (m)   HR R+ 1.67 (IC 0.78-3.58) p = 0.19 PFS (m)   HR R+ 1.96 (IC 1.10-3.5) p = 0.02* DMFS (m)   HR R+ 0 (IC 0-0) p = 0.99
	22 (EEA: 22)	0	RT: 20	R0: 21 R+: 1	4.5	44 (11-104)	NR
	15 (EEA: 15)	0	RT: 5 RT-CHT: 2	R0: 11 R+: 4	26.7	#26 (7-123)	OS (u)   p = 0.138 DSS (u)   p = 0.0253
	14 (Open: 14)	RT/RT-CHT:10 (before or after surgery)		R0: 7 R+: 7	50	37 (4-150)	n.s.



Table II. *continues.*

First author (year)	Study	Demographics			Tumour				
		No. of patients	Age (years) mean or #median (range, IQR or SD)	Gender (M/F)	Histology	Initial location	T Stage	N. Stage	
Nalavenkata 2015 <sup>49</sup>	RCS (Australia-USA 1986-2013)	113	49.7 (SD 13.2)	61/52	ONB: 113	NR	Kadish A: 11 Kadish B: 30 Kadish C: 72	NO: 115 N+: 8	
Nishio 2015 <sup>50</sup>	RCS (Japan 1992-2011)	40 [survival analysis: 35]	58.1 (43-75)	29/11	SCC: 32 ACC: 2 SNAC: 2 MEC: 1 SNUC:1 other: 2	MS: 40	T4a: 26 T4b: 14	NO: 35 N+: 5	
Ogawa 2000 <sup>51</sup>	RCS (Japan 1979-1998)	41	#55 (37-79)	32/9	SCC: 41	MS: 41	T2: 6 T3: 22 T4: 13	NO: 36 N+: 5	
Ono 2018 <sup>52</sup>	RCS (Japan 1998-2016)	76 [salvage surgery: 14]	66 (SD: 10)	61/15 [12/2]	SCC: 70 [12] MEC: 2 [1] SNUC:1 [0] other: 3 [1]	NR	T2: 2 [1] T3: 24 [5] T4a: 44 [6] T4b: 6 [2]	NO: 67 [12] N+: 9 [2]	
Paré 2017 <sup>53</sup>	RCS (France 1998-2012)	68	#63 (17-88)	43/25	SCC: 68	MS: 44 NC: 11 ES: 9 other: 4	T1: 2 T2: 7 T3: 14 T4a: 39 T4b: 6	NO: 56 N1: 4 N2: 8	
Parikh 2021 <sup>54</sup>	RCS (USA 2006-2013)	48	65.8 (19-95)	31/17	SCC: 48	NR	T1-3: 18 T4: 30	NO: 41 N+: 7	
Patel 2012 <sup>55</sup>	RCS (USA 1956-2000)	151	#49.5 (12-82)	88/58 NR: 5	ONB: 151	NR	Kadish A/B: 33 Kadish C: 116	NR	
Patel 2024 <sup>56</sup>	NCDB (USA 2004-2019)	1750 [surgery: 513]	#55 (IQR: 45-65)	312/201	SNAC: [114] ACC: [111] SNUC:[107] SNEC: [71] ONB: [55] SNMM: [47] MEC: [8]	NC: [201] ES: [140] MS: [72] SS: [16] FS: [11] other: [73]	T4b: [513]	NO: [342] N+ : [51] NR: [120]	
Petruzzelli 2015 <sup>57</sup>	RCS (USA 1994-2012)	32	51 (13-77)	21/11	ONB:32	NR	Kadish A: 6 Kadish B: 13 Kadish C: 13	NO: 30 N+: 2	
Qatanani 2023 <sup>58</sup>	NCDB (USA 2004-2016)	173	56.6	114/59	SNUC:173	NR	T1: 9 T2: 10 T3: 14 T4: 62 NR: 76	NO: 173	

	Treatment			Margin status		Follow-up	Outcome
	Surgery (approach)	Previous treatment	Adjuvant treatment	R0/R+/R close/unknown	Rate of positive margins (%)	F.U. (months) mean or #median (range, IQR or SD)	Investigated outcome (model)   association (* significant)
	109 (EEA: 67 Open: 42)	RT: 10	RT: 82	R0: 80 R+: 28 unknown: 5	25.9	41.5 (IQR 58.2)	RRFS (u)   R+ 17.9% vs 5%, p = 0.034*
	40 [35] (Open: 40)	RT: 6 CHT: 10 RT-CHT: 12 surgery + RT: 6	NR	R0: [26] R+: [9]	25.7	#40 (1-158)	OS (u)   p = 0.019*
	41 (Open: 41)	CHT: 16	RT: 41	R0: 14 R+: 27 (R1: 23; R2: 4)	65.9	#93 (25-179)	LCR (u)   p < 0.01*
	29 [14] (Open: 29 [14])	RT-CHT: 29 [14] Surgery: 1 [1]	NR	R0: [7] R+: [7]	50	#60.9 (14.1-147.1)	OS (u)   p = 0.004 LCR (u)   p = 0.005"
	68 (Open: 68)	Surgery: 6 Surgery+RT: 5 CHT-RT: 3 CHT: 40	RT: 39 RT-CHT: 19	R0: 36 R+: 29 unknown: 3	44.6	#68 (IQR: 39-112)	OS (u)   HR R+ 1.82 [0.87-3.79], p = 0.11 LRFS (u)   HR R+ 1.75 [0.76-3.98], p = 0.19
	48 (Open: 48)	CHT: 1	RT: 17 CHT: 21	R0: 23 R+: 25	52.1	40.7 (NR)	OS (u)   RR R+ 0.9, p = 0.79 DFS (u)   RR R+ 1.2, p = 0.74 OS (m)   RR R+ 1.0, p = 0.99 DFS (m)   RR R+ 1.4, p = 0.53
	15 (Open: 151)	Surgery: 50 RT: 51 CHT: 23	RT: 71 CHT: 9	R0: 102 R+: 23 R close: 20 unknown: 6	15.9	#56 (1-323)	OS (u)   p = 0.01* DSS (u)   p = 0.009* RFS (u)   p = 0.01* OS (m)   HR R+ 2.2 (IC 1.1-4.7), p = 0.02* DSS (m)   HR R+ 2.4 (IC 1.1-5.3), p = 0.04* RFS (m)   HR R+ 2.1 (IC 1.1-4.0), p = 0.01*
	[513] ([NR])	[53]	[398]	R0: [174] R+: [102 (R1: 69, R2:33, NR: 100)] unknown: [137]	53.7	NR	OS (u)   p = .059
	32 (EEA: 9 Open: 22 NR: 1)	RT-CHT: 4	RT: 19 RT-CHT: 5	R0: 25 R+: 7	21.9	96.1 (6-240)	NR
	173 (NR)	NR	RT: 34 RT-CHT: 139	R0: 56 R+: 55 unknown: 62	49.5	NR	OS (u)   p < 0.05* OS (m)   HR R+ 4.82 (CI 2.28-10.2), p < 0.001*



