Sinonasal Mucosal Melanoma Survival Outcomes, Recurrence Patterns, and Prognostic Factors: A Systematic Literature Review and Meta-analysis of Publications after 2000

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Abstract

Background Sinonasal mucosal melanoma (SNMM) comprises <1% of all head and neck cancers but has one of the highest 5-year mortalities.

Methods A systematic review and analysis using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analyses) guidelines was conducted on SNMM survival, recurrence, and prognostic factors.

Results A total of 2,379 abstracts were reviewed resulting in 90 studies describing 3347 SNMM patients. Patients were 49.65% male and 66.5 years old. Surgery plus radiation therapy, followed by surgery only, then radiation only were the most common treatments. Chemotherapy and immunotherapy were used in 418 patients and 101 respectively. The 2-, 3-, and 5-year overall survivals are 55.97, 40.09, and 30.35%, respectively. The 5-year disease-free survival and disease-specific survival are 25.56 and 38.04%. The 5-year local, regional, and distant recurrence-free survivals are 42.35, 81.64, and 44.65%. Mean survival after diagnosis was 26.99 months. Local ($n = 650$), regional ($n = 226$), and distant ($n = 723$) failure presented after 19.36, 6.35, and 12.42 months. Sites of metastasis were lung, liver, bone, brain, skin, kidney, and adrenal glands. Distant metastases, disease in the paranasal sinuses, and higher stage were noted to have worse survival outcomes. Positive margins did not significantly impact overall survival in 11/12 studies.

Conclusion Overall survival over 20 years has remained poor with 70% of patients deceased in 5 years. About half of patients will develop distant failure and will thereafter rapidly decline. These data indicate need for advances in treatment of SNMM and new efforts with targeted immunotherapy offer a promising avenue toward improving survival outcomes.

Keywords
- sinonasal mucosal melanoma
- recurrence
- prognosis
- PRISMA
- survival
- immunotherapy

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Introduction

Mucosal melanoma is a rare and aggressive subvariant of melanoma affecting mucosal melanocytes in the head and neck, genitals, and digestive tract. With an annual incidence of 2.2 cases per million,[1] mucosal melanoma comprises less than 1% of head and neck malignancies.[2] Unlike cutaneous melanoma, mucosal melanoma does not have clear risk factors, disease course, or treatment recommendations.[3–8] Even the purpose of the mucosal melanocyte is debated.[3] Although mucosal melanocytes contain the characteristic melanin pigment, they do not receive UV light exposure and do not serve to protect against UV radiation like their cutaneous counterparts. Literature has found that melanocytes in general may play a role in the innate and acquired immune system, so it is hypothesized that immune defense may be the primary purpose of the mucosal melanocytes.[9–11]

Within the head and neck, mucosal melanoma most commonly presents in the sinonasal region.[2] Compared with other sinonasal malignancies, however, mucosal melanoma still only comprises about 4% of tumors and is uncommon enough that epidemiological studies cannot fully analyze it.[3,12] In addition to its rarity, sinonasal mucosal melanoma (SNMM) often presents with insidious and nonspecific symptoms. Most patients diagnosed with SNMM are asymptomatic; however, they may present with nasal obstruction, epistaxis, and/or cranial neuropathies stemming from compression of the orbit or skull base.[13] On exam, these lesions present with a variety of pigmentation ranging from amelanotic and fleshy to full brown to black pigmentation.[8,14]

Due to its rarity, most literature on this disease comes from small case series and 5-year overall survival (OS) has been reported in the range from 0 to 61.5%.[8,14] Some larger databases such as SEER (Surveillance, Epidemiology, and End Results)[15] and the National Cancer Database[16] contain more accurate survival information on SNMM but lack information on recurrence, one of the most challenging aspects of the disease. This study aimed to systematically review recent existing literature on SNMM to analyze outcomes, survival, recurrence patterns, and prognostic factors.

