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Prognostic Factors and Outcomes of De Novo Sinonasal Squamous Cell Carcinoma: A Systematic Review and Meta-analysis

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Abstract

Objective. To review overall survival (OS), recurrence patterns, and prognostic factors of de novo sinonasal squamous cell carcinoma (DN-SCC).

Data Sources. PubMed, Scopus, OVID Medline, and Cochrane databases from 2006 to December 23, 2020.

Review Methods. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Articles were required to report either recurrence patterns or survival outcomes of adults with DN-SCC. Case reports, books, reviews, meta-analyses, and database studies were all excluded.

Results. Forty-one studies reported on survival or recurrence outcomes. The aggregate 5-year OS was 54.5% (range, 18%-75%) from 35 studies (n = 1903). Patients undergoing open surgery were more likely to receive radiation therapy and present at an advanced stage compared to those receiving endoscopic surgery (all $P < .001$). Advanced T stage, presence of cervical nodal metastases, maxillary sinus primary site, and negative human papillomavirus (HPV) status were all correlated with significantly worse 5-year OS. Direct meta-analysis of 8 studies demonstrated patients with surgery were more likely to be alive at 5 years compared to those who did not receive surgery (odds ratio, 2.26; 95% CI, 1.48-3.47; $P < .001$). Recurrence was reported in 628 of 1471 patients from 26 studies (42.7%) with an aggregate 5-year locoregional control rate of 67.1% (range, 50.4%-93.3%).

Conclusion. This systematic review and meta-analysis suggests that the 5-year OS rate for DN-SCC may approach 54.5% and recurrence rate approaches 42.7%. In addition, various tumor characteristics including advanced T stage, positive nodal status, maxillary sinus origin, and negative HPV status are all associated with decreased survival.

Keywords

sinonasal cancer, sinuses, endoscopic surgery, open surgery

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Sinonasal malignancies represent a rare subset of head and neck cancers, with an incidence of 0.83 per 100,000 people.[1] While sinonasal tumors are rare, sinonasal squamous cell carcinoma (SNSCC) is the most common primary sinonasal malignant tumor, accounting for nearly 42% of cases.[1,2] While the incidence of SNSCC appears to be decreasing, 5-year overall survival (OS) rates have remained steady around 50%.[1-3] SNSCC develops from mucosal sites throughout the nasal cavity and paranasal sinuses, with the nasal cavity as the most common site of origin, followed by the maxillary sinus.[1] Squamous cell carcinoma (SCC) of the nasal cavity typically presents with symptoms earlier during the disease course, including epistaxis, pain, and nasal obstruction, while those originating in the paranasal sinuses, particularly the very large maxillary sinuses, tend to present with less overt symptoms and, therefore, at advanced stage.[2,4] Prior reports have identified age, advanced T and N stage, smoking, negative human papillomavirus (HPV) status, poor performance status, and African American race as independent predictors of worse OS, defined as the length of time patients are still alive from the start of treatment, in SNSCC.[3,5-7] While SNSCC has previously been regarded as a single clinical entity, recent studies have investigated de novo SCC (DN-SCC) and inverted papilloma-transformed SCC (IP-SCC) survival and recurrence patterns separately.[8-11] As such, DN-SCC is one subset of SNSCC and is defined as any malignancy arising from the sinonasal cavity or paranasal sinuses that is histologically confirmed as squamous cell

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carcinoma without any trace of papillomatous epithelium in patients with no history of Schneiderian papillomas (exophytic, inverted, and oncocytic).[12,13] Over the past 15 years, DN-SCC has been extensively studied through individual reports. However, there remains a paucity of systematic reviews or meta-analyses investigating the effect of demographic and clinical characteristics on long-term survival and recurrence patterns. Previous reports have investigated the impact of many clinical factors (eg, surgical approach, HPV status, tumor stage, tumor site, nodal status, and margin status) on survival.[7,8,14-18] However, due to the rarity of DN-SCC, these individual studies are limited by their small sample sizes in their ability to correlate prognostic factors of these tumors with survival rates. Therefore, the aim of this study is to comprehensively review the literature to provide current survival and recurrence data on patients with DN-SCC.

Methods

Institutional review board approval was deferred as this study used deidentified data from prior published studies. No review protocol was registered for this study. The study protocol used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[19] A priori, the researchers sought to better understand the survival and recurrence patterns of DN-SCC, along with any factors predictive of worse outcomes. The Population, Intervention, Comparator, and Outcome, and Study Design (PICOS) was used for this review. The population included individuals 18 years of age and older with DN-SCC as their primary etiology. Interventions were all treatments (eg, surgery [resection and/or debulking], no surgery, radiation [RT], surgery + RT, chemotherapy [CT], and CT + RT), and comparators included differences in outcomes by treatment and clinical characteristics (eg, T classification, tumor grade, and HPV status). Primary outcomes included overall survival data as well as recurrence patterns (local, regional, or distant).

Articles including other sinonasal tumors were permitted if DN-SCC demographics, clinical characteristics, and outcomes were separately reported. Articles were required to report either recurrence patterns or survival outcomes to fit inclusion criteria. Articles were restricted to years 2006 to 2020, as a prior review on DN-SCC published in 2007 investigated SCC recurrence before 2006, which roughly also corresponds to the advent of advanced endoscopic skull base surgical techniques for tumor resection.[20] All studies that assessed recurrence outcomes were included in this review, as the researchers were interested in overall recurrence rates. Studies that assessed survival outcomes at less than 5 years and lacked information on recurrence rates were excluded since the researchers were only interested in survival rates at 5 years and beyond. In studies reporting short-term survival (ie, <5 years) and recurrence rates, only recurrence rates were extracted. Studies with heterogeneous sinonasal tumor populations that did not include patient demographics or at least 1 relevant clinical characteristic, such as T stage, nodal status, or tumor grade were excluded, as they did not provide clinical utility. Case reports, books, reviews, meta-analyses, database studies, and unpublished and abstract-only articles were all excluded. This review excluded prior reviews and meta-analyses, as it only investigated primary literature (ie, original articles). We restricted our search to English-language and human subject studies. Individual study reference lists were screened for any studies missed in the literature search. All corresponding authors of studies reporting survival or recurrence outcomes were contacted to request deidentified data.