Table II. *continues.*

First author (year)	Study	Demographics			Tumour				
		No. of patients	Age (years) mean or #median (range, IQR or SD)	Gender (M/F)	Histology	Initial location	T Stage	N. Stage	
Resto 2000 <sup>59</sup>	RCS (USA 1981-1998)	27	#52 (17-77)	14/13	ONB: 27	NR	T1: 11 T2: 10 T3: 6	N0: 22 N+: 5	
Rojas Lechuga 2022 <sup>60</sup>	RCS (Spain 1984-2020)	50	70.4 (SD 12.5)	24/26	SNMM: 50	PNS: 26 NC: 24	T3: 22 T4a: 19 T4b: 9	N0: 43 N1: 7	
Sayed 2017 <sup>61</sup>	RCS (USA 1998-2016)	72	< 60y: 20 ≥ 60y: 52	33/39	SNMM: 72	NC: 50 PNS: 22	T3: 42 T4: 30	N0: 72 N+: 0	
Sun 2020 <sup>62</sup>	RCS (China 1984-2018)	138	#36 (7-81)	91/47	ONB: 138	NR	Kadish A: 1 Kadish B: 25 Kadish C: 112	N+: 34	
Tajudeen 2014 <sup>63</sup>	RCS (India 1991-2011)	14	64 (SD 12)	7/7	SNMM:14	NC: 11 MS: 2 ES: 1	T1: 6 T2: 2 T4a: 6	NR	
Torabi 2019 <sup>64</sup>	NCDB (USA 2004-2014)	556	18-54y: 214 55-64y: 129 65-74y: 119 ≥ 75y: 94	273/283	ACC: 403 MEC: 89 other: 64	MS: 282 NC: 239 ES: 35	T1: 130 T2: 91 T3: 176 T4a: 159	N0: 532 N+: 24	
Tsutsumi 2023 <sup>65</sup>	NCDB (USA 2004-2016)	814	52.6 (SD: 15.1)	492/322	ONB: 814	NR	Kadish A-B: 287 Kadish C-D: 527	NR	
Tsutsumi 2024 <sup>66</sup>	RCS (USA 2014-2020)	22	52 (29-76)	13/9	ONB: 22	NR	Kadish A: 2 Kadish B: 4 Kadish C: 16 Kadish D: 0	N0: 22	
Ungar 2024 <sup>67</sup>	RCS (Israel 2002-2022)	18	55 (23-82)	7/11	ACC:18	MS:8 NC: 3 ES: 3	T4a: 3 T4b: 15	N0: 15 N+: 3	
Vedula 2023 <sup>68</sup>	RCS (USA 2004-2016)	349	≤ 60y: 132 > 60y: 217	219/130	SNAC: 349	NC: 202 ES: 88 MS:59	T1: 136 T2: 77 T3: 52 T4: 84	N0: 349	
Vermassen 2024 <sup>69</sup>	RCS (Belgium 1998-2018)	91	#63 (26-85)	89/2	SNAC (ITAC): 91	NR	T1: 9 T2: 37 T3: 16 T4a: 20 T4b: 9	N0: 91	

	Treatment			Margin status		Follow-up	Outcome
	Surgery (approach)	Previous treatment	Adjuvant treatment	R0/R+/R close/unknown	Rate of positive margins (%)	F.U. (months) mean or #median (range, IQR or SD)	Investigated outcome (model)   association (* significant)
	17 (Open: 17)	RT: 4 CHT: 3	RT: 9 CHT: 1 RT-CHT: 4	R0: 10 R+: 7 unknown: 1	41.2	5.9 (NR)	OS (u)   HR R+ NR (CI NR), p < 0.05* DFS (u)   HR R+ 10.1 (CI 1.1-95.9), p = 0.04*
	46 (EEA: 22 Open: 23)	NR	RT: 20	R0: 15 R+: 14 unknown: 17	48.3	#39.6 (IQR 78.5)	DSS (u)   HR R+ 1.8 (CI 1.0-3.0), p = 0.045* DSS (m)   HR R+ 12.4 (CI 0.6-0.6), p = 0.231
	72 (EEA: 20 Open: 52)	RT:58 (adjuvant) IT (before or after surgery)		R0: 40 R+: 32	44.4	NR	OS (m)   HR R+ 1.55 (CI 0.84-2.85) LRFS (m)   HR R+ 1.37 (0.66-2.88)
	88 (EEA: 45 Open: 43)	RT: 33 CHT-RT: 17	RT: 49 CHT-RT: 3	R0: 38 R+: 50	56.8	#61 (4-231)	NR
	14 (NR)	Surgery: 2 Surgery + RT: 1 IFN+Surgery: 1 IFN: 1 CHT: 1	RT: 8 RT-CHT: 2	R0: 10 R+: 4	28.6	20.7 (1.4-84.5)	OS (u)   p = n.s. LRFS (u)   p = 0.031*
	[506-514] <sup>o</sup> (NR)	0	RT: 293 RT-CHT: 52 CHT: < 10 <sup>o</sup>	R0: 223 R+: 180 unknown: [103-111] <sup>o</sup>	44.7	NR	p < 0.001*
	814 (NR)	0	RT: 562 RT-CHT: 252	R0: 631 R+: 183	22.5	NR	OS (m)   HR R+ 1.44 (CI 1.01-2.05), p = 0.04*
	22 (EEA: 7 Open: 15)	NR	RT: 22	R0: 10 R+: 8 R close: 4	36.4	37 (5-95)	DFS (m)   HR R+ 6.17 (CI 1.05-36.08), p = 0.0436*
	18 (EEA: 4 Open: 14)	RT: 2	RT: 16	R0: 7 R+: 11 (R1: 6; R2: 25)	61.1	240 (NR)	OS (u)   p = 0.356 DSS (u)   p = 0.732
	349 (EEA: 93 Open: 100 NR: 156)	0	RT: 154	R0: 222 R+: 87 unknown: 40	28.2	NR	OS (u)   p = 0.101
	91 (EEA: 51 Open: 40)	NR	RT: 90 CHT: 1	R0: 52 R+: 39 (R1: 9; R2: 30)	42.9	21.5 (7.7-22.1)	OS (u)   HR R+ 2.39 (CI 1.41-4.07), p = 0.0012* DSS (u)   HR R+ 2.88 (CI 1.51-5.49), p = 0.0013* DFS (u)   HR R+ 2.15 (CI 1.21-3.81), p = 0.0083* LRFS (u)   HR R+ 2.35 (CI 1.26-4.39), p = 0.0076* OS (m)   HR R+ 2.14 (CI 1.23-3.71), p = 0.0069* DSS (m)   HR R+ 2.73 (CI 1.36-5.47), p = 0.0047* DFS (m)   HR R+ 1.63 (CI 0.90-2.95) p = 0.1074 LRFS (m)   HR R+ 1.94 (CI 1.01-3.73), p = 0.0475*