Methods

This study was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analyses) guidelines.[17] Three electronic databases (PubMed, Web of Science, and Science Direct) with an identical series of keywords were queried, and the results were collected directly into an electronic literature organization system (Endnote Online). Search entries were as follows: sinonasal mucosal melanoma; sinonasal mucosal melanoma AND Recurrence; sinonasal mucous melanoma AND Recurrence; sinus AND mucosal melanoma AND recurrence; nose AND mucosal melanoma AND recurrence; sinus AND mucosal melanoma AND follow up; nose AND mucosal melanoma AND follow up; sinonasal mucosal melanoma AND follow up; upper airway AND mucosal melanoma. After resulting literature was collected from the three electronic databases into Endnote (Clarivate, Jersey), an initial phase of removing duplicate papers was achieved using a duplicate identifying function of Endnote.

Inclusion and Exclusion Criteria

Study inclusion criteria were (1) full English text available, (2) published in the year 2000 or later, (3) included survival or recurrence data on two or more cases of biopsy-proven SNMM, and (4) cases were not reported in a database or other case series already used in the study. Articles were excluded if they did not report separate statistical analyses of SNMM as opposed to combining sinonasal and oral mucosal melanoma. In cases where one author published multiple articles with patient data from overlapping years, data were extracted from the study that reported a statistic with the largest *n* value to ensure that there were no duplicate patients included in this study's results.

Screening

After initial duplicates were removed automatically, the remaining literature underwent title and abstract review by the primary author. Papers were included for further screening if they reported multiple cases of mucosal melanoma of the head and neck and had a full English text available. The included literature was then sorted alphabetically by first author and full texts were assessed for eligibility. During this stage, remaining duplicate entries not detected by the automatic removal process were individually removed from the inclusion cohort.

Data Extraction

For each included study, data were extracted into a standardized form. Patient demographics, tumor characteristics (2009 TNM stage, site of origin, pigmentation, and margin status), treatment modalities, prognostic factors, recurrence data (number of patients with recurrences, site of recurrence, time until recurrence, and treatment of recurrence), and survival outcomes (2, 3, and 5-year OS, disease-free survival, disease-specific survival, and median survival after diagnosis) were collected. Comparative statistics and regression analysis findings analyzing patient survival outcomes were recorded if available. The year of publication, SNMM sample size, institutions contributing data, data collection period, and study design were noted for each included study.

Statistical Analysis

Statistics were calculated using SPSS Version 28.[18] Results were concluded using calculations weighted by each paper's sample size. To determine the average age of patients at diagnosis, the reported median age of each cohort was weighted by the sample size of the original study and then averaged among the included studies. If the median was not reported, the mean was used in its place. This technique was also used for the calculation of time from diagnosis until recurrence, time from diagnosis until death, and time from recurrence until death.

Results

The electronic database search produced 4,819 results between Web of Science, PubMed, and Science Direct. After duplicates were removed, 2,379 results remained for title and abstract screening. A total of 633 full texts were included to review after initial title and abstract screening. When these full texts were analyzed for inclusion criteria, 90 studies met the requirements for data extraction (►**Fig. 1**).[7,8,13,14,19–104]

Included studies were conducted in 28 different countries with the United States being the most common. Years of publication ranged from 2000 to 2022 with a mode of 2017. Eighty-three studies were retrospective chart reviews, six were case series, and one was a database limited to one country. The average number of patients per paper was 40 patients (range: 2–221, standard deviation [SD]: 43.4).

There were 3,347 patients included in this study. A total of 2,635 patients were included in recurrence analysis and 3,213 patients were included in prognostic factor analysis. Patients were 49.65% male with a mean age of 66.53 years old at diagnosis. A total of 759 (22.9%) of patients were treated in the United States. Treatment information was recorded for 2,731 patients. Of those patients, 2,034 (74.5%) were recorded to have undergone resection. When specified, the most common treatment plan was surgery plus radiation therapy ($n = 824$), followed by surgery only ($n = 453$), then radiation only ($n = 104$). A total of 52.2% of surgeries had an open component, whereas 47.79% were endoscopic only ($n = 602$ and 551, respectively). The surgical approach was not specified in 881 patients. Chemotherapy was used in 418 patients and 101 were treated with immunotherapy. Immunotherapy was most commonly used in patients who presented with recurrent disease or those who presented