A university librarian (L.S.M.) queried 4 databases (OVID Medline, PubMed, Cochrane, and Scopus) from January 1, 2006, to November 1, 2020. The Boolean search term used for the PubMed database is listed in Supplemental Figure S1 (in the online version of the article). Three researchers (J.L.B., A.R., E.S.N.) independently screened all titles/abstracts and full-text reviews after removal of duplicates. Consensus was reached on any disagreements through further discussion. An overview of the selection process is depicted in **Figure 1**.[19] Three researchers (J.L.B., A.R., E.S.N.) used Covidence, a data extraction tool available for systematic reviews, to extract all data from each included trial. Any disagreements were resolved after discussion between the researchers. Three researchers (J.L.B., A.R., E.S.N.) independently reviewed each study. We used Methodological Index for Non-Randomized Studies (MINORS) criteria to assess risk of bias of all nonrandomized studies (see Supplemental Table S1 in the online version of the article).[21] Each item on the MINORS criteria was given a maximum of 2 points, with 0 if not reported, 1 if reported but inadequate, and 2 if reported and adequate. The maximum scores for noncomparative studies and comparative studies were 16 and 24, respectively. For noncomparative studies, a score of 12 to 16 was considered low risk of bias, whereas a score of <12 was considered high risk. Similarly, for comparative studies, scores of 20 to 24 were considered low risk of bias, and scores <18 were considered high risk of bias. Meta-analyses were conducted when 5 or more independent studies reported survival or recurrence information on patients with DN-SCC reporting on the same variables (eg, surgery vs no surgery, radiation vs chemoradiation).

We calculated pooled survival and recurrence data through weighted averages from all reporting studies. We used χ^2 tests to compare pooled data between various interventions (eg, surgery vs surgery + radiation) and clinical characteristics (eg, early vs advanced stage). We used Review Manager version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, 2019) for the meta-analysis. We used both a binary fixed-effects model with low heterogeneity (I^2 <50%). Review Manager provided odds ratios (ORs) as the summary measure, and the ORs and 95% CIs were then placed on forest plots.[22] Review Manager provided funnel plots for each outcome to provide risk of bias for each outcome and to depict the relationship between study size and effect size (**Figure 2**). P values <.05 were considered statistically significant.

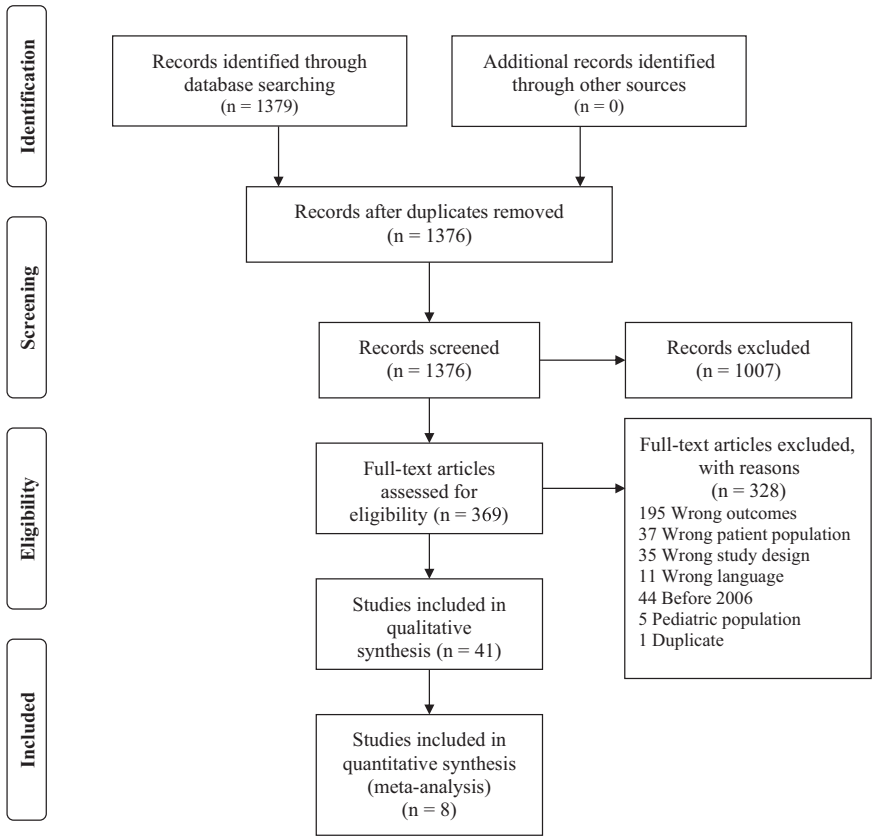

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

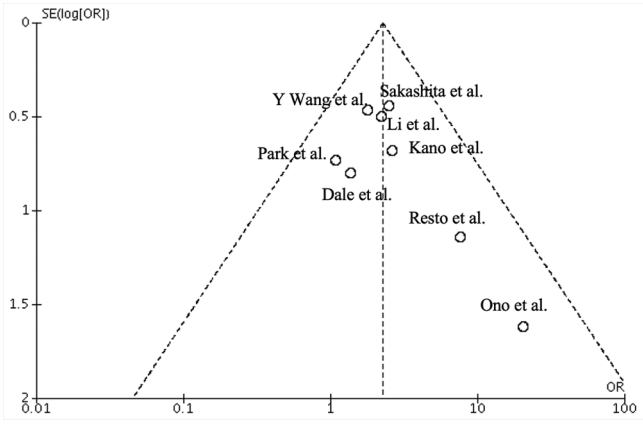

Figure 2. Funnel plot of studies to assess for study bias evaluation.

