

Recurrence rates of de-novo versus inverted papilloma-transformed sinonasal squamous cell carcinoma: a meta-analysis*

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Abstract

Background: There is a paucity of reporting on recurrence patterns of de-novo sinonasal squamous cell carcinoma (DN-SCC) and inverted-papilloma-transformed sinonasal squamous cell carcinoma (IP-SCC).

Method: A systematic literature review queried studies comparing recurrence patterns in patients with both DN-SCC and IP-SCC. Primary outcomes included local and regional recurrence and rates of distant metastasis. Of the 595 studies screened, eight were included.

Results: Patients with DN-SCC had significantly higher rates of positive margins, advanced T classification (T3/T4), treatment with chemotherapy and radiotherapy. There were no significant differences in local recurrence or regional recurrence. Overall risk of distant metastasis was lower in IP-SCC. DN-SCC, compared to IP-SCC, is more likely to present with advanced TNM classification and have positive margins after surgical resection, which may affect rates of distant metastasis and recurrence.

Conclusions: The findings in this study suggest IP-SCC may be a less aggressive malignancy compared to DN-SCC, with the possibility of a reduced role for adjuvant therapy in IP-SCC. Further studies are required to better understand differences in tumor biology and treatments strategies between IP-SCC and DN-SCC.

Key words: de-novo, inverted papilloma, recurrence, sinonasal, squamous cell carcinoma

Introduction

Sinonasal tumors are rare neoplasms with a reported incidence of 0.83 per 100,000 people, with sinonasal squamous cell carcinoma (SCC) being the most common malignant histology across all locations within the sinonasal tract, accounting for 41.9% of cases ⁽¹⁾. SCC arises de-novo, or in association with inverted papilloma (IP), a benign tumor of the sinonasal tract ^(1,2). Inverted papilloma-associated SCC (IP-SCC) occurs with malignant transformation of IP, where tumors arise synchronously (i.e., IP and SCC both present on pathology) or metachronously (i.e., after surgical resection of IP) ⁽³⁾. Because IP is a benign tumor, it has been previously speculated that IP-SCC portends a better prognosis than de-novo SCC (DN-SCC) even after malignant transformation due to early IP resection and surveillance for metachronous tumors ⁽⁴⁾. Recent systematic reviews have inves-

tigated survival and recurrence outcomes of IP-SCC and DN-SCC separately. For instance, a review of 28 studies demonstrated 62% aggregate 5-year OS and 24% recurrence in IP-SCC alone ⁽⁵⁾. Similarly, a systematic review of 41 studies reported 55% 5-year OS and 43% recurrence in patients with DN-SCC ⁽⁶⁾. The apparent survival and recurrence differences in these reviews provides evidence for DN-SCC and IP-SCC being distinct entities, though survival outcomes between DN-SCC and IP-SCC had not been directly compared through a systematic review and meta-analysis until recently ^(4,7-14). Recently, Lee et al. directly compared these studies and reported significantly worse survival DN-SCC (HR 1.87, 95% CI, 1.24-1.84) ⁽¹³⁾. Taken alone, this preliminary meta-analysis on survival differences suggested IP-SCC may be a distinct, less aggressive tumor than DN-SCC.

At the present time, however, there are no reviews directly comparing clinicopathologic characteristics, treatment strategies, and recurrence rates between tumors. As such, the primary objective of this meta-analysis is to comprehensively investigate potential differences in tumor characteristics, treatment strategies, and recurrence patterns between DN-SCC and IP-SCC to better understand the differences in these tumors. Herein, we review the literature on SCC and perform a meta-analysis on the existing reports comparing outcomes between DN and IP-SCC.

Materials and methods

This study is exempt from Institutional Review Board approval as it contains only de-identified data accessed through the published literature. A comprehensive literature review was performed through PubMed, OVID Medline, Cochrane, and Scopus databases using the Boolean search terms included in Appendix 1. We queried all studies published from inception through August 2020.