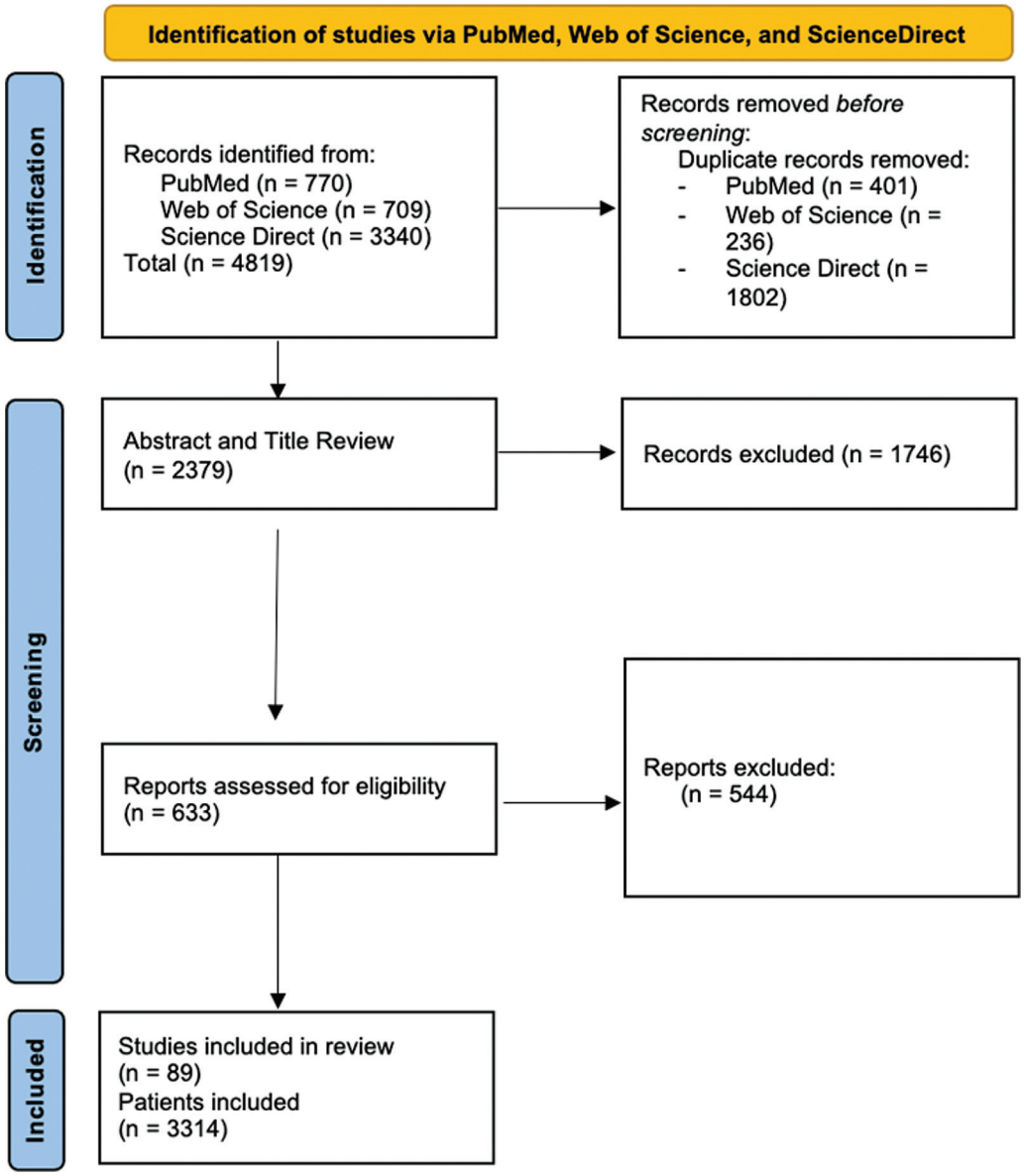

Fig. 1 PRISMA schematic describing literature review and screening process. PRISMA. Preferred Reporting Items for Systematic Reviews and Meta- Analyses.

initially with distant metastases. A total of 111 patients were treated with palliative intent.

