Higher rate of local recurrence in sinonasal squamous cell carcinoma arising from inverted papilloma compared to de novo tumours *

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Dear Editor:

Squamous cell carcinoma (SCC) is the most common histological subtype of sinonasal malignancies. Due to non-specific symptoms, sinonasal SCC (SNSCC) is often diagnosed late, posing challenges for management. SNSCC can arise de novo (DN-SCC) or from the malignant transformation of inverted papilloma (IP-SCC). Prior studies have reported inconsistent outcomes comparing these two subtypes [1-6]. This study compares recurrence patterns and survival outcomes of DN-SCC and IP-SCC, identifies predictors of recurrence and survival, and aims to inform clinical decision-making and patient counselling.

We retrospectively analysed 85 patients with SNSCC treated with primary surgery, including 60 patients diagnosed with DN-SCC and 25 with IP-SCC (Figure S1). Baseline characteristics and treatment details were summarized in Table S1 and follow-up durations were comparable between groups. The IP-SCC group exhibited a significantly higher 5-year local recurrence (LR) rate than the DN-SCC group (60.6% vs. 12.7%, p=0.001; Figure 1A). This elevated LR risk may stem from the recurrent nature of inverted papilloma (IP) or inadequate surgical margins, particularly in cases initially misdiagnosed as benign papillomas and treated more conservatively. These findings underscore the importance of achieving wide surgical margins, even when IP is suspected preoperatively.

No significant differences were observed in nodal recurrence or distant metastasis (Table S2 and Figure S2). Multivariate analysis revealed that both IP-SCC and advanced T stage were independently associated with increased LR risk (Table S3), with hazard ratios of approximately 4.5 and 2.9, respectively. Although the LR rate difference by T stage (T3–T4 vs. T1–T2: 31.1% vs. 18.2%) only approached statistical significance (p = 0.059; Figure 1B), the trend supported its inclusion in the multivariate model. Notably, all IP-SCC recurrences occurred within 50 months postoperatively, suggesting that intensive follow-up should be prioritized in the first 4–5 years for high-risk patients.

Disease-specific survival (DSS) and overall survival (OS) were comparable between DN-SCC and IP-SCC (p=0.418 & p=0.442; Figure 1C, 1D). Our results align with prior case series reporting similar 5-year OS (~55%) for both subtypes (Table S4). In contrast, a meta-analysis suggested higher mortality in DN-SCC [7]. It included a 1989 study (contributing nearly 25% of total weight) which predated widespread adoption of endoscopic approaches and modern pathological classification. Tumours labeled as "poorly differentiated SCC" may now be reclassified as sinonasal undifferentiated carcinoma or other entities based on advances in immunohistochemistry and molecular profiling [8]. Additionally, it didn't report patient details including T stage and treatment modality, limiting assessment of their impact on survival differences.

Another meta-analysis previously suggested no difference in LR between DN-SCC and IP-SCC [9]. In contrast, our study included only patients who underwent primary surgery, thereby minimizing treatment-related heterogeneity. The discrepancy in findings may stem from differences in case selection. Moreover, the DN-SCC group in the meta-analysis had significantly higher rates of positive surgical margins and more advanced T stage—both factors known to increase LR risk—which may have offset the potential difference in LR between the two tumour subtypes.

To explore the impact of recurrence on prognosis, we stratified DSS and OS by LR status. Patients with LR had significantly worse 5-year DSS than those without (43.7% vs. 91.6%, p < 0.001; Figu-