This meta-analysis included series that compared DN-SCC and IP-SCC treatment and recurrence outcomes to ensure internal validity. Non-English or non-human studies, case reports, reviews, meta-analyses, and books and documents were excluded. Although exclusion of non-English studies may reduce the number of patients and limit the applicability of findings, the authors were limited by their ability to only accurately review studies written in English. The included studies' references were also evaluated to ensure inclusion of all pertinent publications. All article abstracts were independently reviewed and evaluated by two separate authors (J.B. and K.G.). Study selection, data collection processes, data items, and analyses were all performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁽¹⁵⁾. Our search yielded 595 non-duplicate studies all of which were screened for eligibility (Figure 1). Two researchers (JB and EN) independently reviewed each study. We used the Newcastle-Ottawa scale for cohort studies to assess risk of bias of all non-randomized studies (Table 1)⁽¹⁶⁾. Each item on the Newcastle-Ottawa scale was given a maximum of 1 point for each of the 8 categories. Studies with scores higher than 7 were deemed high quality. Extracted data included patient demographic and clinical characteristics. Primary outcomes included local recurrence rates, regional recurrence (i.e., metastatic disease to the neck), and rates of distant metastasis. We used pooled analysis to compare baseline characteristics between DN-SCC and IP-SCC. Independent Student's t-tests (to compare means) and chi-square tests were used for continuous and categorical variables, respectively. The six outcome variables were compared between DN-SCC and IP-SCC using Review Manager version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, 2019) with a binary random-effects model to assess odds ratios (OR) as the summary measure⁽¹⁷⁾. ORs

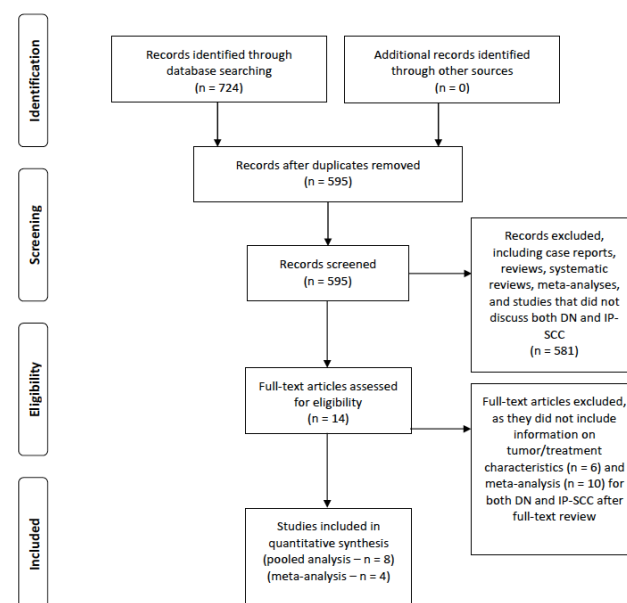


Figure 1. Flowchart of included studies.

and 95% confidence intervals (CI) were obtained and mapped on forest plots for each outcome variable, with p-values < 0.05 considered statistically significant. DN-SCC was used as the reference in all OR reporting (i.e., OR=1). Funnel plots were created to identify to examine the relationship between sample size and effect sizes for primary outcome measures between studies and to identify any outliers that might represent bias, heterogeneous study populations, or effects due to chance.

Results

Of the 595 non-duplicate studies screened and assessed for eligibility, each included study (n=8) provided data on one or more of the following: TNM classification, margin status, treatment type, local recurrence, regional recurrence, and distant metastasis^(4,7-12,14). Of these 8 studies, 4 contained information on local recurrence, regional recurrence, and distant metastasis, all of which were used in the meta-analysis^(7,8,11,12). The study selection process and reasons for study exclusions are included in Figure 1. Study characteristics, including patient demographics of all included studies are listed in Table 2. The number of synchronous (n = 129) and metachronous (n = 79) cases were reported from a total of 208 IP-SCC patients from six studies (4-9).

Pooled analysis comparing baseline and treatment characteristics between groups are shown in Table 3. Patients with DN-SCC had significantly higher rates of positive margins (p=0.005), advanced T classification (T3/T4) (p=0.002), treatment with chemotherapy (<0.001) and radiotherapy (p=0.003), whereas patients with IP-SCC were significantly more likely to present with early T classification (T0/T1/T2) (p<0.001) and receive surgical treatment (p<0.001). Outcome variables are listed in Table 4 for local recur-

Table 1. The quality of all seven non-randomized studies using the Newcastle-Ottawa Scale. This scale has a scoring system based on its three domains (i.e., selection, comparability, and outcomes). The selection, comparability, and outcomes domains contain 4, 1 and 3 variables with a corresponding maximum of 4, 1 and 3 asterisks, respectively. The higher number of asterisks indicated higher quality studies.