Survival Outcomes

The average 2-, 3-, and 5-year OS are 55.97, 40.09, and 30.35%, respectively. The 5-year disease-free survival and disease-specific survival are 25.56 and 38.04%. The 5-year local, regional, and distant recurrence-free survivals are 42.35, 81.64, and 44.65%. The weighted average survival after diagnosis was 26.99 months. Patients treated in the United States had statistically higher 5-year OS compared with those treated elsewhere ($t(2116) = 8.323$, $p < 0.001$, U.S. avg $= 33.39$ (10.49), other country average $= 28.85$ (11.79)).

Recurrence

Local ($n = 650$), regional ($n = 226$), and distant ($n = 723$) failure presented after 19.36, 6.35, and 12.42 months, respectively, after first curative treatment. After local recurrence, patients died after 10.5 months on average; however, only one paper reported that statistic. Patients died 4.15 months after distant metastasis on average. Average time from any recurrence until death was 50.9 months. The most to least common sites of metastasis specified were lung, liver, bone, brain, kidney, and adrenal glands ($n = 91$, 75, 53, 29, 6, and 4). There were 30 distant metastases that traveled to sites not specified.

Prognostic Factors

The prognostic findings within the literature review are described in ►**Table 1**. Patients with distant metastases, disease in the paranasal sinuses, and higher stage were noted in multiple studies (6, 10, and 15, respectively) to have a statistically significant worse survival outcome. Positive margins after resection were not a significant factor in OS in 11 out of 12 studies, which analyzed it. Nine studies compared endoscopic versus open approaches with six finding no difference in outcomes between approaches and three finding that endoscopic approaches have statistically better outcomes. Adjuvant radiation was analyzed in 17 studies with 15 finding no difference in patient outcomes, 1 finding better patient outcomes, and 1 study finding worse patient outcomes with adjuvant radiation. Immunotherapy use was evaluated in three studies. It was found to be associated with increased survival in one study with the remaining two finding no difference in survival.

Immunotherapy

There were nine studies[30,36,46,61,63,65,66,77,88] that reported isolated survival data on patients who received immunotherapy. In total, 51 patients who received immunotherapy were included in this subanalysis. The 5-year OS for these patients was 38.36%. The average time until progression for these patients was 15.8 months ($n = 17$, SD $= 10.1$). There was a wide variety of treatment regiments including ipilimumab alone ($n = 7$), pembrolizumab alone ($n = 3$), ipilimumab plus pembrolizumab ($n = 2$), pembrolizumab plus nivolumab ($n = 3$), vemurafenib ($n = 1$), interferon alpha ($n = 14$), interleukin-2 ($n = 9$), and the Bacillus Calmette–Guérin (BCG) vaccine ($n = 10$). Interferon alpha, interleukin -2, and BCG vaccine therapy was used in an adjuvant regimen ($n = 33/33$), whereas pembrolizumab, nivolumab, ipilimumab, and vemurafenib were mostly used in a salvage setting ($n = 13/16$ salvage, 2/16 adjuvant, and 1/16 neoadjuvant). There were three studies that evaluated the prognostic value of immunotherapy. One study found better prognosis with immunotherapy treatment,[88] and two found no difference.[36,66]

Discussion

This study is the largest to date that collectively analyzes and reports survival outcomes, recurrence patterns, and prognostic factors of SNMM. Survival and disease outcomes remain poor for this disease, with a 5-year OS rate of 30.35% and a 5-year disease-free survival of 25.56%. SNMM has a propensity for recurrence with most occurring distantly. Distant metastasis is most likely to be seen in the lungs, liver, bone, and brain, highlighting the importance of obtaining serial brain imaging in addition to positron emission tomography scans. Worse outcomes are seen in tumors that are a higher stage, are in the paranasal sinuses, and present with distant metastases. Of note, survival was found to be better in the United States compared with other countries included in this analysis. No additional factor was able to be isolated between these groups to explain this finding. This suggests that there may be underlying exposure, population, or structural healthcare variable such as access to care or likelihood of incidental discovery that may be contributing to this difference.

Several treatment strategies have been employed with mixed results including endoscopic versus surgical resection, en bloc versus piecemeal resection, radiation, chemotherapy, and immunotherapy use. The most popular treatment approach utilized was surgical resection with adjuvant radiation. Interestingly, while surgical treatment was heavily associated with increased survival, margin status after surgical treatment was not found to be a significant predictor of survival in all but one study that explored it. Studies have suggested that mucosal melanoma expresses a unique pathway of hematological spread,[78] so perhaps at the time of surgery, the malignancy has already seeded the blood making margin status of less consequence.