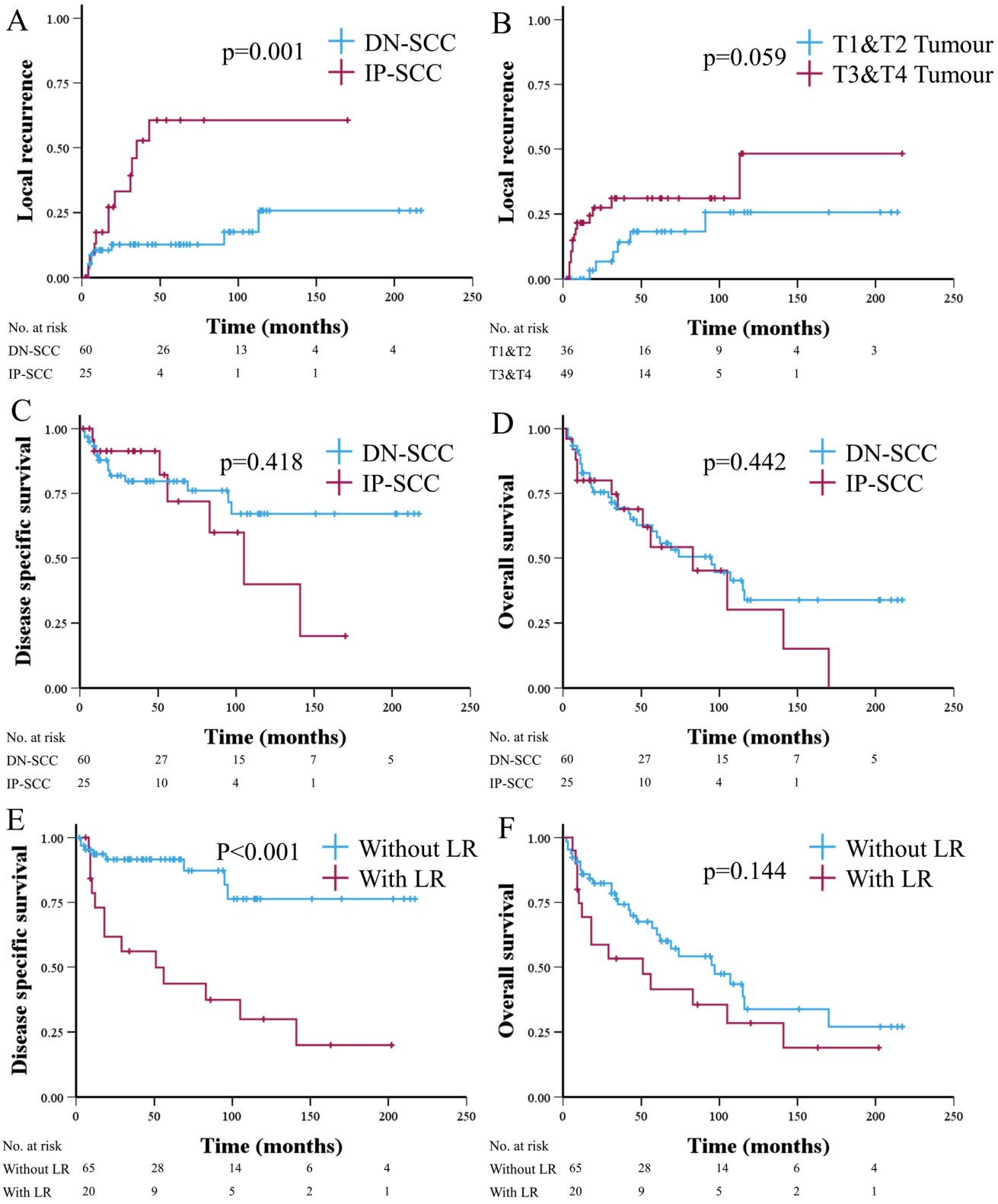

Figure 1. Kaplan-Meier analysis (A) Local recurrences between IP-SCC and DN-SCC; (B) Local recurrence between early (T1&T2) and advanced (T3&T4) stage tumours; (C) Disease-specific survival between IP-SCC and DN-SCC; (D) Overall survival between IP-SCC and DN-SCC; (E) Disease-specific survival based on the presence or absence of local recurrence; (F) Overall survival based on the presence or absence of local recurrence.

re 1E). In multivariate analysis, older age (>70 years), advanced T stage, and distant metastasis independently predicted poorer OS (Table S3).

In conclusion, IP-SCC is associated with significantly higher LR risk compared to DN-SCC, although OS remains similar. Given that LR substantially worsens DSS, and that IP-SCC and advanced T-stage are predictors of recurrence, these patients warrant wide excision with adequate margins and intensive surveillance, particularly in the first few years postoperatively.

Abbreviations

SCC, squamous cell carcinoma; SNSCC, sinonasal squamous cell carcinoma; DN-SCC, de novo squamous cell carcinoma; IP-SCC, squamous cell carcinoma arose from the malignant transformation of inverted papilloma; LR, local recurrence; IP, inverted papilloma; DSS, disease specific survival; OS, overall survival.