| Newcastle-Ottawa Scale for Cohort Studies | | | | | | | | |
|---|--|------------------------------------|---------------------------|--|--|-----------------------|--|---|
| Source | Selection | | | Comparability | | Outcomes | | |
| | Representativeness of the exposed cohort | Selection of the nonexposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of design and analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur? | |
| Li et al., 2020 ⁽⁸⁾ | * | * | * | * | * | * | * | * |
| Quan et al., 2020 ⁽¹²⁾ | * | * | * | * | * | * | * | * |
| Yasumatsu et al., 2020 ⁽¹⁰⁾ | * | * | * | * | * | * | * | * |
| Yu et al., 2017 ⁽⁹⁾ | * | * | * | * | * | * | * | * |
| Yan et al., 2017 ⁽⁴⁾ | * | * | * | * | * | * | * | * |
| Lobo et al., 2017 ⁽¹¹⁾ | * | * | * | * | * | * | * | * |
| de Almeida et al., 2015 ⁽¹⁰⁾ | * | * | * | * | * | * | * | * |
| Lavertu et al., 1989 ⁽¹⁴⁾ | * | * | * | * | * | * | * | * |

rence, regional recurrence, and distant metastasis.

Local recurrence

Local recurrence data was assessed in four studies for a total of 528 patients, including 356 and 172 reported patients with DN-SCC and IP-SCC, respectively ^(7,8,11,12). Local recurrence in DN-SCC and IP-SCC occurred in 29.7% and 30.2%, respectively, with no significant difference in recurrence rates (OR 1.27, 95% CI, 0.84-1.93; $p = 0.26$) (Figure 2).

Regional recurrence

Three studies contained information on regional recurrence for a total of 421 patients, including 272 and 149 patients with DN and IP-SCC, respectively ^(7,8,11). Regional recurrence between cohorts was noted in 13.2% and 18.1%, respectively, with no significant difference between groups (OR 1.37, 95% CI, 0.76-2.47; $p = 0.30$) (Figure 2).

Distant metastasis

Distant metastasis data was found in four of the included studies for a total of 538 patients ^(7,8,11,12). There were 366 and 172 patients with DN and IP-SCC, respectively, and distant metastasis was observed in 12.3% and 5.8%, respectively. Patients with DN-SCC were 2.6 times more likely to have distant metastasis

compared to IP-SCC patients (OR 0.39, 95% CI, 0.19-0.79; $p = 0.010$) (Figure 2).

Risk of bias within studies

The summary of risk of bias assessment for publications included in this meta-analysis based on the Newcastle-Ottawa Scale is displayed in Table 1 (16). All eight studies scored 8 out of 8, indicating high quality of the included studies in this meta-analysis.

Publication bias

A funnel plot was created for each of the three outcome variables (Figure 3). In the funnel plots, the x-axis represented effect size, in the form of OR, and the y-axis displayed standard error. Risk of bias was assessed for each outcome variable, with no individual study outside the 95% CI boundaries for all outcome variables, indicating low risk of bias.

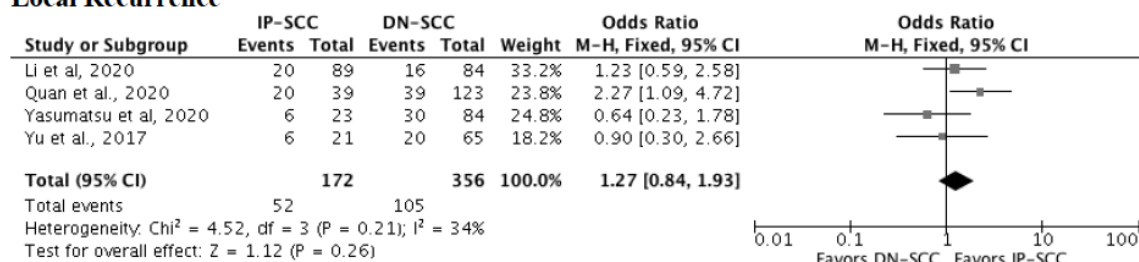
Discussion

In this review and meta-analysis, our findings demonstrate different presentation, treatment strategies and outcomes between DN-SCC and IP-SCC. Patients with IP-SCC were significantly more likely to present with early T classification, receive surgery and obtain negative margin status after surgery. Patients with DN-

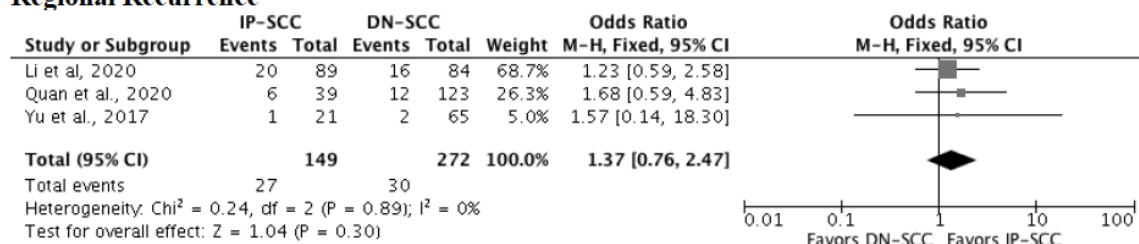
Table 2. Summary of clinical characteristics, including patient demographics, for all included studies. SNSCC = sinonasal squamous cell carcinoma; DN-SCC = de novo sinonasal squamous cell carcinoma; IP-SCC = inverted papilloma-transformed sinonasal squamous cell carcinoma; SD = standard deviation.