**Table II. continues.**

First author (year)	Study	Demographics			Tumour				
		No. of patients	Age (years) mean or #median (range, IQR or SD)	Gender (M/F)	Histology	Initial location	T Stage	N. Stage	
Wang 2024 <sup>70</sup>	RCS (China 2009-2021)	441	< 60y: 243 ≥ 60y: 190	310/131	SCC: 441	NC: 191 MS: 147 ES: 80 other: 23	T1-2: 44 T3: 90 T4: 307	N0: 368 N+: 73	
Zafereo 2008 <sup>71</sup>	RCS (USA 1989-2004)	18	58.4 (38-85)	11/7	ONB:18	NR	Kadish A: 2 Kadish B: 7 Kadish C: 9	N0: 14 N+: 4	
Zhou 2024 <sup>72</sup>	RCS (China 2008-2021)	22	53.6 (25-80)	14/8	SNAC (nITAC): 22	NC: 15 MS: 10 ES: 7	T1-T2: 7 T3-T4: 15	N0-N1: 20 N2: 2	

ACC: adenoid cystic carcinoma; CHT: chemotherapy; Comb., combined approach; CSS: cancer specific survival; DFS: distant free survival; DMFS: distant metastasis free survival; DRFS: distant recurrence free survival; IMPT: intensity modulated particle therapy; IQR: interquartile range; IT: immunotherapy; ITAC: intestinal type adenocarcinoma; LRC: locoregional control; LRFs: local recurrence free survival; type adenocarcinoma; NR: not reported; n.s.: not significant; ONB: olfactory neuroblastoma; OR: odds ratio; OS: overall survival; PFS: progression free survival; PNS: paranasal sinuses; RCS: retrospective cohort study; SD: standard deviation; SNAC: sinonasal adenocarcinoma; SNC: sinonasal carcinoma; SNEC: sinonasal neuroendocrine carcinoma; SNUC: sinonasal undifferentiated carcinoma; SS: sphenoid sinus; T: tumour stage

**Table III. Reporting of margin status and definition.**

Criterion and description	No. of studies
<b>Distinction R1/R2</b>	
Yes	8 <sup>14,15,18,31,52,68,70,71</sup>
No	56
<b>Use of frozen sections</b>	
Yes	7 <sup>23,42,48,58,64,67,70</sup>
Not reported	57
<b>Close margin defined</b>	
Yes	8 <sup>15,20,32,44,48,54,56,67</sup>
Not reported	56
<b>Distance threshold</b>	
Any	8
< 5 mm (considered close)	5 <sup>15,32,44,48,54</sup>
< 5 mm (considered R1)	2 <sup>38,39</sup>
< 2 mm (considered R1)	1 <sup>44</sup>
< 1 mm (considered R1)	2 <sup>27,54</sup>
Not reported	56

R1: microscopically infiltrated margin; R2: macroscopic residual disease.

a correlation between negative surgical margins and better recurrence rates and survival outcomes <sup>3,4,23,40,76-79</sup>. The result of the present review seems to confirm this trend, even

though the interpretation of them must be approached with caution due to the significant heterogeneity among studies. While the pooled analysis suggests a detrimental impact of positive margins on survival, statistical significance was reached in only 10 of 28 individual OS studies. This variability may reflect methodological differences among studies or inherent limitations of the present analysis, which will be further discussed below.

**Overall margin infiltration rates**

Regardless of histology, this study found a high overall rate of margin infiltration (33.2%), in line with other review of the literature <sup>4</sup>, highlighting the technical challenges in achieving negative margins in sinonasal malignancies, irrespective of the surgical approach. Historically, one of the main criticisms of endoscopic approaches was their supposed inability to achieve en-bloc resection (Cover figure). However, no clear evidence supports the superiority of en-bloc over piecemeal resection in terms of oncologic outcomes. Even craniofacial resection, theoretically enabling en-bloc excision, has shown high rates of margin infiltration, with one of the largest multicentric study on open resections <sup>79</sup> reporting positive margins in 31.5% of 1,307 cases. While endoscopic resections were initially reserved for early-stage tumours, advancements in technology and surgical expertise have extended their indications to advanced malignancies. A recent multicentric retrospective study on endoscopically treated sinonasal malignancies <sup>77</sup> found an

	Treatment			Margin status		Follow-up	Outcome
	Surgery (approach)	Previous treatment	Adjuvant treatment	R0/R+/R close/unknown	Rate of positive margins (%)	F.U. (months) mean or #median (range, IQR or SD)	Investigated outcome (model)   association (* significant)
	387 (EEA: 270 Open: 97)	RT-CHT: 122	RT-CHT: 245	R0: 127 R+: 240 (R1: 127; R2: 113)	65.4	54 (2.1-162.9)	LFR (u)   OR 2.35 (CI 1.32-4.16), $p < 0.01^*$ OS (m)   HR R2 vs R0/1 1.88 (CI 1.27-2.80), $p = 0.002^*$ PFS (m)   HR R2 vs R0/1 1.96 (CI 1.36-2.83), $p < 0.01^*$
	17 (EEA: 3 Open: 14)	RT: 2 RT-CHT: 1	RT: 6 RT-CHT: 3 CHT: 1	R0: 12 R+: 2 unknown: 3	14.3	66 (1-312)	DSS (u)   $p = 0.003^*$ RFS (u)   $p = 0.0006^*$
	19 (EEA: 9 Open: 10)	CHT: 1	RT: 6 RT-CHT: 2	R0: 15 R+: 4	21.1	#48.5 (3-144)	OS (u) $p = 0.192$

urrence free survival; DSS: disease specific survival; EEA: endoscopic endonasal approach; ES: ethmoid sinus; F: female; FS: frontal sinus; HR: hazard ratio; ICIs: immune checkpoint inhibitors; IFN: interferon; (m), multivariate analysis; M: male; MM: mucosal melanoma; MS: maxillary sinus; MSGT: minor salivary gland tumours; NC: nasal cavity; NCDB: national cancer database; nITAC: non-intestinal prospective cohort study; RFS: recurrence free survival; RR: relative risk; RRFs: regional recurrence free survival; RT: radiotherapy; RT-CHT: radio-chemotherapy; SCC: squamous cell carcinoma; SD: standard deviation; T: target therapy; (u): univariate analysis; #median; \*exact number not disclosed as per NCDB use agreement.