Authorship contribution

Study idea and design: MHD, YWC, YTC; data collection: all authors; data analysis: MHD, YTC; manuscript writing: MHD, YTC; draft edition: all authors; final approval: all authors.

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Conflict of interest

None.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Materials and Methods

Patients

This study included patients diagnosed with SNSCC who were treated at the Department of Otolaryngology–Head and Neck Surgery at Taipei Veterans General Hospital between 2001 and 2023. Data were collected from the medical record database of the hospital. Patients who did not undergo primary surgery in their treatment were excluded to minimize discrepancies in treatments. Patients with incomplete data, carcinoma in situ, palliative intent, or a follow-up period of less than six months were also excluded. The study protocol was approved by the institutional review board (2020-06-004CC). All data were analysed anonymously, with individual consent waived as deemed unnecessary.

Data collection, outcome measurement and treatment

Patients were categorized into two groups—DN-SCC and IP-SCC—based on pathological diagnosis from surgical specimens evaluated by pathologists. The final tumour stage and treatment plan were confirmed by the multidisciplinary team based on the tumour, node and metastasis (TNM) staging systems of the American Joint Committee on Cancer (AJCC) and National Comprehensive Cancer Network (NCCN) guidelines in effect at the time. Patients were instructed to have follow-up visits monthly during the first year, every two months in the second year, and every three months afterward. Sinoscopy assessments were conducted at each follow-up visit, with any suspicious lesions biopsied by a rhinologist. The biopsy specimens were then examined by the pathologist to confirm the presence or absence of tumour recurrence. Annual assessments included sinus computed tomography or magnetic resonance imaging as well as abdominal sonography, chest computed tomography, and whole-body bone scans with the aim of detecting nodal recurrence (NR) and distant metastasis (DM).

The follow-up duration was defined as the time from the initiation of treatment to the last recorded hospital visit, outpatient follow-up, or death. DSS was defined as the time from the initiation of treatment to death specifically from SNSCC. OS was defined as the time from the initiation of treatment to death from any cause. Analysis focused on clinical characteristics, recurrence rates, survival outcomes, and predictive and prognostic factors.

Statistical analysis

Categorical data were analysed using the chi-square test and Fisher's exact test, as appropriate. A two-tailed t-test was employed for comparisons between two continuous variables. The Kaplan-Meier method was used to analyse recurrence, metastasis, and survival outcomes, with differences in these univariate outcomes assessed using the log-rank test. Multivariate analysis of predictive and prognostic factors was performed using the Cox proportional hazards model. A p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 29; IBM Corp., Armonk, NY, USA).

Limitation

This study has limitations. First, endoscopic piecemeal resections limited accurate assessment of surgical margins, potentially affecting recurrence rates. Second, the long study period (2001–2023) may introduce heterogeneity in outcomes due to evolving surgical techniques; however, IP-SCC and DN-SCC were evenly distributed over time (Figure S4). Third, IP-SCC patients had prior surgery for IP, possibly altering local anatomy. To evaluate the potential effect of prior IP surgery on recurrence patterns, we conducted an additional analysis excluding these patients, which yielded consistent results (Figure S5). Finally, HPV status was not assessed due to the retrospective design; future studies should address this factor.

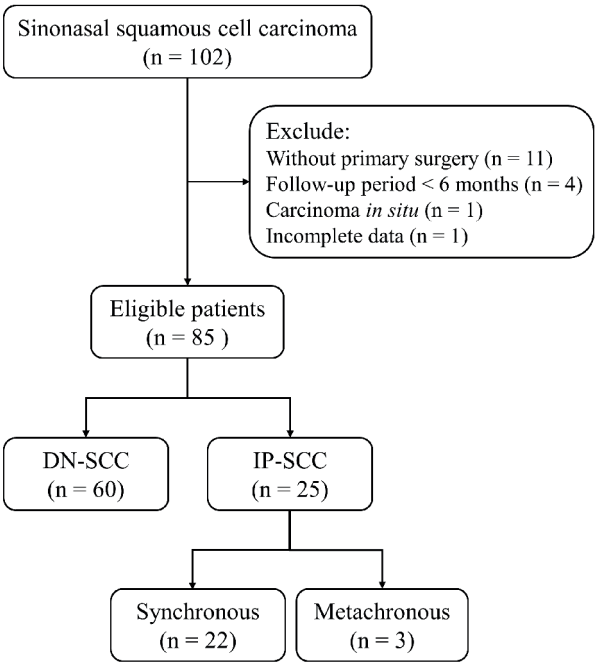

Figure S1. Flow chart for the selection and categorization of patients.