| Study | Study Years | Sample Size | SNSCC type (# of patients) | Gender (men), No. (%) | Mean age \pm SD, years | Positive Smoking History, No. (%) | Early T classification (T1s/T1/T2), No. (%) | Advanced T classification (T3/T4), No. (%) | Negative Margin Status, No. (%) | Chemotherapy, No. (%) | Radiation, No. (%) | Surgery, No. (%) | N classification, % with NO |
|---|-------------|-------------|----------------------------|-----------------------|--------------------------|-----------------------------------|---|--|---------------------------------|-----------------------|--------------------|------------------|-----------------------------|
| Li et al., 2020 ⁽⁸⁾ | 2005-2018 | 173 | DN-SCC† (n = 84) | 62 (69.7%) | 53.0 \pm 11.6 | 36 (42.9%) | 9 (10.7%) | 75 (89.2%) | 46 (64.8%) | -- | 80 (95.2%) | 84 (100%) | 95.2% |
| | | | IP-SCC§ (n = 89) | 66 (78.6%) | 55.7 \pm 13.1 | 26 (29.2%) | 23 (25.9%) | 66 (74.2%) | 54 (60.7%) | -- | 73 (82%) | 89 (100%) | 98.9% |
| Quan et al., 2020 ⁽¹²⁾ | 2010-2017 | 162 | DN-SCC (n = 123) | 90 (73.2%) | 57.2 \pm 12.5 | 45 (36.9%) | 12 (9.8%) | 108 (87.8%) | -- | 94 (73.4%) | 123 (100%) | 96 (78%) | 82.9% |
| | | | IP-SCC (n = 39) | 25 (64.1%) | 58.2 \pm 12.5 | 13 (33.3%) | 2 (5.1%) | 36 (92.3%) | -- | 14 (35.9%) | 39 (100%) | 37 (94.9%) | 92.3% |
| Yasumatsu et al., 2020 ⁽¹⁰⁾ | 1990-2016 | 117 | DN-SCC (n = 94) | 67 (71.3%) | 63.8 | -- | 13 (13.8%) | 81 (86.2%) | 40 (42.6%) | -- | 94 (100%) | 94 (100%) | 91% |
| | | | IP-SCC (n = 23) | 14 (60.9%) | 60.5 | -- | 5 (21.7%) | 18 (78.3%) | 8 (34.8%) | -- | 23 (100%) | 23 (100%) | 90% |
| Yu et al., 2017 ⁽⁹⁾ | 1990-2014 | 117 | DN-SCC (n = 65) | 48 (73.8%) | 58.8 \pm 12.8 | -- | 12 (18.5) | 53 (81.5%) | -- | -- | -- | 37 (56.9%) | 13.8% |
| | | | IP-SCC (n = 21) | 17 (80.9%) | 60.9 \pm 10.3 | -- | 9 (42.9%) | 12 (57.1%) | -- | -- | -- | 19 (90.5%) | 0% |
| Yan et al., 2017 ⁽⁴⁾ | 2000-2015 | 66 | DN-SCC (n = 28) | 15 (53.6%) | 62.5 \pm 13.2 | 20 (71%) | 11 (39.3%) | 17 (60.7%) | 28 (100%) | -- | 25 (89.2%) | 28 (100%) | 100% |
| | | | IP-SCC (n = 38) | 25 (65.8%) | 59.9 \pm 11.5 | 24 (63%) | 20 (52.6%) | 18 (47.4%) | 38 (100%) | -- | 24 (63.2%) | 38 (100%) | 100% |
| Lobo et al., 2017 ⁽¹¹⁾ | 1995-2015 | 117 | DN-SCC (n = 88) | 56 (63.6%) | 63 | 56 (64%) | 18 (20.5%) | 60 (68.2%) | -- | 22 (25%) | 60 (68.2%) | 74 (83.1%) | 64% |
| | | | IP-SCC (n = 29) | 19 (65.5%) | 64 | 16 (55%) | 7 (24.1%) | 15 (51.7%) | -- | 6 (28.6%) | 16 (55.2%) | 28 (96.6%) | 69% |
| de Almeida et al., 2015 ⁽¹⁰⁾ | 2000-2012 | 34 | DN-SCC (n = 21) | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| | | | IP-SCC (n = 13) | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Lavertu et al., 1989 ⁽¹⁴⁾ | 1977-1986 | 54 | DN-SCC (n = 43) | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| | | | IP-SCC (n = 11) | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |

Local Recurrence



Regional Recurrence



Distant Metastasis

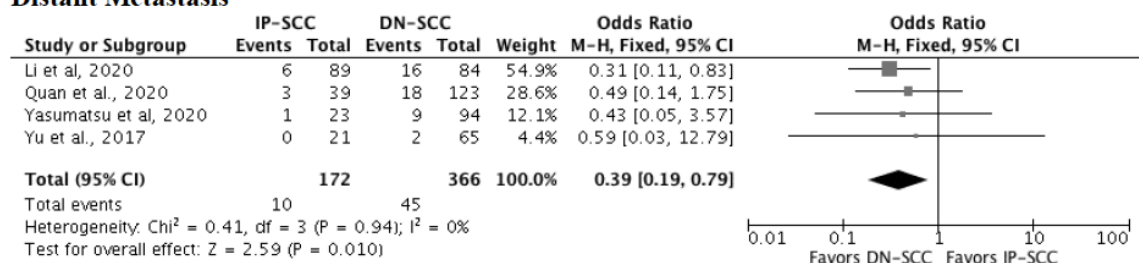


Figure 2. Forest plots of local recurrence, regional recurrence and distant metastasis (top to bottom). Forest plots demonstrate OR's of 1.27 ($p = 0.26$), 1.37 ($p = 0.30$), 0.39 ($p = 0.010$) for local recurrence rate, regional recurrence rate, and rates of distant metastasis respectively. Lines signify 95% CI and boxes signify point estimates and size representation of each study. Box size correlates with each study's size effect. IP-SCC = Inverted papilloma-transformed sinonasal squamous cell carcinoma; DN-SCC = de novo sinonasal squamous cell carcinoma; CI = confidence interval; M-H = Mantel-Haetzel effect; OR = odds ratio.

SCC, conversely, were significantly more likely to present with advanced T classification and receive radiation and chemotherapy. We also report significantly higher rates of distant metastasis in DN-SCC compared to IP-SCC. Specifically, our ORs demonstrate that DN-SCC was 2.6 times more likely to present with distant metastasis than IP-SCC. Furthermore, we report no significant difference in local and regional recurrence rates between aggregate data for DN-SCC and IP-SCC cases. While it is still unclear whether tumor biology and behavior differs between tumors, it is important to understand noted differences in clinicopathologic characteristics, treatment strategies, recurrence rates and survival outcomes when treating these cohorts.

To our knowledge, this is the first meta-analysis to compare recurrence rates between DN-SCC and IP-SCC. Previously, we have reported survival and recurrence outcomes of both IP-SCC and DN-SCC alone as systematic reviews. The systematic review on DN-SCC included 43 studies and reported aggregate survival and recurrence information⁽⁶⁾. The systematic review on

IP-SCC included 28 studies with reporting of similar outcomes measures⁽⁵⁾. However, most studies in these reviews did not include both DN-SCC and IP-SCC and did not directly compare outcomes differences between the two tumors through a meta-analysis. A recent meta-analysis by Lee et al. aimed to address this problem by directly comparing survival outcomes between IP-SCC and DN-SCC⁽¹³⁾. However, they did not report information on differences in presentation, treatment types, and recurrence patterns. Therefore, this meta-analysis sought to identify studies that directly compared these outcomes that had not been previously investigated to better understand any differences between these tumors.

While IP-SCC commonly arises from IP, treatment strategies for IP-SCC parallel that of DN-SCC given its previously demonstrated more aggressive nature, with surgery and possible adjuvant radiation as a mainstay of treatment in primary disease^(10,18–20). Given the similar treatment strategies for IP-SCC and DN-SCC, questions remain on whether these tumors are distinct entities.