Systemic treatment modalities such as chemotherapy[100] and, more recently, immunotherapy[88] have demonstrated some association with improved survival and is a promising area of active exploration.[105,106] The emergence of immunotherapy was first discussed within the realm of SNMM in the mid-2000s.[107] While it has mostly been used as a salvage or adjuvant treatment, some authors have suggested there may be a role for immunotherapy in the initial treatment regimen.[108] Additionally, we identified and analyzed three studies that evaluated immunotherapy as a prognostic factor in SNMM. Dréno et al evaluated 5-year OS in mucosal melanoma patients who received interferon alpha therapy and found there was no difference in survival compared with patients who did not receive that therapy. Meerwein et al evaluated monoclonal antibody immunotherapies in the setting of

Table 1 Collection of studies that analyze prognostic factors of sinonasal mucosal melanoma with associated statistical results

Author	Year	*n*	Variables without survival significance	Variables with survival significance	Statical findings
Almutuawa	2020	20	Age, gender, ethnicity, smoking history, AJCC staging (7th edition), margin status, adjuvant RT, bone invasion, ulceration, periorbital involvement, recurrence		Multivariate hazard ratio (HR) (95% CI)
				Open resection vs. endoscopic resection	19.93 (2.14–185.4), $p = 0.009$
				Lymphatic invasion	0.05 (0.004–0.7), $p = 0.031$
Amit	2018	198	Sex, age, T3 vs. T4a, nodal metastasis, margin status, local invasion, mitoses > 1, ulceration, tumor thickness, bone invasion, adjuvant RT, adjuvant CT		Univariate HR (95% CI)
				Paranasal vs. nasal	1.95 (1.25-2.94), $p = 0.003$
				Pathologic T stage T4b vs. T3	2.02 (1.14-3.4), $p = 0.04$
				Distant metastasis	4.01 (1.93-7.49), $p = 0.0006$
Bachar	2008	49	Sex, tumor site, stage, margin status, and adjuvant RT, adjuvant CRT		Univariate log-rank test
				Age > 50 at diagnosis (worse survival)	$p = 0.02$
Cao	2017	33	Open vs. endoscopic resection		Univariate log-rank test
Caspers	2017	51	Age, sex, tumor site, involved sinuses, endoscopic vs. open surgery, adjuvant RT, radiation dose, local recurrence, nodal metastasis		Univariate HR (95% CI)
				High Adult Comorbidity Evaluation-27 Score	5.02 (1.17-21.6), $p = 0.03$
				AJCC 7th edition tumor stage 4 vs. 3	2.34 (1.09-5.02), $p = 0.03$
				Positive margins	3.27 (1.23-8.68), $p = 0.02$
				Distant metastasis	2.50 (1.14-5.45), $p = 0.02$
					Multivariate HR (95% CI)
				Positive margins	$p = 0.048$
Cheng	2007	23	Gender, margin status		Univariate log-rank test
				Nasal cavity vs. paranasal sinus (paranasal worse)	$p = 0.001$
				Distant metastasis	$p < 0.001$
Çomoğlu	2018	21	Treatment modality, nodal metastasis, margin status, location of disease, age		Univariate log-rank test
				Mitotic activity (worse with higher activity)	$p = 0.037$
Dauer	2008	61	Presence of melanin, necrosis, nuclear pleomorphism, histological subtype, depth of invasion, and ulceration		Univariate Cox relative risk, RR (95% CI)
				Nonseptum location	2.7 (1.3–5.6), $p = 0.01$
				Maxillary sinus origin	2.3 (1.2–4.3), $p = 0.01$
				Tumor size	1.5 (1.1–1.9), $p = 0.003$
Dréno	2017	44	Age, gender, use of RT, use of CT, use of IT		Univariate log-rank test
				Headache, facial pain, and V2 anesthesia	$p = 0.02$
				Origin in sinus vs. nasal cavity	$p = 0.03$
				AJCC 6th edition T3-4 vs. T1-2	$p = 0.003$
				AJCC 7th edition T4 vs. T3	$p = 0.006$