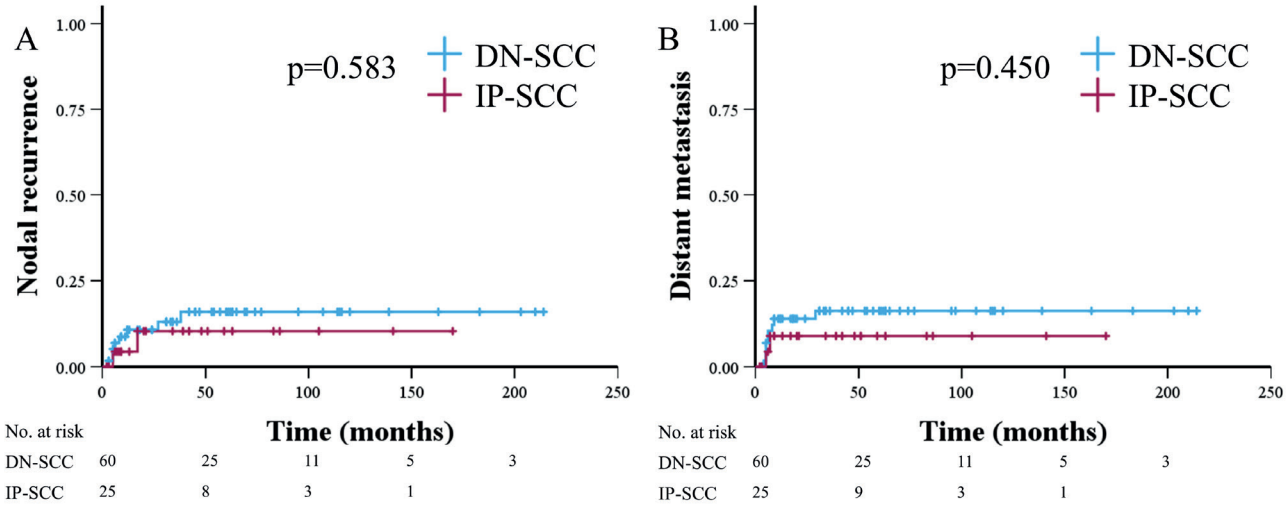

Figure S2. Kaplan-Meier analysis (A) Nodal recurrence between IP-SCC and DN-SCC; (B) Distant metastasis between IP-SCC and DN-SCC.

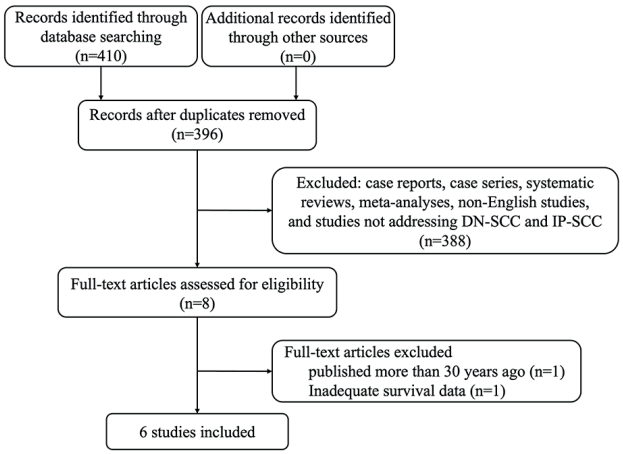

Figure S3. Flow chart for the literature review.