overall margin infiltration rate of 20.5%, with the highest rates observed in MSGC (43%), SNUC/SNEC (33.3%), and SNMM (32.2%). Similarly, Abdelmeguid et al.<sup>80</sup> reported that negative margins were achieved in 87.4% of sinonasal cancer patients treated at the MD Anderson Cancer Center, despite nearly 40% of patients being affected by T4a or T4b staged disease. Finally, a recent international collaborative study<sup>82</sup> on skull base malignancies further reinforced these findings, reporting an overall margin infiltration rate of 26%, with significant variations depending on the surgical approach. Specifically, positive margins were identified in 32% of open resections, 25% of combined approaches, and only 18% of purely endoscopic procedures. These data suggest that, while the open approach is often reserved for more advanced tumours, the endoscopic technique can achieve comparable, if not superior, margin status in appropriately selected cases.

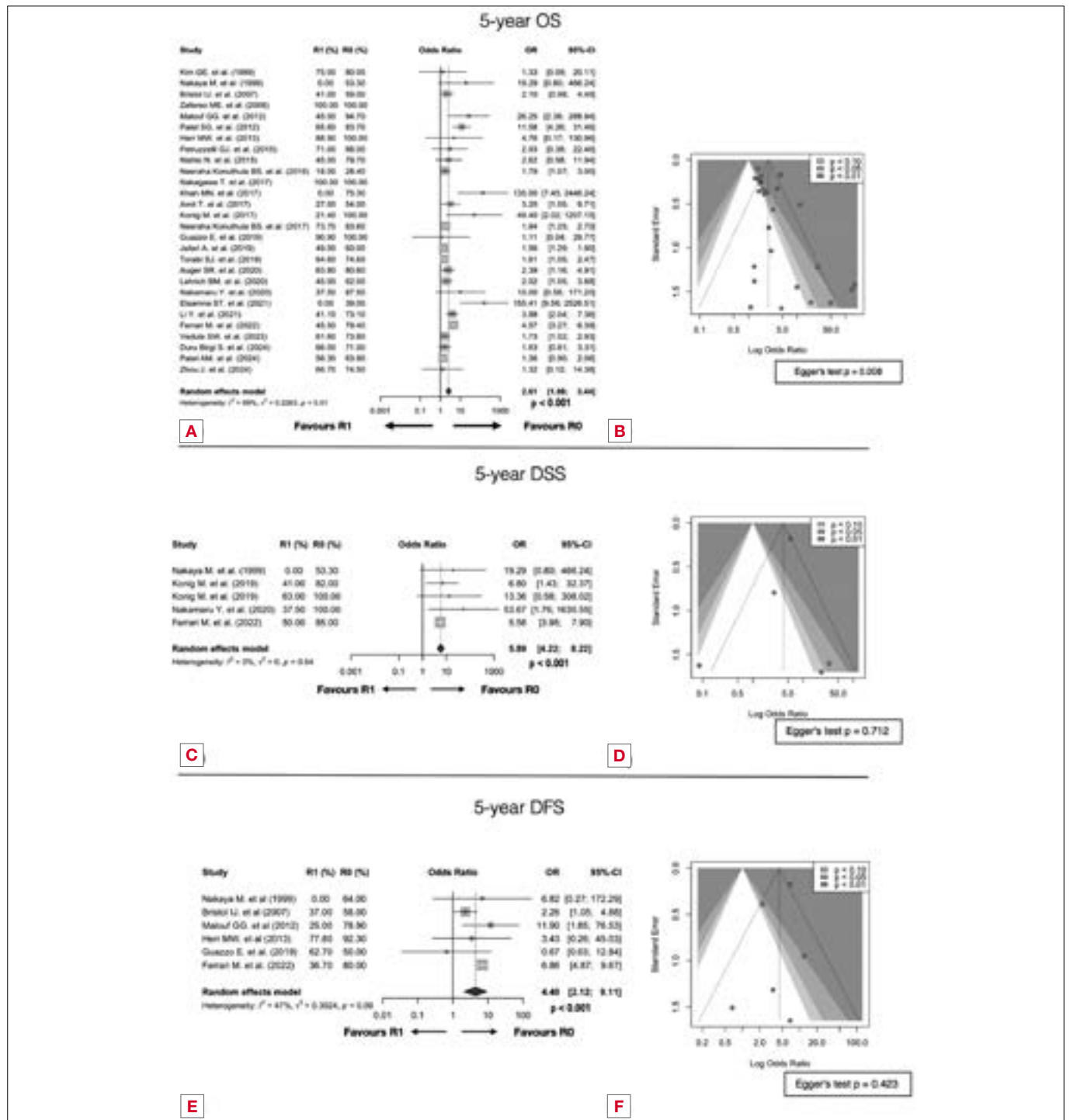
However, it is important to emphasise that such margin infiltration rates remain higher than those observed in other head and neck sites<sup>73</sup>, underscoring the inherent challenges of sinonasal malignancies, irrespective of the surgical approach used for resection<sup>4</sup>. Addressing these limitations should be a key focus of future efforts aimed at improving oncologic outcomes.