Results

Summary of Demographics, Clinical Characteristics, and Interventions

A total of 41 studies, all retrospective in design, were identified for this review. There were no randomized clinical trials or prospective studies identified. A total of 2191 patients with DN-SCC with information on survival and/or recurrence rates were identified from the 41 studies. Median age was reported in 33 studies (mean, 61.3 years; range, 53-68 years). Twenty-two studies reported information on follow-up data, with an aggregate median time to follow-up of 47.4 months (range, 18-102 months). Overall, 1355 of 2191 (61.8%) patients received RT, and 951 of 2191 (43.4%) patients received CT. Overall, 1406 of 2191 (64.2%) patients received surgery. Of the 38 studies that included surgical patients, 20 provided information on open vs endoscopic surgical approach. Of these 20 studies (n = 824) differentiating between open and endoscopic approach, 613 of 824 (74.4%) were treated with an open approach, and 211 of 824 (25.6%) were treated endoscopically. This study did not include individual data as the study members did not receive individual participant data from the included studies. Detailed information on patient demographics by individual study and overall is listed in **Table 1** and **Table 2**, respectively.

MINORS Criteria Scores

All 41 studies were nonrandomized, retrospective reviews. MINORS scores were averaged for both noncomparative (n = 28) and comparative (n = 13) studies. Among the 28 noncomparative studies, the average MINORS score was 12 (range, 10-14). The average MINORS score of the remaining 13 comparative studies was 19.8 (range, 18-24). MINORS scores for individual studies are listed in Supplemental Table 1 (in the online version of the article).

Survival Data

Treatment type. All 44 studies included information on survival data, with 35 (n = 1903) reporting on 5-year

Table 1. Baseline Characteristics of the 41 Studies Included.