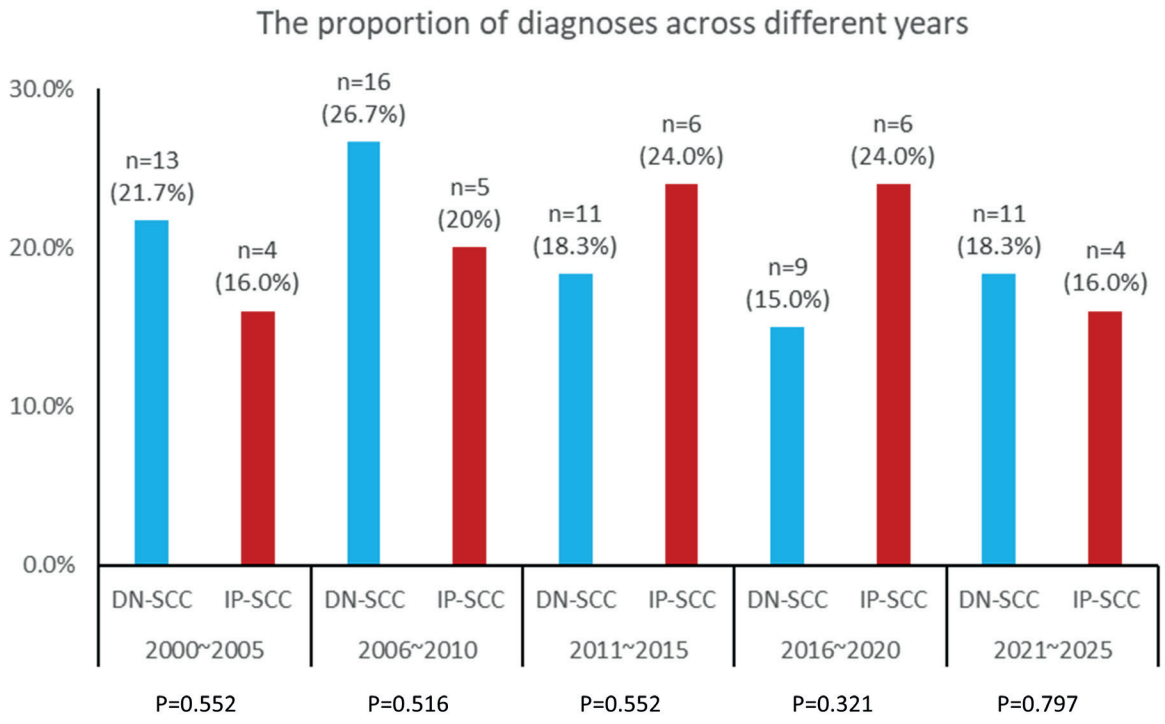

Figure S4. Proportions of DN-SCC and IP-SCC diagnoses over two decades.

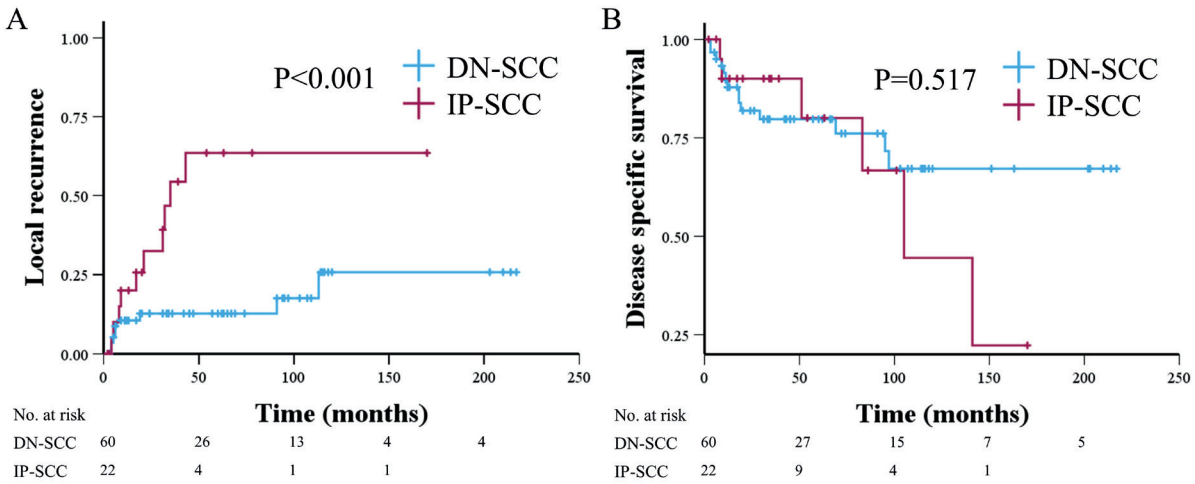

Figure S5. Kaplan-Meier analysis excluding patients with prior IP surgery (A) Local recurrence between IP-SCC and DN-SCC; (B) Disease specific survival between IP-SCC and DN-SCC.