#### *Histology-specific considerations: differences in the prognostic impact and rates of margin infiltration*

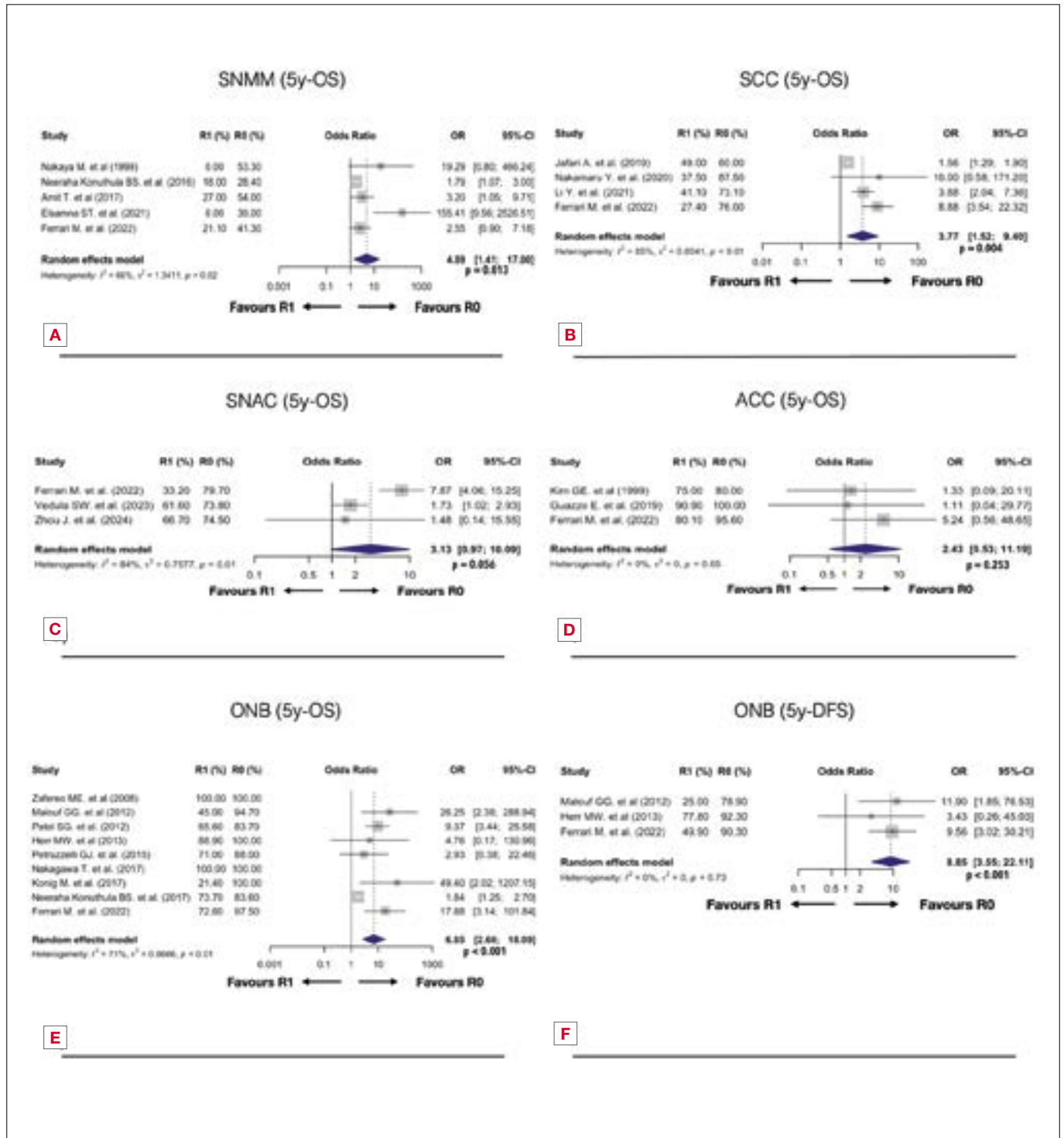
Recent literature has demonstrated the association between

the negative prognostic effect of margin involvement and the specific histology considered<sup>1,22,4,77</sup>. The present review also highlighted differences in the prognostic impact of surgical margins among different histologic types, reinforcing the role of histology as a key determinant of sinonasal cancer prognosis and treatment selection.

ONB, SCC, and SNMM showed the strongest associations between negative margins and improved OS, suggesting that complete tumour resection is particularly crucial in these histotypes. This aligns with existing literature for SCC and ONB. For ONB, infiltrated postoperative margins are among the most recognised negative prognostic factors, along with advanced Kadish stage, high Hyams grade, and nodal metastases<sup>26,38</sup>. Moreover, for ONB negative margin resection is also associated with a decreased risk of delayed recurrence in the neck, which has been demonstrated to be a significant predictor of mortality despite subsequent therapy<sup>3,49</sup>. Similarly, the critical role of achieving negative margins in SCC is well-documented in the literature<sup>76</sup>. Notably, the NCDB study by Jafari et al.<sup>30</sup> found that macroscopically involved margins were associated with survival outcomes comparable to those of patients treated with upfront non-surgical strategies, underscoring the importance of meticulous surgical planning to achieve at least macroscopically negative margins. Torabi et al.<sup>78</sup> further reinforced the prognostic value of negative margin resection in an NCDB review of 2,968 surgically treated patients



**Figure 2.** Results of the meta-analysis evaluating the impact of surgical margin status on 5-year OS, DSS, and DFS across 30 studies on sinonasal malignancies. (A) Forest plot for 5-year OS, displaying individual study ORs with 95% CIs, along with the pooled effect estimate (OR = 2.61, 95% CI: 1.98-3.44,  $p < 0.001$ ); (B) Funnel plot for 5-year OS, assessing potential publication bias (Egger's test,  $p = 0.008$ ), suggesting possible small-study effects; (C) Forest plot for 5-year DSS, showing the pooled OR (5.89, 95% CI: 4.22-8.22,  $p < 0.001$ ), with low heterogeneity ( $I^2 = 0%$ ,  $p = 0.64$ ); (D) Funnel plot for 5-year DSS, indicating no significant asymmetry (Egger's test,  $p = 0.712$ ). (E) Forest plot for 5-year DFS, showing a pooled OR of 4.4 (95% CI: 2.12-9.11,  $p < 0.001$ ), with moderate heterogeneity ( $I^2 = 47%$ ,  $p = 0.09$ ); (F) Funnel plot for 5-year DFS, revealing no strong evidence of publication bias (Egger's test,  $p = 0.423$ ).



**Figure 3.** Results of the meta-analysis assessing the impact of surgical margin status on 5-year OS across different histological subgroups and 5-year DFS for ONB. Each forest plot presents individual study ORs with 95% CIs, along with the pooled effect estimate for each histology. Heterogeneity across studies was quantified using the  $I^2$  statistic and Cochran's Q test. (A) Sinonasal mucosal melanoma (SNMM): OR = 4.89 (95% CI: 1.41-17,  $p = 0.013$ ); (B) Squamous cell carcinoma (SCC): OR = 3.77 (95% CI: 1.52-9.4,  $p = 0.004$ ); (C) Sinonasal adenocarcinoma (SNAC): OR = 3.13 (95% CI: 0.97-10.09,  $p = 0.056$ ); (D) Adenoid cystic carcinoma (ACC): OR = 2.43 (95% CI: 0.53-11.19,  $p = 0.253$ ); (E) Olfactory neuroblastoma (ONB): OR = 6.85 (95% CI: 2.6-18.09,  $p < 0.001$ ); (F) Olfactory neuroblastoma (ONB) for DFS: OR = 8.85 (95% CI: 3.55-22.11,  $p < 0.001$ ).

with sinonasal SCC, where positive margins were associated with decreased OS (hazard ratio [HR] 1.672, 95% CI: 1.464-1.908) and a higher likelihood of requiring additional therapy (OR 1.966, 95% CI: 1.597-2.421). The likelihood of positive margins was higher in cases with advanced T-category (T4a vs T1), ethmoid sinus localisation (vs nasal cavity), and treatment at lower-volume centres, whereas the surgical approach (endoscopic vs. open) did not significantly impact margin status.