First author	Study design	MINORS criteria score	No. of patients with DN-SCC	Outcomes	Male/female, No. (%)	Median age, y	Median follow-up, mo	Negative margins, No. (%)	Negative HPV status, No. (%)	Neck dissection, No. (%)	Orbital exenteration, No. (%)	T classification, No. (%)		N classification, No. (%) of patients with N0	Tumor grade, No. (%)			Treatment, No. (%)			
																		Surgery			
												T1/T2	T3/T4		Well differentiated	Moderately differentiated	Poorly differentiated	Open	Endoscopic	Radiation	Chemotherapy
Arnold[23]	Retrospective	18	38	5-year OS; 10-year OS	28 (73.7)/10 (26.3)	61	—	—	—	—	—	20 (52.6)	18 (47.4)	—	—	—	—	16 (42.1)	6 (15.8)	16 (42.1)	3 (8.3)
Brown[25]	Case-control	18	18	5-year OS; 5-year RR	10 (55.6)/8 (44.4)	62	102	8 (44.4)	—	13 (72.2)	11 (61.1)	2 (11.1)	16 (88.9)	—	—	—	—	18 (100)		15 (83.3)	
Castelnau-Marchand[26]	Retrospective	20	104	5-year OS; 5-year RR; 5-year LRC	62 (59.6)/42 (40.4)	64	54	—	—	37 (35.6)	7 (6.7)	17 (16.3)	87 (83.7)	—	—	—	—	75 (72.1)		61 (58.7)	46 (44.2)
Choi[27]	Retrospective	12	17	5-year OS	13 (76.5)/4 (23.5)	65	—	—	—	—	1 (5.9)	0 (0)	17 (100)	—	—	—	—	12 (11.8)	0 (0)	17 (100)	17 (100)
Chowdhury[14]	Case-control	18	26	5-year OS; 5-year RR	19 (70.4)/7 (26.9)	66	—	—	10 (38.5)	—	—	5 (23.8)	21 (80.8)	—	—	—	—	26 (100)		—	—
Cohen[7]	Retrospective	12	47	3-year OS; 3-year RR; 3-year LRC; 5-year OS	28 (59.6)/19 (40.4)	—	—	30 (69.8)	25 (53.2)	—	—	15 (32)	32 (68)	36 (77)	—	—	—	43 (91)		16 (38)	11 (26)
Dale[29]	Retrospective	12	30	3-year OS; 5-year OS	20 (66.7)/10 (33.3)	66	48	—	2 (6.7)	0 (0)	0 (0)	21 (70)	9 (30)	29 (96.7)	—	—	—	15 (50)		15 (50)	9 (30)
de Almeida[8]	Case-control	18	21	5-year OS; 5-year LRC	—	—	—	—	—	—	—	—	—	—	—	—	—	0 (0)	21 (100)	—	—
Duru Birgi[30]	Retrospective	14	43	5-year OS; 5-year LRC	25 (58.1)/18 (41.9)	67	32	6 (26.1)	—	14 (32.6)	—	12 (27.9)	31 (72.1)	40 (93)	7 (16.3)	18 (41.7)	10 (23.2)	23 (53.5)	2 (4.7)	43 (100)	6 (14.0)
Ebara[31]	Retrospective	12	27	5-year OS; 5-year RR	19 (70.4)/8 (29.6)	66	42.1	—	—	—	—	0 (0)	27 (100)	23 (85.2)	—	—	—	10 (37)		27 (100)	27 (100)
Guan[32]	Retrospective	12	59	RR	41 (69.5)/18 (30.5)	56	28	13 (56.5)	—	—	—	10 (16.9)	49 (83.0)	41 (69.4)	10 (16.9)	11 (18.6)	31 (52.5)	23 (40.0)		59 (100)	50 (85.2)
Hinerman[33]	Case-control	18	54	5-year OS	34 (63.0)/20 (37)	62	18	—	—	4 (6.9)	1 (1.9)	2 (3.7)	96.3)	45 (83.3)	—	—	—	12 (22.2)	0 (0)	54 (100)	10 (18.5)
Hirakawa[34]	Retrospective	12	58	5-year OS; 5-year LRC	51 (87.9)/7 (12.1)	60	40	48 (82.8)	—	—	25 (43.1)	3 (5.2)	55 (94.8)	46 (79.3)	25 (43.1)	12 (20.7)	3 (5.2)	58 (100)		—	43 (74.1)
Homma[15]	Retrospective	12	25	5-year OS	17 (68)/8 (32)	65	—	—	—	—	—	7 (32)	15 (68)	25 (100)	—	—	—	2 (8)	10 (40)	7 (32)	15 (60)
Homma[35]	Retrospective	12	54	5-year OS; 5-year LRC	43 (79.6)/11 (20.4)	60	—	—	—	—	—	1 (1.9)	53 (98.1)	42 (77.8)	—	—	—	0 (0)	0 (0)	54 (100)	54 (100)
Jang[16]	Retrospective	12	42	5-year OS	36 (85.7)/6 (14.3)	60	—	—	—	—	—	0 (0)	42 (100)	42 (100)	—	—	—	0 (0)	0 (0)	42 (100)	34 (9.5)
Janik[4]	Retrospective	12	47	5-year OS; 5-year RR	30 (63.8)/17 (36.2)	61	33.7	—	—	—	—	34 (72.3)	13 (27.7)	41 (87.2)	7 (14.9)	29 (61.7)	11 (23.4)	32 (68.1)		5 (8.8)	5 (8.8)
Kaneko[36]	Retrospective	12	36	5-year OS	27 (75)/9 (25)	63	30.1	—	—	—	—	3 (8.3)	33 (91.7)	33 (91.7)	—	—	—	6 (16.7)	0 (0)	36 (100)	36 (100)
Kano[17]	Retrospective	12	118	5-year OS	87 (73.7)/31 (26.3)	64	—	—	—	—	—	0 (0)	118 (100)	95 (80.5)	—	—	—	64 (54.2)	0 (0)	22 (19)	19 (16)