Table S1. Patient demographics and characteristics.

Mean ± SD	DN-SCC (n=60)	IP-SCC (n=25)	p
Gender			0.406
Female	14 (23.3%)	8 (32.0%)	
Male	46 (76.7%)	17 (68.0%)	
Age (years)	61.2 ±15.1	60.7 ±15.6	0.887
Follow-up time (months)	64.2 ± 60.2	48.3±44.4	0.236
Symptoms duration (months)	6.8 ±17.4	8.0 ±13.3	0.765
Smoking	16 (26.7%)	7 (28.0%)	0.900
Tumour origin			0.371
Nasal cavity	42 (70.0%)	15 (60.0%)	
Paranasal sinus	18 (30.0%)	10 (40.0%)	
T stage			0.205
T1	18 (30.0%)	5 (20.0%)	
T2	6 (10.0%)	7 (28.0%)	
T3	11 (18.3%)	4 (16.0%)	
T4	25 (41.7%)	9 (36.0%)	
Nodal involvement	8 (13.3%)	0 (0%)	0.098 †
Distant metastasis	1 (1.7%)	1 (4.0%)	0.504 †
TNM stage			0.123
Stage I	17 (28.3%)	5 (20.0%)	
Stage II	5 (8.3%)	7 (28.0%)	
Stage III	10 (16.7%)	4 (16.0%)	
Stage IV	28 (46.7%)	9 (36.0%)	
Surgery technique			0.798
Endoscopic	44 (73.3%)	19 (76.0%)	
Open/Combined	16 (26.7%)	6 (24.0%)	
Neoadjuvant therapy	2 (3.3%)	0 (0%)	1.000 †
Postoperative Chemotherapy	30 (50.0%)	9 (36.0%)	0.238
Postoperative Radiotherapy	44 (73.3%)	18 (72.0%)	0.900

† Fisher's exact test; SD = standard deviation

Table S2. Outcomes of recurrence and distant metastasis.

	Local recurrence	Nodal recurrence	Distant metastasis
IP-SCC (n=25)	11 (44.0%)	2 (8.0%)	2 (8.0%)
DN-SCC (n=60)	9 (15.0%)	8 (13.3%)	9 (15.0%)
p value	0.004*	0.716 †	0.495 †

† Fisher's exact test; *statistical significance ($p < 0.05$).

Table S3. Predictive factors for local recurrence and overall survival.

	5-year Local recurrence				5-year Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	5-year LR (%)	p	HR (95% CI)	p	5-year OS (%)	p	HR (95% CI)	p
IP-SCC / DN-SCC	60.6% / 12.7%	0.001*	4.52(1.79-11.43)	0.001*	54.3% / 58.1%	0.442	1.80(0.90-3.60)	0.099
Age <70 / Age >70	30.5% / 17.2%	0.248			64.5% / 44.9%	0.031*	2.09(1.12-3.90)	0.020*
Male / Female	25.4% / 28.1%	0.835			56.0% / 60.2%	0.541		
Smoking / No smoking	22.1% / 27.7%	0.663			46.2% / 60.3%	0.326		
Origin: Nasal cavity / Paranasal sinus	19.9% / 39.5%	0.075			60.0% / 48.5%	0.784		
T stage: T1-T2 / T3-T4	18.2% / 31.1%	0.059	2.86 (1.07-7.63)	0.036*	66.3% / 50.7%	0.064	2.05(1.05-4.00)	0.035*
Pure endoscopic / Open, Open-assist	23.4% / 35.5%	0.495			57.8% / 53.0%	0.007*	1.62(0.83-3.17)	0.158
Adjuvant therapy / Without adjuvant therapy	28.9% / 20.4%	0.471			57.7% / 57.3%	0.993		
Distant metastasis / No distant metastasis					15.2% / 62.7%	<0.001*	5.10(2.08-12.50)	<0.001*

*statistical significance ($p < 0.05$); CI = confidence interval; LR = local recurrence; OS = overall survival.