The prognostic impact of margin infiltration and OS for SNMM observed in our meta-analysis contrasts with some of the literature regarding this specific histology. In the multicentric experience of the European group reported by Ferrari et al.<sup>22</sup>, SNMM was the only histology where the impact of negative margin resection did not show a statistically significant association with survival. This discrepancy may be attributed to the influence of specific studies in the pooled analysis, particularly Elsamna et al.<sup>21</sup>, which reported an exceptionally strong prognostic impact of surgical margins. Additionally, the high heterogeneity ( $I^2 = 66\%$ ) and the presence of small-study effects suggested by the funnel plot and Egger's test ( $p = 0.031$ ) indicate potential variability in patient populations, tumour characteristics, or treatment strategies across studies. Further investigation is needed to better define the prognostic role of infiltrated margins in SNMM<sup>4</sup>, as well as the impact of surgery in the evolving therapeutic landscape, particularly in light of the emerging role of immunotherapy<sup>82,83</sup> and adjuvant proton beam therapy<sup>84</sup>.

Of note, the present meta-analysis found no statistically significant impact of negative margin resection on OS for ACC and SNAC. In SNAC, the lack of statistical significance in our meta-analysis may be attributed to the limited sample size and the high heterogeneity among included studies ( $I^2 = 84\%$ ), reducing the power to detect a significant association. Nonetheless, the observed trend ( $p = 0.056$ ) suggests that the impact of negative margins on OS may become more evident with larger and more homogeneous datasets, as emerged in the recent consensus paper on sinonasal malignancies<sup>4</sup>. However, in ACC, the lack of statistical significance may stem from the inherent challenges in achieving clear margins. ACC is characterised by perineural invasion and widespread microscopic submucosal tumour dissemination, making complete resection challenging or unfeasible, with reported R+ rates ranging from 63% to 85%<sup>3,75,85,86</sup>. Moreover, even when surgical margins are reported as negative, skip lesions along nerve pathways may compromise the reliability of a truly margin-negative resection<sup>87,88</sup>. The prognostic impact of positive

margins in ACC remains therefore controversial<sup>4</sup>. Some studies have reported a detrimental effect on survival, while others have not identified a significant association. Michel et al.<sup>89</sup> and Amit et al.<sup>90</sup> observed that positive margins were linked to lower 5-year OS and DFS, while Thompson et al.<sup>91</sup> did not find margin status to be an independent risk factor for DSS and DFS ( $p = 0.128$ ). Wiseman et al.<sup>92</sup> noted a higher local recurrence rate among patients with positive margins compared to those with negative margins (41.7% vs 22.2%,  $p = 0.34$ ), and further highlighted that local recurrence itself was a significant negative prognostic factor for 5-year OS ( $p = 0.05$ ). The present review reinforces these controversial reports, highlighting ACC as the histology with the highest margin infiltration rate (61.5%). To note, a similarly high rate of margin infiltration was also observed in SNAC (42.9%) and SNUC (43.4%), suggesting that margin involvement is a critical issue not only in ACC but also in other aggressive sinonasal malignancies. For SNUC, the high rate of margin infiltration likely reflects both its biological aggressiveness and historical challenges in classification. Over the years, the diagnostic criteria for SNUC have evolved, and this category may have encompassed various poorly differentiated sinonasal carcinomas with distinct biological behaviours. Such undifferentiated tumours often present as high-stage lesions and surgical resection might not infrequently fail to achieve true negative margins. Multimodal treatment strategies – such as induction chemotherapy followed by chemoradiation or surgery based on treatment response – have become the standard of care. The fact that, historically, some cases may have been misclassified and treated primarily with surgery could partly explain the high rate of margin infiltration in this histology<sup>93</sup>.

The high margin infiltration rate in SNAC (42.9%) is more complex to interpret, as multiple factors may have contributed to this finding. Some studies such as König et al.<sup>36</sup>, Li et al.<sup>42</sup>, Zhou et al.<sup>72</sup> involved small patient cohorts, potentially inflating the infiltration rate due to selection bias. However, Vermassen et al.<sup>69</sup>, who analysed a larger cohort, also reported a high rate of positive margins, though their series included a significant proportion of high-stage tumours treated with open approaches, which may have influenced the results. In contrast, Vedula et al.<sup>68</sup>, in another large cohort study, reported a lower margin infiltration rate (28.2%), aligning more closely with large series on SNAC<sup>2,77,94</sup>. This suggests that margin infiltration in SNAC may vary significantly depending on cohort size, tumour stage distribution, and surgical approach.

### *Heterogeneity in margin definition and assessment: the need for standardisation*

The results of this review underscore that margin control remains a significant challenge, not only in terms of infiltration rates, as discussed previously, but also due to the substantial variability in how margins are defined, assessed, and managed across studies.

The distinction between R1 (microscopic infiltration) and R2 (macroscopic infiltration) was explicitly reported in only 8 studies, and also close margins were formally defined in just 8. Notably, in survival analyses, close margins were inconsistently classified, being grouped with either R0 (negative margins) or R+ (positive margins) across different studies, further complicating the interpretation of their prognostic impact. The absence of standardised classification not only limits the ability to compare results across studies, but also raises uncertainties about the actual prognostic relevance of close margins. Similarly, while some studies defined margins using a threshold distance in millimetres, this was a minority finding among the reviewed literature. To date, there is no robust evidence supporting a precise definition of an adequate resection margin. A strict distance threshold, as well as the principle of a close margin – concepts often translated from head and neck surgical oncology – may not be directly applicable to this anatomical region. The application of a millimetre-based cutoff may be feasible in open en-bloc resections, but its clinical utility is limited in endoscopic surgery, where margin assessment is influenced by visualisation, instrumentation, and anatomical constraints.<sup>4</sup>

One of the studies included deserves particular mention as it is the one that most clearly defined margin assessment. Ferrari et al.<sup>22</sup> explicitly reported that margins were assessed according to the multi-bloc technique, in which resection is performed using an oriented disassembly approach. This method preserves the spatial orientation of the removed structures, enabling a three-dimensional reconstruction of the margin status. In this regard, some teams have proposed the use of anatomical diagrams to precisely document resection margins and facilitate future multidisciplinary discussions on tumour management<sup>95</sup>. However, no standardised approach has been established, and each institution currently manages this critical aspect of intraoperative margin assessment independently. This lack of standardisation inevitably introduces bias in the interpretation of surgical outcomes.