Table 3. Comparison of baseline characteristics and treatment strategies between cohorts. DN- SCC = de novo squamous cell carcinoma; IP-SCC = inverted papilloma-transformed sinonasal squamous cell carcinoma.

| | DN-SCC, No. (%) | IP-SCC, No. (%) | P-value | 95% Confidence Interval | |
|----------------------------|-----------------|-----------------|-------------------|-------------------------|-------------|
| | | | | Lower Bound | Upper Bound |
| Margin Status (% negative) | 114/211 (54.0%) | 100/145 (68.9%) | 0.0049* | 4.58% | 24.59% |
| Gender (% male) | 338/487 (69.4%) | 166/234 (70.9%) | 0.67 | -5.74% | 8.43% |
| Mean age | 59.7 | 59.9 | 0.92 | | |
| History of Smoking | 157/328 (47.9%) | 79/191 (41.4%) | 0.22 | -3.37% | 14.15% |
| Early T classification | 75/487 (15.4%) | 66/235 (28.2%) | <0.001* | 6.40% | 19.56% |
| Advanced T classification | 394/487 (80.9%) | 165/234 (70.5%) | 0.0018* | 3.77% | 17.33% |
| Chemotherapy | 116/211 (54.9%) | 20/68 (29.4%) | <0.001* | 12.07% | 37.11% |
| Radiotherapy | 382/422 (90.5%) | 175/213 (82.2%) | 0.003* | 2.81% | 14.56% |
| Surgery | 418/487 (85.8%) | 229/234 (97.9%) | <0.001* | 8.08% | 15.62% |

Table 4. Summary of local recurrence, regional recurrence, and distant metastasis for all included studies in the meta analysis. SNSCC = sinonasal squamous cell carcinoma; DN-SCC = de novo sinonasal squamous cell carcinoma; IP-SCC = inverted papilloma-transformed sinonasal squamous cell carcinoma.

| Study | Sinonasal SNSCC Type | Local Recurrence, No. (%) | Regional Recurrence, No. (%) | Distant Metastasis, No. (%) |
|--|----------------------|---------------------------|------------------------------|-----------------------------|
| Li et al., 2020 ⁽⁸⁾ | DN-SCC | 16 (19.0%) | 9 (10.7%) | 16 (19.0%) |
| | IP-SCC | 20 (22.5%) | 12 (13.5%) | 6 (6.7%) |
| Quan et al., 2020 ⁽¹²⁾ | DN-SCC | 39 (31.7%) | 12 (9.8%) | 18 (14.6%) |
| | IP-SCC | 20 (51.3%) | 6 (15.4%) | 3 (7.7%) |
| Yasumatsu et al., 2020 ⁽¹⁰⁾ | DN-SCC | 20 (30.7%) | 2 (3.1%) | 2 (3.1%) |
| | IP-SCC | 6 (28.6%) | 1 (4.8%) | 0 (0%) |
| Yu et al., 2017 ⁽⁹⁾ | DN-SCC | 30 (32%) | -- | 9 (9%) |
| | IP-SCC | 6 (26%) | -- | 1 (4%) |

This question has persisted for decades, as Lavertu et al. reported survival differences between DN-SCC and IP-SCC as early as in 1989 ⁽¹⁴⁾. Since then, several reports have provided survival information on both tumors. One large single-institutional study of 113 patients with DN-SCC by Lee et al. reported a 5-year OS of 59.5% ⁽²¹⁾. A separate study by Li et al. reported a 5-year OS of 63% with IP-SCC. Recently, Lee et al.'s meta-analysis demonstrating significantly different survival outcomes between IP-SCC and DN-SCC provided evidence these tumors are in fact distinct ⁽¹³⁾. The results from our meta-analysis now provide further information on differences between these tumors. However, it is unclear whether the different rates of distant metastasis and OS suggest that these malignancies should be treated as distinct entities. While DN-SCC presented at more advanced stage disease, DN-SCC and IP-SCC appear to have similar locoregional recurrence rates to the efficacy of current surgical approaches as well as the application of chemoradiotherapy for patients with positive margins. Possible explanations to this finding include

consistent application of surgical oncologic principles to both tumor subtypes, or perhaps a more aggressive treatment regimen for DN-SCC compared to IP-SCC, including more common use of postoperative chemotherapy and radiotherapy as also demonstrated by this study.

As shown in this study, patients with DN-SCC presented with more advanced TNM stage and had significantly higher rates of positive surgical margins compared to IP-SCC. These findings offer one explanation to higher rates of distant metastasis in DN-SCC patients reported in this study and worse OS reported by Lee et al. ⁽¹³⁾. The higher rates of positive margins may also explain why patients with DN-SCC were significantly more likely to receive multimodal treatment (e.g., chemotherapy, radiation therapy), often in the neoadjuvant and/or adjuvant setting, in addition to upfront definitive treatment (e.g., surgery).