Kermer[37]	Retrospective	12	36	5-year OS; 5-year RR	—	63	—	28 (77.8)	—	5 (13.9)	—	5 (13.9)	31 (86.1)	31 (86.1)	—	—	—	36 (100)	0 (0)	—	—
Kim[38]	Retrospective	20	30	5-year OS	18 (60)/12 (40)	57	42	—	—	—	—	15 (50)	15 (50)	27 (90)	5 (7.8)	17 (56.7)	6 (20)	30 (100)		30 (100)	15 (100)
Kondo[39]	Retrospective	12	26	5-year OS	18 (69.2)/8 (30.8)	64	—	—	—	—	—	4 (15.4)	22 (84.6)	18 (69.2)	—	—	—	22 (84.6)	0 (0)	24 (92.3)	24 (92.3)
Kreeft[40]	Retrospective	12	25	5-year OS; 5-year LRC	—	—	—	9 (36)	—	—	1 (1.4)	—	—	—	—	—	—	25 (100)	0 (100)	—	—
Li[18]	Retrospective	12	93	5-year OS	63 (67.7)/30 (32.3)	56	—	—	—	10 (10.8)	7 (7.5)	0 (0)	93 (100)	76 (81.7)	0	37 (39.8)	41 (44.1)	34 (36.6)	38 (40.9)	93 (100)	67 (72.0)
Li[10]	Case-control	20	84	5-year OS; 5-year RR	62 (73.8)/22 (26.2)	53	—	—	—	17 (20.2)	5 (6.0)	9 (10.7)	75 (89.3)	80 (95.2)	—	—	—	65 (77.4)	19 (22.6)	—	—
Michel[41]	Retrospective	12	33	5-year OS; 10-year OS	27 (81.8)/6 (18.2)	—	66	18 (100)	—	0	—	15 (45.4)	18 (54.50	31 (93.9)	—	—	—	16 (48.5)	2 (6.1)	9 (27.3)	17 (51.5)
Nakamaru[42]	Retrospective	12	15	5-year OS; 5-year LRC	—	—	—	11 (73.3)	—	—	—	11 (73.3)	4 (26.7)	—	—	—	—	0 (0)	15 (100)	7 (46.7)	2 (13.3)
Ock[43]	Retrospective	12	21	3-year OS; 5-year OS	15 (71.4)/6 (28.6)	57	83.1	—	—	—	—	1 (4.8)	20 (95.2)	14 (66.7)	—	—	—	6 (28.6)		14 (66.7)	21 (100)
Ono[44]	Retrospective	20	63	5-year OS	51 (81.0)/12 (19.0)	68	—	—	—	—	—	0 (0)	63 (100)	55 (87.3)	28 (44.4)	27 (42.9)	8 (12.7)	13 (20.6)		63 (100)	63 (100)
Ono[45]	Retrospective	12	14	3-year OS; 5-year OS	11 (78.6)/3 (21.4)	60	22.5	6 (66.7)	—	—	—	0 (0)	14 (100)	13 (96.9)	—	—	—	9 (64.3)	0 (0)	5 (35.7)	5 (35.7)
Paré[46]	Retrospective	12	68	5-year OS; 5-year RR	43 (63.2)/25 (36.8)	63	68	—	—	—	—	9 (13.2)	59 (86.8)	56 (82.4)	—	—	—	68 (100)	0 (0)	58 (85.3)	59 (86.8)
Park[47]	Retrospective	20	73	5-year OS	51 (69.9)/22 (30.1)	63	23	12 (52.2)	—	11 (15.1)	—	15 (20.5)	58 (79.5)	—	—	—	—	21 (28.8)		73 (100)	51 (69.9)
Quan[11]	Case-control	20	123	5-year OS; 5-year RR; 5-year LRC	90 (73.2)/30 (26.8)	—	56	—	—	0 (0)	—	12 (9.8)	108 (87.8)	102 (82.9)	—	—	—	34 (27.6)	62 (50.4)	123 (100)	94 (76.4)
Resto[54]	Retrospective	12	33	5-year OS	—	—	43.2	—	—	—	—	—	—	—	3 (9.1)	8 (24.2)	7 (21.2)	25 (75.8)		33 (100)	—
Russo[6]	Retrospective	12	54	5-year OS; 5-year RR; 5-year LRC	27 (50)/27 (50)	56	—	—	—	—	8 (14.8)	0 (0)	54 (100)	50 (92.6)	—	—	—	37 (68.5)		54 (100)	24 (44.4)
Sakashita[48]	Retrospective	12	87	5-year OS; 5-year LRC	63 (72.4)/24 (27.6)	65	52	—	—	—	25 (28.7)	0 (0)	87 (100)	73 (83.9)	—	—	—	48 (55.2)		49 (56.3)	35 (40.2)
Santos[49]	Retrospective	12	58	5-year OS; 5-year RR	35 (60.3)/23 (39.7)	59	—	20 (60.6)	—	—	—	0 (0)	58 (100)	48 (82.8)	4 (6.9)	45 (77.6)	9 (15.5)	33 (56.9)		40 (69.0)	5 (8.6)
Toyomasu[50]	Retrospective	20	59	3-year OS; 3-year LRC; 5-year OS; 5-year LRC	45 (76.3)/17 (23.7)	60	30	—	—	—	—	4 (6.8)	49 (83.1)	55 (93.2)	—	—	—	0 (0)	0 (0)	59 (100)	0 (0)
Wang[51]	Retrospective	12	98	5-year OS	75 (76.5)/23 (23.5)	57.5	36	—	—	15 (15.3)	—	17 (17.3)	81 (82.7)	75 (76.5)	32 (32.7)	33 (33.7)	33 (33.7)	50 (51.0)	15 (15.3)	19 (19.4)	19 (19.4)
Wang[52]	Retrospective	12	140	5-year OS; 5-year RR; 5-year LRC	108 (77.1)/32 (22.9)	54	92.3	—	—	—	14 (10)	0 (0)	107 (76.4)	113 (80.7)	—	—	—	119 (85)	21 (15)	140 (100)	39 (27.9)
Yasumatsu[53]	Case-control	20	94	RR	67 (71.3)/28.7)	—	—	40 (42.6)	—	9 (9.6)	—	13 (13.8)	81 (86.2)	85 (90.4)	—	—	—	94 (100)		6 (6.4)	—