The concept of a layered margin, as described by Castelnovo et al.<sup>2</sup> where margin negativity is determined by the deepest layer of the resection, is likely the most commonly technique employed today. This approach relies on direct

intraoperative visualisation of tumour extension combined with an assessment of the presence or absence of infiltration. In recent years, additional intraoperative tools have shown promising results in optimising margin assessment. For example, neuro-navigation has demonstrated improved margin status in advanced malignancies of the anterior craniofacial region<sup>96</sup>. Moreover, fluorescence-guided surgery has emerged as a promising technique to better delineate tissue invasion and assist in defining surgical margins through enhanced visualisation<sup>97</sup>.

Frozen section analysis remains a fundamental intraoperative tool, offering real-time guidance on the need for additional resection. Given the potential for submucosal, subperiosteal, and perineural spread in sinonasal malignancies, gross tumour identification alone is insufficient to define resection margins, reinforcing the rationale for intraoperative margin assessment. However, while frozen sections are widely employed in sinonasal tumour surgery, their use was explicitly reported in only 7 studies included in this review, suggesting a potential underreporting. Although frozen section analysis has limitations – particularly the potential for misinterpretation of microscopic infiltration in intraoperative analysis, which is especially relevant in certain challenging histotypes such as SNMM<sup>61,98</sup> or in case of perineural invasion in ACC<sup>86</sup> – it remains a crucial tool for surgical decision-making and optimising oncologic outcomes in most of the cases as stated in a recent international consensus<sup>4</sup>.

This variability in margin assessment underscores an important limitation when interpreting the prognostic impact of surgical margins. Without a standardised definition, comparing rates of recurrence and survival across studies becomes challenging, as different criteria may lead to significant discrepancies in margin status classification. More importantly, such a variability has consequences in clinical practice, where different margins definition might translate in differences in indication for adjuvant treatment. These findings emphasise the need for a more consistent, evidence-based approach to definition of surgical margins in sinonasal malignancies, which could ultimately improve cross-study comparisons and enhance prognostic accuracy.

### *Limitations of the study*

This systematic review and meta-analysis provide valuable insights into the prognostic impact of surgical margins in sinonasal malignancies. However, several limitations must be considered when interpreting their findings.

First, the retrospective nature of all studies included, some of which are based on national cancer databases, introduces

potential selection and reporting biases. Furthermore, evidence of publication bias – particularly in OS analyses and in SNMM and ONB subgroups – suggests that smaller studies with non-significant results may be underrepresented. Significant heterogeneity was observed across studies and within specific subgroups (ONB, SCC, and SNAC), likely reflecting differences in study design, patient populations, histotypes, surgical approaches, and (neo-)adjuvant treatments. This variability is further compounded by the rarity and biological diversity of sinonasal malignancies, making large, homogeneous cohorts difficult to assemble. Consequently, most published literature consists of single-centre studies with relatively small sample sizes and short follow-up periods. The inclusion of studies spanning several decades (1956-2022) further adds clinical variability, as major advancements in diagnostic classification, staging, and treatment protocols have occurred over time. Importantly, the lack of standardised margin definitions and reporting criteria further complicates direct comparisons across different cohorts.

Despite the pivotal role of surgery in management of sinonasal tumours, oncologic outcomes are influenced by multiple factors, including histology, grade, stage, anatomical location, and the feasibility of (neo-)adjuvant therapy. Given that most included studies lacked sufficient outcome stratification based on these prognosticators, this review could not fully assess their interplay with margin status. This limitation restricts detailed subgroup analyses and control for confounders, underscoring the need for standardised reporting and more granular stratification in future studies.

Oncological outcomes were assessed at the 5-year time-point, with only a few studies providing longer follow-up data, despite the extended patient recruitment period. The limited availability of long-term data prevented further analysis beyond this timeframe, which may be particularly relevant for histotypes such as ACC and ONB, where late recurrences are not uncommon.

Finally, while this meta-analysis focused on OS, DSS, and DFS, it did not assess recurrence patterns or the impact of margin status on local, regional, and distant recurrence. These factors were beyond the scope of the study and could not be thoroughly addressed. Future research should explore these aspects, as margin status may significantly influence recurrence patterns, which, in turn, are critical for long-term prognosis and treatment decisions.

## Conclusions

This systematic review and meta-analysis confirms the

prognostic significance of surgical margins in sinonasal malignancies. While not all studies demonstrated a significant association between margin status and survival, a clear trend emerged, highlighting the negative impact of resection within infiltrated margins.

The prognostic relevance of surgical margins, as well as the rate of margin infiltration, is strongly influenced by tumour histology, reaffirming its critical role in the management of sinonasal cancers. The high rate of margin infiltration observed across studies underscores the inherent challenges of surgical treatment in this anatomical region, driven by both tumour biology and complex local anatomy. Moreover, significant heterogeneity persists in the definition and management of surgical margins, limiting comparability across studies and complicating the interpretation of oncologic outcomes. These findings emphasise the urgent need for standardised surgical protocols and margin assessment criteria to enhance consistency in clinical practice and facilitate meaningful comparisons in future research.

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The authors declare no conflict of interest.

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### Author contributions

ADA, EC: contributed equally to this work and share first authorship; ADA, EC, MB: conceptualization; ADA, EC, MF, PG, AD, PN: methodology; ADA, EC, AL, GS, GD, GM: data curation, literature search, study selection, data extraction; ADA, EC, PG, MF, AD: statistical analysis; MF, PG, AD, PN, MB, ADA, EC: validation, writing and original draft preparation; ADA, EC, GM, GS, AL, GD, MF, PG, AD, PN, MB: writing, review, and editing; ADA, EC, MB, PC: visualization; MB, PC: supervision; PN, PC, MB: project administration. All authors have read and agreed to the published version of the manuscript.

### Ethical consideration

Not applicable.