There also may be difference in etiology these two entities

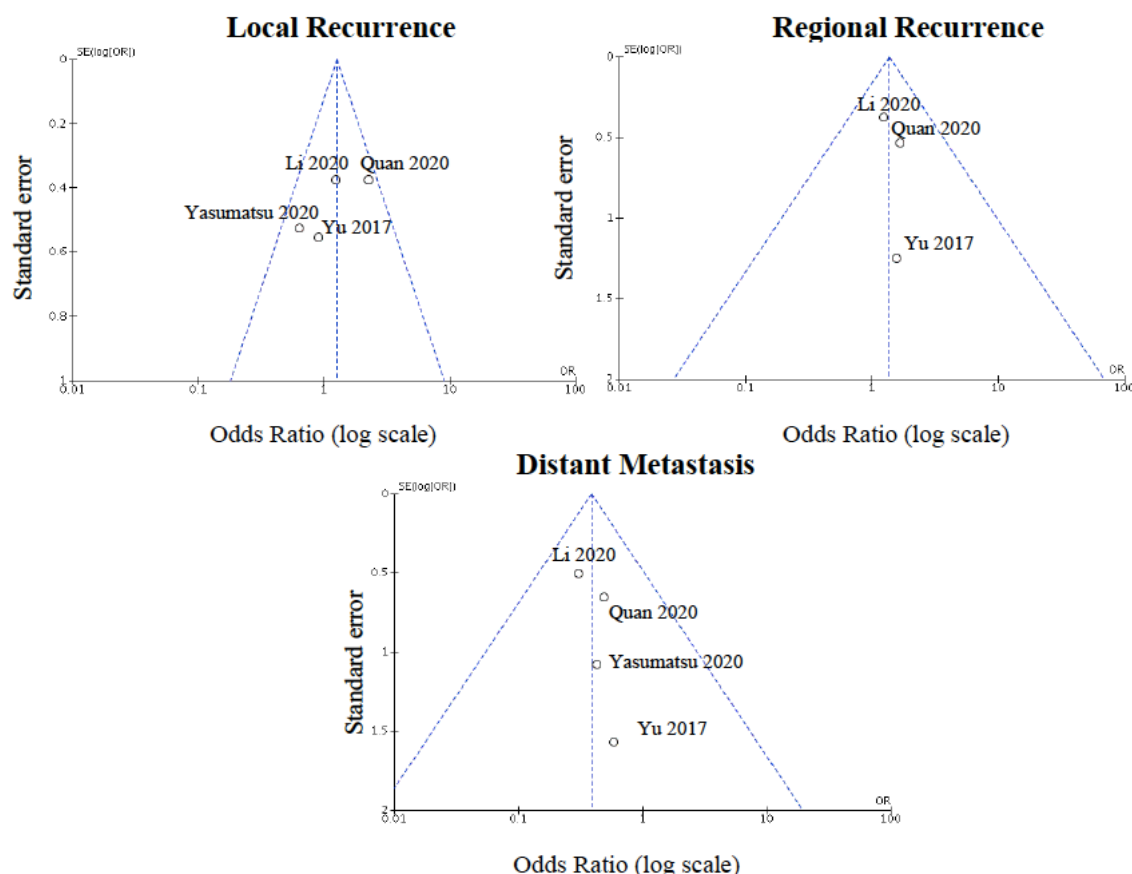


Figure 3. Funnel plots of the 3 outcome variables for study bias evaluation. The x-axis represents effect size, in the form of OR, and the y-axis displays standard error. Dotted lines on the left and right represent 95% confidence interval with a fixed population treatment effect. Any study beyond the boundaries may represent systematic bias. There were no studies outside the 95% confidence intervals among all 3 outcome variables.

that further elucidate survival differences between DN-SCC and IP-SCC. Traditional risk factors for DN-SCC include smoking and occupational carcinogen exposures such as glues, leather dust chrome, nickel, arsenic, and formaldehyde^(22–28). Smoking is not only a risk factor for DN-SCC but also can be coexistent with other comorbidities that may worsen OS in this subset of patients^(29,30). Recent data also suggests the role of high-risk human papilloma virus (HPV) as a causative agent in sinonasal SCC, as prior studies suggest its prevalence in about 30% of sinonasal SCC^(19,31–41). Low-risk HPV is also a known risk factor for IP, which can subsequently undergo malignant transformation to IP-SCC^(42,43). Recent studies have reported low-risk HPV in IP-SCC, suggesting there may be higher prevalence of low-risk HPV in IP-SCC that could provide an explanation to the improved survival and recurrence rates compared to DN-SCC. Furthermore, given the association of HPV with IP, it is feasible that HPV positivity may be higher in patients with IP-SCC compared to DN-SCC, as previously noted by Yamashita et al.⁽³⁹⁾. Recent literature has suggested that HPV may play an etiologic role in some sinonasal SCC and therefore explain improved survival as with other viral-induced malignancy, though this has not been definitively

proven or widely accepted⁽³⁸⁾.