Abbreviations: DN-SCC, de novo sinonasal squamous cell carcinoma; HPV, human papillomavirus; LRC, locoregional control rate; MINORS, Methodological Index for Non-Randomized Studies; OS, overall survival; RR, recurrence rate; —, data not available.

Table 2. Number of Studies and Patients Reported by Demographic and Tumor Characteristics.

Variable	No. (%)	No. of studies reported
Sex		
Male	1459/2061 (70.8)	36
Female	602/2061 (29.2)	
T stage		
1/2	270/2055 (13.1)	38
3/4	1785/2055 (86.9)	
Human papillomavirus status		
Positive	66/103 (64.1)	3
Negative	37/103 (35.9)	
Tumor grade		
1	118/499 (23.6)	9
2	229/499 (45.9)	
3	152/499 (30.5)	
Margin status		
Positive	324/573 (56.5)	13
Negative	249/573 (43.5)	
N classification		
N0	1540/1821 (84.6)	31
N+	281/1821 (15.4)	

OS.[4,6-8,10,11,14-18,23-55] The weighted mean overall 5-year OS in this review was 54.5% (range, 18%-75%). Five-year OS data available on all patients undergoing surgery, open and endoscopic surgery, no surgery, radiation, surgery alone, surgery and RT, CT, and CT and RT are reported in **Table 3**. On pooled data analysis, 5-year OS was comparable between endoscopic and open surgical approach (69.9% vs 60.0%; 95% CI, 0.96-2.55; $P = .09$). Compared to endoscopic surgery, open surgery had significantly higher rates of receiving RT (65.2% vs 59.4%; 95% CI, 1.52-3.02; $P < .001$) and presented at more advanced (T3/T4) stage (95.6% vs 84.7%; 95% CI, 0.07-0.44; $P < .001$). Given the paucity of studies providing survival data comparing similar outcomes, our meta-analysis was limited to comparing survival data between patients receiving surgery and no surgery. Eight studies provided 5-year OS rates of both surgery and no surgery, with 5-year OS rates of 56.7% and 47.4%, respectively.[17,18,29,45,47,48,51,54] Direct meta-analysis demonstrated patients with surgery were more likely to be alive at 5 years compared to those who did not receive surgery (OR, 2.26; 95% CI, 1.48-3.47; $P < .001$), with the observed survival difference occurring in the absence of study heterogeneity ($I^2 = 0$) (**Figure 3**). **Figure 2** shows the funnel plot with a roughly asymmetrical distribution, signaling the presence of publication bias among the 8 studies included in the meta-analysis. However, all studies fall within the 95% CI, indicating a low risk of bias between the individual studies. There were no significant differences in RT (95.2% vs 89.5%; 95% CI, 0.85-6.18; $P = .09$) or CT (78.5% vs 70.0%; 95% CI, 0.62-3.94; $P = .34$) rates between surgery and no-surgery groups. On pooled data analysis, combined surgery and RT did not provide a survival benefit compared to surgery alone (58.5% vs 54.3%; 95% CI, 0.73-1.26; $P = .84$). Patients who underwent surgery and RT presented at more advanced stage than patients receiving surgery alone (96.4% vs 79.0%; 95% CI, 0.08-0.26; $P < .001$). On aggregate data analysis, there were no significant differences in 5-year OS between CT and combined CT and RT (66.7% vs 58.5%; 95% CI, 0.46-1.09 $P = .07$). The remaining treatment specific survival data are listed in **Table 3**.

Tumor characteristics. Twelve studies (n = 926) provided 5-year OS survival rates by T classification. Of these studies, the reported 5-year OS between early (n = 49) and advanced (n = 877) stage disease was 68.9% and 50.6%, respectively, with early T stage portending a significantly improved 5-year OS compared to advanced stage on pooled analysis (95% CI, 0.24-0.84; $P < .001$). In the 9 studies (n = 632) reporting negative cervical nodal status (N0, n = 516) and/or positive cervical metastases (N+, n = 116) survival data, 5-year OS rates for N0 and N+ rates were 54.8% and 44.3%, respectively, on pooled analysis (95% CI, 0.44-0.92; $P = .008$).[16-18,38,39,43,44,51,52] Of the 14 studies including information on surgical margin status, only 1 study (n = 15) provided survival data based on margin status.[42] In the individuals with positive (n = 4) and negative (n = 11) margins, reported 5-year OS rates were 37.5% and 87.5%, respectively. Two studies (n = 176) reported 5-year OS data on tumor grade.[18,51] Five-year OS rates by well-differentiated (n = 32), moderately differentiated (n = 70), and poorly differentiated (n = 74) tumor grade were 46.9%, 46.0%, and 41.2%, respectively, with no significant differences in OS between groups (95% CI, 0.50-1.86; $P = .24$). Two studies (n = 48) reported HPV-specific 5-year OS outcomes.[7,14] The 5-year OS rates for HPV negative (n = 22) and HPV-positive (n = 26) individuals were 0% and 45%, respectively (95% CI, 0.003-0.23; $P < .001$). Five-year OS rates of tumors originating from the maxillary sinus and nasal cavity plus ethmoid sinus were 45.0% and 63.1%, respectively (95% CI, 0.34-0.67; $P < .001$). This study combined nasal cavity and ethmoid sinus survival rates in concordance with prior studies reviewed in the literature. The 5-year OS rates of tumors originating from frontal and sphenoid sinuses were not assessed, as these data were not readily available from the literature.

Recurrence Data

Our search yielded 11 original studies reporting 5-year recurrence rates (RRs) and/or 3- and 5-year locoregional control rate (LRC) of DN-SCC. Pooled 5-year RR for the 2 studies (n = 96) reporting on this outcome was 20.5% (range, 7.0%-31.0%).[6,16] The pooled 3-year LRC for the 4 studies (n = 181) reporting this outcome was 48.5% (range, 0%-58.5%),[33,36,44,48] and pooled 5-year LRC for the 7 studies (n = 442) that reported this outcome was 67.1% (range, 50.4%-93.3%).[6,8,34,35,42,48,51] The 5-year LRC rates for patients undergoing surgery (n = 53), combined surgery and RT (n = 92), RT (n = 62), CT (n = 40), and combined CT and

Table 3. Pooled Overall Survival Data, Recurrence Rates, and Locoregional Control Rates for De Novo Sinonasal Squamous Cell Carcinoma by Patient/Tumor Characteristic and Intervention Type.

Variable	5-year RR, No. (%)	3-year LRC, No. (%)	5-year LRC, No. (%)	5-year OS, No. (%)
Interventions				
Surgery	—	—	53 (64.3)	468 (59.4)
Surgery alone	—	—	37 (74.9)	29 (54.3)
Open	—	—	—	138 (60.0)
Endoscopic	—	—	—	75 (69.9)
No surgery	—	—	—	89 (48.8)
Radiation (RT)	20 (20.5)	42 (51.6)	62 (64.6)	237 (51.5)
Surgery + RT	—	—	92 (65.5)	177 (58.5)
Chemotherapy (CT)	—	—	40 (93.3)	86 (66.7)
Concomitant CT/RT	—	94 (72.6)	36 (65.8)	172 (58.5)
Characteristics				
T classification				
1/2	—	—	—	34 (68.9)
3/4	—	—	—	430 (50.6)
N0	—	—	—	273 (54.8)
N+	—	—	—	51 (44.3)
Surgical margin status				
Positive	—	—	—	2 (37.5)
Negative	—	—	—	10 (87.5)
Tumor grade				
Grade 1	—	—	—	15 (46.9)
Grade 2	—	—	—	32 (46.0)
Grade 3	—	—	—	30 (41.2)
HPV status				
Positive	—	—	—	7 (45.0)
Negative	—	—	—	0 (0.0)

Abbreviations: HPV, human papillomavirus; LRC, locoregional control; OS, overall survival; RR, recurrence rate; —, data not available.