(*Continued*)

Table 1 (*Continued*)

Author	Year	*n*	Variables without survival significance	Variables with survival significance	Statical findings
Fuji	2014	20	T stage, use of concurrent CT, FDG-PET signal level, and tumor size		Univariate log-rank test
				Undifferentiated morphology	$p = 0.018$
Göde	2017	17	Tumor origin, regional metastases, tumor size, T stage, number of mitoses, staining positive for Melan A, S100, HMB-45, presence of necrosis or C-KIT positivity		Cox regression analysis
Gras-Cabrerizo	2015	20	Tumor origin		Univariate log-rank test
				Advanced Thompson stage	$p = 0.006$
				AJCC 7th edition TNM stage for SMM	$p = 0.05$
				AJCC 7th edition TNM stage for sinonasal carcinoma	$p = 0.006$
Jangard	2012	186	Type of primary treatment		Univariate log-rank test
				Male sex	$p = 0.038$
				Age > 60	$p = 0.040$
				Epistaxis vs. nasal congestion only	$p = 0.046$
Kanetaka	2011	13	Lymphokine-activated killer (LAK) cell therapy use, margin status		Univariate log-rank test
Kerr	2011	17	Tumor microvascular density		Cox regression analysis
Khademi	2011	18	Age, sex, total dose of radiotherapy, size of primary tumor		Univariate HR (95% CI)
				Common basic stage	5.79 (1.65–20.41), $p = 0.006$
				Initial complete response to treatment	13.41 (1.57–114.92), $p = 0.018$
					Multivariate HR (95% CI)
				Common basic stage	22.17 (1.66–296.06), $p = 0.019$
Koivunen	2012	50	Primary tumor location, involvement of palate, frontal sinus, nasopharynx, infraorbit		Multivariate log-rank test
				AJCC 7th edition T stage	$p = 0.01$
				Involvement of sphenoid sinus	$p = 0.01$
Lai	2019	92	Surgery plus RT vs. surgery plus CRT		Univariate log-rank test
				Surgery alone vs. surgery plus RT	$p = 0.003$
				Surgery alone vs. surgery plus CRT	$p = 0.002$
Ledderose	2022	27		Tumor-infiltrating lymphocyte score (worse with less lymphocytes)	Univariate log-rank test
					$p < 0.05$
Lund	2012	115	Adjuvant RT, sex, age, tumor site		Mantel– Cox proportional hazard test
				Positive lymph nodes at diagnosis	$p < 0.001$
				Endoscopic vs. open approach	$p = 0.013$

Table 1 (*Continued*)

Author	Year	*n*	Variables without survival significance	Variables with survival significance	Statical findings
Lundberg	2019	58	Gender, endoscopic vs. open surgery, adjuvant RT		Univariate log-rank test
				Age > 70	$p = 0.036$
				Sinus vs. nasal cavity origin	$p = 0.038$
				7th UICC stage IV vs. III	$p = 0.003$
				T4 vs. T3 tumors	$p = 0.006$
				Positive lymph nodes at diagnosis	$p < 0.001$
Manton	2019	31	Age, gender, primary site, smoking history, use of RT, margin status, time from diagnosis to surgery		Cox's proportional hazard ratio
				Stage IVB vs. III	3.87 (1.02, 14.74), $p = 0.047$
Martin	2004	20	Age, gender, melanosis, site involved, radiotherapy dose, or fraction size		Cox's proportional hazard ratio
				UICC 6th edition T stage 3 or 4	4.3 (1.1 – 6.1), $p < 0.05$
Meerwein	2019	34	Use of IT, T stage		Univariate log-rank test
				Residual disease	$p < 0.001$
Michel	2013	35	Depth of invasion		Univariate log-rank test
				Distant metastasis	$p = 0.032$
				7th edition AJCC SMM stage IVb or IVc	$p = 0.012$
				AJCC 7th edition TNM stage for sinonasal carcinoma T3–4 vs. T1–2	$p = 0.012$
Miglani	2017	22	Endoscopic vs. open approach		Univariate log-rank test
				Treatment with curative intent	$p = 0.042$
Mochel	2015	32	Margin status, T stage, in situ vs. invasion, histological presentation, ulceration, nodal metastasis, mitotic figures, intraepithelial melanocytic proliferation		Univariate log-rank test
				Tumor necrosis	$p = 0.04$
Mohr	2016	18	Completeness of resection		Univariate log-rank test
Moya-Plana	2019	68			Univariate log-rank test
				Paranasal vs. nasal	$p < 0.001$
Nakaya	2004	16	Margin status		Univariate log-rank test
Samstein	2017	78	Age, use of RT, gender, margin status, resection status		Multivariate HR
				Sinus vs. nasal cavity origin	3.41, $p < 0.05$
				AJCC 7th edition T stage (higher stage worse)	0.43, $p < 0.05$
				Post-RT PET standard uptake value < 4	0.24, $p < 0.05$
Shi	2010	33	Peritumoral tumor-associated macrophages density	Intratumor tumor-associated macrophages density (higher density worse)	Univariate log-rank test
					$p = 0.036$
Soares	2018	31	Age, gender, use of adjuvant therapy, tumor origin, mitotic		Multivariate HR (95% CI)