Other explanations of differences between DN-SCC and IP-SCC include molecular differences that may impact clinical behavior and outcomes. For instance, a recent study reported a higher prevalence of EGFR mutations in IP-SCC that are less frequently observed in DN-SCC⁽⁴⁴⁾. Additionally, a recent study demonstrated progressive upregulation of several genes unique to malignant transformation of IP-SCC that may impact different outcomes compared to DN-SCC^(45,46). Other possible differences include p16 overexpression, low p53 reactivity, and high Ki-67 labeling index in IP-SCC⁽⁴⁷⁾. These mutations appear to be different than traditional molecular biomarkers of DN-SCC, such as TP53^(25,47,48). Other explanations for the differences in baseline characteristics include differences in the years of each publication, as DN-SCC may be diagnosed at a later stage prior to wide adoption of nasal endoscopy. Conversely, the majority of data on IP-SCC may be reported by rhinology practices, where these tumors tend to be detected at earlier, perhaps even clinically silent presentations, as opposed to head and neck centers where patients tend to present with more symptomatic disease.

Nonetheless, our results highlight the importance of providers recognizing these differences in presentation and behavior, which may affect rates of OS and distant metastasis.

The current study has several limitations. Our analysis included cases of synchronous and metachronous IP-SCC, as prior studies included both. While survival and recurrence rates may differ between IP-SCC types, prior studies have grouped these types together on analysis, thus preventing comparison of outcomes between synchronous and metachronous IP-SCC tumors. Although it has been previously hypothesized that metachronous IP-SCC tumors may portend better prognosis due to early detection and tumor surveillance, at least a majority of the included IP-SCC tumors were synchronous and still resulted in improved overall survival compared to DN-SCC. Our study also was unable to report on mean recurrence time, as prior studies did not report this information. Our study was unable to assess the impact of sinonasal tumor location on recurrence rates as they were not adequately reported in prior studies. Our analysis was also not able to distinguish the impact of different surgical approaches (e.g., endoscopic versus open), which may affect survival and recurrence rates and has been reported to be a factor for IP outcomes^(49–51). Additionally, there were significant differences in baseline characteristics in this meta-analysis, which could contribute to outcome differences between DN-SCC and IP-SCC. Additionally, there is potential for study and reporting bias, as there may be a propensity for studies with positive outcomes to be published. However, the existing interval validity among all

included studies should control for these confounders. Finally, the paucity of studies comparing DN-SCC and IP-SCC overall may limit the findings in our study, and in this particular study, prevent to ability to perform matched comparisons. Future systematic reviews may provide additional information about survival outcomes in these cohorts, since more studies of DN-SCC and IP-SCC would be included.

Conclusions

Our review of the literature demonstrates that DN-SCC is a more aggressive tumor than IP-SCC, as patients with DN-SCC were more likely to present with advanced TNM classification and have positive margins. These results will aid providers in understanding the different recurrence patterns between DN-SCC and IP-SCC when counseling and treating both groups of patients.

Authorship contribution

Conception and design: ECK. Acquisition of data: JLB, KG. Analysis and interpretation of data: JLB, KG, CCLT, ECK. Drafting of the manuscript: JLB, KG, ECK. Critical revision of the manuscript: CCLT, NDA, JNP, ECK. All authors approved the final version of the manuscript.

Conflict of interest

None.

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SUPPLEMENTARY MATERIAL

Appendix 1. Complete list of included search terms for this meta-analysis.

Search Terms

- "de novo" OR inverted AND papilloma OR inverting AND papilloma
- squamous AND cell AND carcinoma AND of AND head AND neck OR carcinoma, AND squamous AND cell
- sinonasal OR sinonasal OR nasal AND cavity OR nasal AND sinuses OR paranasal AND sinuses
- "Sinonasal tumors" OR "sinonasal tumor" OR "sinus tumor" OR "Sinonasal SCC" OR snscc OR "Sinonasal Squamous Cell Carcinoma" OR paranasal AND sinus AND neoplasms
- "de novo scc" OR ip-scc
- recurrence OR relapse OR recrudescence OR neoplasm AND recurrence
- local OR survival OR survival OR disease free AND survival OR survival AND analysis OR survival AND rate OR mortality OR morbidity OR prognosis OR treatment AND outcome.