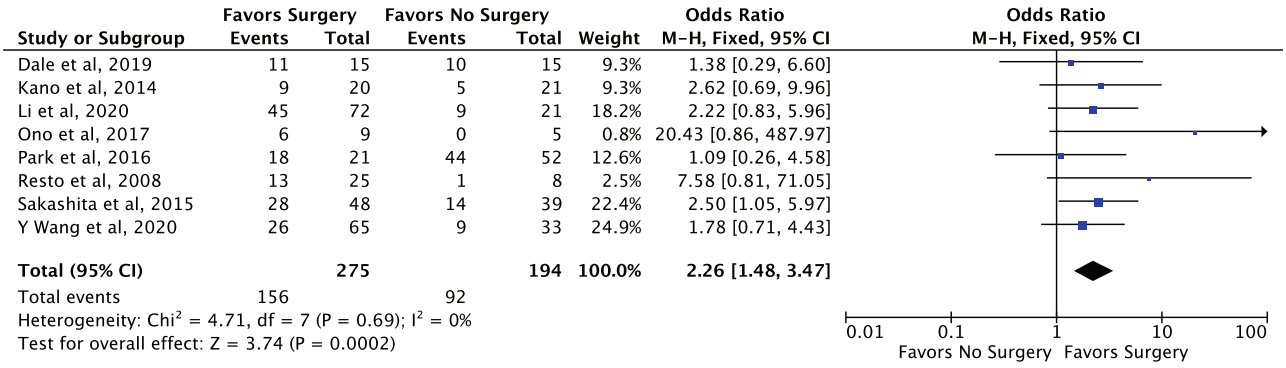

Figure 3. Meta-analysis of 5-year overall survival (OS). M-H, Mantel-Haenszel effect; OR, odds ratio.

RT (n = 36) were 64.3%, 65.5%, 64.6%, 93.3%, and 65.8%, respectively. The 3- and 5-year RR and LRC rates by treatment type are shown in **Table 3**. Overall, relapse (local, regional, and/or distant) occurred in 628 of 1471 (42.7%) patients, among the 26 studies that reported individual case data on this measure.*

*References 4, 6, 8, 10, 11, 16, 18, 25, 26, 30-33, 35, 37, 38, 40-42, 44, 46, 47, 49-51, 53.

Discussion

In this review, we identified 41 studies that investigated survival and/or recurrence rates of DN-SCC. In studies with the highest level of evidence, the pooled overall 5-year OS for DN-SCC was 54.5%, with 5-year OS varying significantly by intervention and tumor characteristics. On meta-analysis of 8 studies, surgery receipt significantly improved 5-year OS compared to no surgery. Overall, recurrence (local, regional,

and distant) occurred in 42.7% of patients. As prior individual studies on DN-SCC survival and recurrence are generally from single institutional experiences and have relatively low sample sizes for examining a rare malignancy, this systematic review should better aid physicians in understanding survival and recurrence patterns in this cohort of patients.

Compared to other sinonasal tumors, a report by Turner and Reh[2] on 5-year relative survival of sinonasal cancer demonstrated esthesioneuroblastoma (ENB) and adenoid cystic carcinoma as having relatively good prognosis, SCC and sinonasal adenocarcinoma having relatively intermediate prognosis, and sinonasal melanoma and sinonasal undifferentiated carcinoma (SNUC) having relatively poor prognosis. A study by Jethanamest et al[56] corroborated these prior findings on ENB, demonstrating a 62.1% 5-year OS rate, which is higher than our reported 54.5% 5-year OS for DN-SCC. Furthermore, Kuan et al[57] found a 5-year OS rate of 30% in patients with SNUC, much lower than our reported 5-year OS for DN-SCC. These results highlight DN-SCC as having intermediate prognosis compared to other sinonasal cancers.

SCC can occur on its own (de novo) or in conjunction with other tumors, most commonly inverted papilloma (IP).[58] While DN-SCC and IP-SCC share similar treatment strategies (radical surgery ± radiotherapy), recent reports have demonstrated different survival and recurrence patterns between these distinct tumors.[9,10,59] A recent meta-analysis, for example, reported DN-SCC as a more aggressive tumor portending worse survival outcomes than IP-SCC.[9,60] While this recent meta-analysis, which reported a similar 5-year OS rate (56%) in patients with DN-SCC, focused on survival outcomes between DN-SCC and IP-SCC, it did not assess the impact of treatment and clinical characteristics on survival.