(*Continued*)

Table 1 (*Continued*)

Author	Year	*n*	Variables without survival significance	Variables with survival significance	Statical findings
			rate, vascular invasion, neural invasion, cell morphology	AJCC 7th edition stage IV vs. III	7.351 (1.392–38.821), $p = 0.019$
				High expression of p-Akt1	65.726 (6.491–665.549), $p < 0.001$
Sun	2014	65	Adjuvant RT, sex, primary tumor site, cTNM classification, CT		Multivariate HR (95% CI)
				Distant metastasis	4.428 (1.453–13.495), $p = 0.009$
				Surgery vs. no surgery	0.445 (0.235–0.842), $p = 0.013$
				Use of biotherapy	0.495 (0.260–0.943), $p = 0.032$
Swegal	2013	25	Open vs. endoscopic resection		Univariate log-rank test
Tajudeen	2014	14	Sex, treatment modality, AJCC T stage		Univariate log-rank test
				Perineural or lymphovascular invasion	$p = 0.021$
Thariat	2011	25	Age		Univariate HR (95% CI)
				En bloc resection	6.4 (1.6–25.0), $p = 0.003$
				Local control	3.4 (1.0–11.9), $p = 0.044$
Thompson	2003	115	Geographic location with respect to 40 degrees N latitude, duration of symptoms, tumor thickness, presence of fibrosis, tumor necrosis, use of adjuvant therapy		Univariate log-rank test
				Obstruction only vs. epistaxis	$p = 0.02$
				Nasopharynx tumors	$p < 0.001$
				Tumor > 3 cm	$p = 0.005$
				Undifferentiated morphology	$p = 0.033$
				>10 mitotic figures per 10 HPFs	$p = 0.026$
				Disease recurrence	$p < 0.001$
				Age > 60	$p = 0.029$
Vandenhende	2011	17	Margin status, adjuvant RT, open vs. endoscopic approach, tumor location		Univariate log-rank test
Wang	2020	35	Age, gender, MRI features, CT enhancement		Univariate log-rank test
				Paranasal vs. nasal	$p = 0.04$
				Post operative RT (worse prognosis with RT)	$p = 0.02$
				AJCC 7th edition T4 vs. T3 tumors	$p = 0.02$
Wang	2022	117	Sex, age, side, location, size, histological type, melanin particles, nuclear fission, tumor-infiltrating lymphocytes, PD-L1 expression		Univariate log-rank test
				AJCC 7th edition T stage	$p < 0.05$
Won	2015	155	Age, smoking, tumor size, morphology, presence of skip lesions, pigmentation, AJCC 7th edition T stage, AJCC 7th edition TNM stage, local recurrence, nodal recurrence, use of neck dissection,		Multivariate Cox regression, HR (95% CI)
				Male sex	2.053 (1.222–3.448), $p = 0.007$
				Sinus vs. nasal cavity origin	

Table 1 (*Continued*)