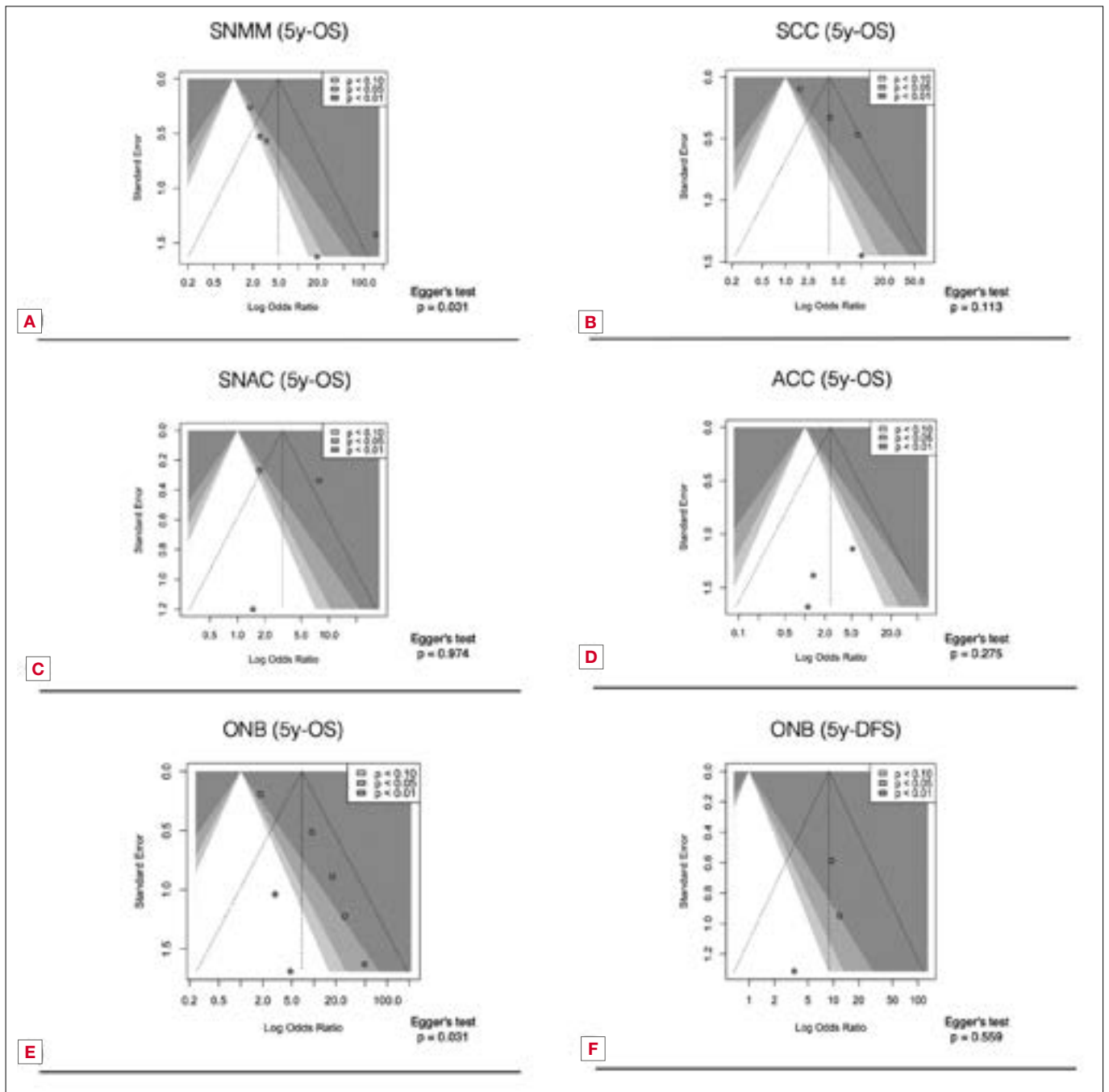
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**Supplementary Figure 1.** Funnel plots of the meta-analysis on 5-year OS across different histological subgroups (SNMM, SCC, SNAC, ACC, ONB) and 5-year DFS for ONB. Egger's test p values are reported for publication bias assessment.

**Supplementary Table S1. Search queries for database search**

PubMed, Filters: NO	("sinonasal" OR "nasal" OR "nose" OR "ethmoid" OR "maxillary" OR "sphenoid" OR "paranasal" OR "frontal sinus") AND ("neoplasm" OR "cancer" OR "sinonasal neoplasm" OR "paranasal neoplasm" OR "sinonasal tract neoplasm" OR "carcinoma"[Mesh] OR "adenocarcinoma" OR "neuroendocrine carcinoma" OR "undifferentiated carcinoma" OR "olfactory neuroblastoma" OR "esthesioneuroblastoma" OR "squamous cell carcinoma" OR "neuroendocrine carcinoma" OR "melanoma" OR "adenoid cystic carcinoma" OR "salivary gland carcinoma") AND ("margin" OR "pathological" OR "surgical margin" OR "histology" OR "margin status" OR "Margin to depth ratio") AND ("prognosis" OR "outcome" OR "survival" OR "impact" OR "failure pattern" OR "risk-tailored")
Scopus, Filters: NO	TITLE-ABS-KEY ("sinonasal" OR "nasal" OR "nose" OR "ethmoid" OR "maxillary" OR "sphenoid" OR "paranasal" OR "frontal sinus") AND TITLE-ABS-KEY ("neoplasm" OR "cancer" OR "sinonasal neoplasm" OR "paranasal neoplasm" OR "sinonasal tract neoplasm" OR "carcinoma" OR "adenocarcinoma" OR "neuroendocrine carcinoma" OR "undifferentiated carcinoma" OR "olfactory neuroblastoma" OR "esthesioneuroblastoma" OR "squamous cell carcinoma" OR "neuroendocrine carcinoma" OR "melanoma" OR "adenoid cystic carcinoma" OR "minor salivary gland carcinoma") AND TITLE-ABS-KEY ("margin" OR "surgical margin" OR "margin status" OR "Margin to depth ratio") AND ("prognosis" OR "outcome" OR "survival" OR "impact" OR "failure pattern" OR "risk-tailored")
Web of Science, Filters: NO	("sinonasal" OR "nasal" OR "nose" OR "ethmoid" OR "maxillary" OR "sphenoid" OR "paranasal" OR "frontal sinus") AND ("neoplasm" OR "cancer" OR "sinonasal neoplasm" OR "paranasal neoplasm" OR "sinonasal tract neoplasm" OR "carcinoma" OR "adenocarcinoma" OR "neuroendocrine carcinoma" OR "undifferentiated carcinoma" OR "olfactory neuroblastoma" OR "esthesioneuroblastoma" OR "squamous cell carcinoma" OR "neuroendocrine carcinoma" OR "melanoma" OR "adenoid cystic carcinoma" OR "minor salivary gland carcinoma") AND ("margin" OR "pathological" OR "surgical margin" OR "histology" OR "margin status" OR "Margin to depth ratio") AND ("prognosis" OR "outcome" OR "survival" OR "impact" OR "failure pattern" OR "risk-tailored")