Our study pooled survival data of patients with DN-SCC to determine the effect of this tumor's different characteristics on survival outcomes. Our aggregate data analysis showed a clear correlation between 5-year OS and T stage, as advanced stage tumors were associated with worse 5-year OS rate compared to early stage tumors (50.6% vs 68.9%). This information seems to corroborate the observations seen in previous studies investigating prognostic factors related to survival in SNSCC and sinonasal adenocarcinoma.[3,61,62] However, our review provides novel information specifically on the influence of T stage on DN-SCC survival, as the prior studies did not differentiate among SNSCC subtypes. For N stage, our pooled analysis showed N0 disease had a significantly improved OS in comparison to N+, aligning with previous reports on SNSCC and nasal cavity cancers.[63-65] In addition, although we identified a trend of decreased survival associated with higher tumor grade, this difference did not reach statistical significance. Prior studies on SNSCC and nasal cavity cancers similarly reported a correlation between higher tumor grade and worse survival, although their findings were statistically significant.[64,65] Regarding HPV status, our pooled data showed HPV-positive DN-SCC was associated with significantly improved OS than HPV-negative DN-SCC. Multiple studies have also shown this correlation between HPV-positive DN-SCC and a better prognosis.[66-69] While the mechanism of improved survival in HPV-associated DN-SCC is still unclear, the survival benefit could potentially be due to increased responsiveness to different treatment modalities or to improved apoptotic response secondary to lack of mutated p53 in HPV-associated head and neck cancers.[67,68,70-72] Finally, we evaluated the effect of tumor margin status on OS; however, only 1 study provided survival data on margin status, showing a correlation between negative tumor margins and improved OS compared to positive tumor margins. A more recent study of the National Cancer Database also correlated negative tumor margins with better OS.[73] Although DN-SCC and IP-SCC survival rates have been recently investigated in a systematic review and meta-analysis, aggregate analysis on prognostic factors affecting DN-SCC survival has yet to be thoroughly reported. The paucity of this reporting makes this review's findings on various tumor characteristics, including nodal status and HPV status, an important addition to the literature.

Prior studies have reported DN-SCC recurrence rates between 13% and 56%, with our calculated rate of 43% falling in this range.[26,74] The previously published data, however, come from single and multi-institutional studies, and to our knowledge, our review is the first study to provide composite recurrence data for DN-SCC. In contrast to other head and neck malignancies, sinonasal tumors often exhibit unique recurrence patterns as they tend to recur far beyond the 5-year disease-free period. In a recent study, the recurrence rate after a 5-year disease-free period for patients with SNSCC was 31%.[75] In our review, however, we were not able to assess long-term recurrence rates for DN-SCC or the timing of recurrence due to the lack of reporting in the included studies. The study by Arnold et al[23] was the only study to report 10-year OS rate, which was 57%. With the exception of patients receiving only CT, 5-year LRC was comparable among the different treatment types (64%-66%). The significantly higher 5-year LRC for patients receiving CT (93%) is based on a very small patient sample (n = 44) and should be interpreted with caution. Overall, the data on recurrence rates and LRC are relatively insufficient and highlight the need for more detailed reporting on these measures to develop future evidence-based guidelines on sinonasal tumor surveillance.

The present study has several limitations. Given the challenges of conducting prospective studies to assess survival outcomes of DN-SCC, all studies were nonrandomized and retrospective in design. In addition, there is potential for both study and reporting bias given the propensity for studies with more favorable outcomes to be published, as evidenced by the asymmetric funnel plot (**Figure 2**) of our meta-analysis. Another limitation was the variability in included studies in defining and reporting DN-SCC–specific outcomes. Given the heterogeneity in treatments, this study did not differentiate between the various chemotherapy or radiotherapy regimens and types of therapy (eg, adjuvant vs neoadjuvant), preventing us from drawing additional treatment-specific conclusions. This study is unable to discern strong conclusions from survival difference by T classification, N classification, tumor grade, and HPV status despite efforts to control certain

confounding variable between groups. Furthermore, the potential impact of surgical margin status on survival for DN-SCC is difficult to determine given these oncologic outcomes were very poorly reported by the individual institutions included in our study.[76] Finally, the significance of different anatomic sites of sinonasal cancers cannot be understated, as clinically occult tumors present a diagnostic challenge by remaining asymptomatic for extended periods of time. In many cases, these tumors only become detected after they have grown large enough to invade local structures and cause functional compromise. This inevitably presents a source of protopathic bias that may directly affect both OS and RR, as well as possibly overestimate survival rates. As our study only compared survival trends between tumors of the maxillary sinus and nasal cavity/ethmoid sinus origins, there is a need for updating reporting of survival-specific information on tumors originating from the frontal and sphenoid sinuses. While these limitations necessitate a more careful interpretation of the results, the data obtained through this meta-analysis provide valuable information not otherwise feasible through prospective studies.

Conclusion

De novo sinonasal squamous cell carcinoma is a rare tumor with poorly defined recurrence rate and long-term overall survival. Our aggregate data yielded a 42.7% RR and 54.5% 5-year OS in patients with DN-SCC. Advanced T stage, positive nodal status on presentation, maxillary sinus origin, and negative HPV status were all correlated with worse 5-year OS. However, our review revealed inadequate reporting on other important characteristics shown to affect survival, including surgical margins status. Future studies should focus on determining long-term OS and RR beyond 5 years for these tumors. Ultimately, by establishing a better understanding of DN-SCC recurrence and survival patterns, these studies could help develop a more tailored surveillance and treatment algorithm for this cancer.

Author Contributions

Emily S. Nguyen, design, data acquisition and analysis, drafting; **Adwight Risbud**, design, data acquisition and analysis, drafting; **Jack L. Birkenbeuel**, design, data acquisition and analysis, drafting; **Linda S. Murphy**, design, data acquisition, drafting; **Khodayar Goshtasbi,** design, data analysis, drafting, revising for content; **Jonathan C. Pang**, design, data analysis, drafting, revising for content; **Arash Abiri**, design, data analysis, drafting, revising for content; **Brandon M. Lehrich**, design, data analysis, drafting revising for content; **Yarah M. Haidar**, design, data interpretation, revising for content, final approval; **Tjoson Tjoa**, design, data interpretation, revising for content, final approval; **Edward C. Kuan**, design, data interpretation, revising for content, final approval.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

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