Table S4. Summary of previous studies comparing IP-SCC and DN-SCC.

	No. of patients (IP-SCC vs. DN-SCC)	Years	LR rate (IP-SCC vs. DN-SCC)	p value	NR rate (IP-SCC vs. DN-SCC)	p value	DM rate (IP-SCC vs. DN-SCC)	p value	5-year DSS (IP-SCC vs. DN-SCC)	p value	5-year OS (IP-SCC vs. DN-SCC)	p value
de Almeida et al. [1]	34 (12 vs. 21)	2000-2012	N/A		N/A		N/A		N/A		86.0% vs. 75.0%	0.240
Yan et al. [4]	66 (28 vs. 38)	2000-2015	N/A		N/A		N/A		10-year DSS 89.6% vs. 65.6%	0.047*	10-year OS 84.6% vs. 62.3%	0.065
Yu et al. [6]	86 (21 vs. 65)	1990-2014	28.6% vs. 30.8%	N/A	4.8% vs. 3.1%	N/A	0% vs. 3.1%	N/A	61.5% vs. 52.8%	0.437	58.3% vs. 39.5%	0.043*
Quan et al. [3]	162 (39 vs. 123)	2010-2017	51.3% vs. 15.4%	0.027*	15.4% vs. 9.8%	0.330	7.7% vs. 14.6%	0.261	N/A		58.6% vs. 62.9%	0.584
Yasumatsu et al. [5]	107 (23 vs. 84)	1990-2016	26.0% vs. 32.0%	N/A	N/A		4.3% vs. 9.6%	N/A	3-year DSS 62.7% vs. 62.0%	0.750	N/A	
Li et al. [2]	173 (89 vs. 84)	2005-2018	22.5% vs. 19.0%	0.579	13.5% vs. 10.7%	0.577	6.7% vs. 19.0%	0.015*	N/A		63.3% vs. 55.4%	0.390
Present study	85 (25 vs. 60)	2001-2023	44.0% vs. 15.0%	0.004*	8.0% vs. 13.3%	0.716	8.0% vs. 15.0%	0.495	71.9% vs. 79.7%	0.418	54.3% vs. 58.1%	0.442

*statistical significance ($p < 0.05$); LR = local recurrence; NR = nodal recurrence; DM = distant metastasis; DSS = disease specific survival; OS = overall survival; N/A = not available. (Please refer to Table S5 and Figure S3 for the search strategy in this literature review).

Table S5. Complete search strategy.

Database	Query
Pubmed 127 results on 01/19/25	((((("Nose"[Mesh] OR "Nose Neoplasms"[Mesh] OR "Nose Diseases"[Mesh]) OR ("Paranasal Sinus Diseases"[Mesh] OR "Paranasal Sinuses"[Mesh] OR "Maxillary Sinus Neoplasms"[Mesh] OR "Head and Neck Neoplasms"[Mesh] OR "Paranasal Sinus Neoplasms"[Mesh])) AND ("Carcinoma, Squamous Cell"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck"[Mesh])) AND ("Papilloma"[Mesh] OR "Papilloma, Inverted"[Mesh])) AND ("Survival"[Mesh] OR "Mortality"[Mesh] OR "mortality" [Subheading] OR "Disease-Free Survival"[Mesh] OR "Survival Analysis"[Mesh] OR "Survival Rate"[Mesh] OR "Progression-Free Survival"[Mesh] OR "Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])
Ovid medline 279 results on 01/19/25	Nose Neoplasms/ or Paranasal Sinus Neoplasms/ or sinonasal.mp. or Paranasal Sinuses/ AND Survival Rate/ or Disease-Free Survival/ or Survival Analysis/ or Progression-Free Survival/ or Survival/ AND squamous cell carcinoma.mp. or Carcinoma, Squamous Cell/
Cochrane 4 results on 01/19/25	Mesh descriptor: [Nose Diseases or Nose or Nose Neoplasms or Paranasal Sinus Diseases or Paranasal Sinus Neoplasms] AND MeSH descriptor: [Carcinoma, Squamous Cell] AND MeSH descriptor: [Survival or Survival Analysis or Survival Rate or Disease-Free Survival]