Author	Year	*n*	Variables without survival significance	Variables with survival significance	Statical findings
			adjuvant RT, adjuvant CT, adjuvant CRT		1.832 (1.102–3.044), $p = 0.020$
				Distant metastasis	1.783 (1.054–2.925), $p = 0.035$
				Open resection vs. endoscopic resection	1.702 (1.007–2.875), $p = 0.047$
Yin	2019	54	Expression of CD45, CD3, CD8, CD4, CD20, CD56, or CD68, age, sex, site, pigmentation		Multivariate HR (95% CI)
				Progression of disease	12.365 (2.290–66.779), $p = 0.003$
				Postoperative CT	0.204 (0.045–0.924), $p = 0.039$
				AJCC 8th edition stage	0.066 (0.007–0.615), $p = 0.048$
Zhu	2018	64	CD44 expression		Multivariate HR
				HER4 expression (worse prognosis)	3.51, $p < 0.05$

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; CRT, chemoradiography; CT, computed tomography; FDG-PET, fluorodeoxyglucose–positron emission tomography; MRI, magnetic resonance imaging; RT, radiotherapy; TNM, Tumour, Node, Metastasis; UICC, Union for International Cancer Control.

SNMM and concluded that there was no difference in OS, however, did find that these therapies offered an opportunity for increased progression-free survival in the salvage setting. Particularly, combination therapy such as ipilimumab plus pembrolizumab or ipilimumab plus nivolumab demonstrated the best results with progression-free survival up to 16 months in their sample. Sun et al explored the role of biotherapies, including BCG vaccine prior to 1998 and interferon-alpha versus interleukin-2 therapy after 1998 and found that there was borderline statistical significance for improved OS in patients receiving one of these therapies in the adjuvant therapies (5-yr OS 50.9%, $p = 0.076$). However, upon multivariate analysis, they found that use of biotherapy was independently a predictor of improved survival, (hazard ratio = 0.495, 95% confidence interval: 0.260–0.943, $p < 0.05$).

Recurrence of this disease proves to be the most challenging aspect in successful treatment. The propensity for distant and local recurrence contributes to the low survival rates. SNMM is not as likely to recur at regional lymph nodes; however, when SNMM does recur into the lymph nodes, its spread occurred twice as fast as distant recurrence and three times as fast as local recurrence. Nodal metastases outcomes demonstrated a mixed impact on prognosis, but multiple studies did show worse survival outcomes with nodal metastases[60] or higher TNM stage.[41,48,100] This could suggest that patients with nodal metastases present with more aggressive disease in turn warrant more aggressive treatment both locally and systemically. Given that this disease does not respect margin status, systemic treatment is likely to play a key role in disease control; however, more research is needed to support this hypothesis given the limited availability of data.

The authors acknowledge that there were several limitations of this study including reporting bias, the potential for outdated data, and grouped statistical analysis. As a systematic literature review depends upon the caliber of previously published data, it must be discussed that up to 75% of otolaryngology publications demonstrating risk for bias.[109] In particular, outcome reporting bias may be problematic, particularly in the setting of a disease that has a relatively low OS. While bias is inescapable, the authors believe that data presented in the current study provide valuable insights on a rare disease entity. Additionally, the authors limited inclusion criteria to only literature published in the year 2000 or later as to try to limit the use of outdated cases; however, some studies presented the entire cohort of SNMM experienced at a single institution that include more historic cases. Lastly, our statistical methods aimed to properly weigh and combine reported data. The median was chosen to decrease the impact of outliers; however, this was not possible for all included studies. In some cases, the mean was utilized when the median was not available. The authors felt like the inclusion of means was favorable to using median data only as to consider the highest number of cases. If assuming that data are normally distributed, the mean and median of a dataset should be approximately equal.

Conclusion

In conclusion, this meta-analysis serves as the largest study of SNMM and includes 3,347 patients. OS for SNMM remains poor with a 5-year OS of 30.35%. SNMM recurs in over 50% of patients with the most common sites of recurrence being local and distant metastases to the lung, liver, and bone. More research is needed to identify further treatment strategies toward SNMM; however, this study found the most

common approach to treatment to be combined surgery and adjuvant radiation. The role of immunotherapy shows promise to play a larger role in the treatment of SNMM in the future with the aim of improving survival.

Conflict of Interest
None declared.

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