# Sinonasal mucosal melanomas: defining profiles for better survival outcomes*

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## Abstract

**Background**: Sinonasal mucosal melanoma is an aggressive malignancy with a 5-year survival rate ranging from 20% to 39%. Despite the evolving surgical and radiotherapy techniques, and introduction of immune-checkpoint inhibitor therapy, overall survival rates remain poor.

**Methodology**: A retrospective cohort study was conducted at the Hospital Clínic de Barcelona and the Hospital de la Santa Creu i Sant Pau between 1984 and 2020; primary outcome measures were 3 and 5-year melanoma-specific survival (MSS). Kaplan-Meier survival analysis and Cox proportional hazards model were performed to identify predictors of survival.

**Results**: Fifty patients were included, the mean age was 70.4, MSS at 3 and 5 years was 51.2%, and 29.5%, respectively. The median follow-up was 39.6 months during which 46% presented locoregional recurrence and 36%, metastasis. The univariate and multivariate analyses found as survival predictors the N category, the treatment received, the surgical margins and the mitotic index.

**Conclusions**: We found an overall 5-year MSS of 29.5%. Those patients with intention-to-cure (stages III and IVa) treated by surgery that were N0 at diagnosis, with < 10 mitoses per HPF showed a 5-year MSS rate of 74.1%. More studies will be needed to adequately define the patients' profiles that will benefit from a better survival outcome.

**Key words**: sinonasal, mucosal, melanoma, survival, outcomes

## Introduction

Sinonasal mucosal melanoma (SNMM) is a rare and aggressive malignancy, represents over 50 to 70% of head and neck mucosal melanomas [1,2] that predominantly affects adults over 60 years of age with a similar gender distribution [3,4]. It has a poor prognosis with a 5-year survival rate ranging from 20% to 39% [1]. Its poor life expectancy can be attributed to the aggressive nature of the disease, the advanced stages at diagnosis, probably due to being oligosymptomatic at early stages, the lack of visibility, and the proximity to vital neurovascular structures [5]. SNMM is histologically similar to cutaneous melanoma in its positivity for the markers *S-100*, *HMB-45* and vimentin [6], and is thought to share a common cell of origin, the dendritic melanocytes [7,8]. Mucosal melanoma is genetically distinct as it harbors

*N-RAS* or *KIT* mutations more often than the *BRAF* mutations observed in cutaneous melanoma [9-11]. Furthermore, mucosal melanomas show low tumor mutational burden (2/mutations/megabase), as compared to cutaneous melanomas (13 mutations/megabase) [12]. These differences in SNMM suggest distinct neoplastic processes with potentially divergent responses to targeted therapeutics and probably more similar to less immunologically active tumor types [8].

Treatment recommendations are predominantly based on small retrospective series and extrapolated data from cutaneous melanoma studies [13]. The National Comprehensive Cancer Network (NCCN) guideline recommends surgical resection and to consider adjuvant radiation for resectable tumors [14]. Despite the evolving techniques by endoscopic approach, the introduction of conformal radiation therapy techniques, and systemic therapy options, including immune-checkpoint inhibitor therapy (ICI), overall survival (OS) rates for patients with SNMM remain poor [13].

SNMM have a median survival of 25–30 months and distant metastasis are the main limiting factor for long-term survival [15,16]. The aim of our cohort study is to find profiles of patients with better survival outcomes, and determine which factors influence this evolution.

## Materials and methods

### Study design and patients

We conducted a retrospective study of 50 consecutive SNMM patients treated at the Hospital Clínic de Barcelona and Hospital de la Santa Creu i Sant Pau (Barcelona, Spain) between July 1984 and July 2020. The inclusion criterion was the pathology confirmation of mucosal melanoma; patients with tumors that originated outside the sinonasal tract were excluded.

Patients' demographics (age and sex), lesion site (nasal cavity or paranasal sinuses), stage (III, IVa, IVb or IVc), TNM (tumor (T), lymph nodes (N), and distant metastasis (M)), treatment modalities (surgery, surgery and adjuvant radiotherapy, or palliative), surgical approach (endonasal endoscopic or open), pathologic data (melanin presence, cellularity, ulceration, mitoses, lymphovascular invasion, perineural invasion, thickness and surgical margins), and disease status were collected. All patients were re-staged according to the American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition [17]. The following dates were recorded: diagnosis, surgery, start and end of treatment, tumor recurrence, lymph node recurrence, metastasis, and last follow-up or death.

The primary outcome measures were 3 and 5-year Overall Survival (OS), melanoma-specific survival (MSS), and melanoma-free survival (MFS). Local and regional recurrence was defined by pathological confirmation presented over 6 months after the completion of treatment. Patients with high radiologic suspicion of melanoma in any cervical lymph node were considered as a regional recurrence. Metastasis was defined through pathological confirmation or highly suggestive PET/CT of SNMM metastasis. The index date was set as the first day of initial treatment. Failure in MFS was defined as any evidence of disease following completion of the initial treatment.

Targeted next generation sequencing (NGS) using Oncomine 22 or Target/DX Focus comprehensive assay were performed including *AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FGFR3, KRAS, MAP2K1, MET, NOTCH1, NRAS, PIK3CA, PTEN, SMAD4, STK11* and *TP53* genes.

The research study was reviewed and approved by the Ethical Committee of the institution (HCB/2020/1454) and conformed to the principles outlined in the Declaration of Helsinki.

### Statistical analysis

Mean and standard deviation was described for variables with normal data obtained by Shapiro-Wilk test. Median with interquartile range (IQR) was obtained for survival time.

MSS was described for the categorical variables (age, sex, tumor location, T, N, M, stage, first line treatment, surgical approach, surgical margins, and treatment period), 95% confidence interval of the proportions was obtained by Wilson methods. The $\chi^2$ test was used to evaluate the relationship between categorical variables.

A Kaplan-Meier survival analyses by stages was performed in all patients for MSS and MFS, and by hospital for MSS. Differences in survival rates were compared using the log-rank test.

The Cox proportional hazards model was used in the univariate and multivariate analyses to identify factors that were predictive of survival. MSS was considered as the dependent variable, and T (T3 vs. T4a), N (N0 vs. N1), first line treatment (surgery vs. surgery and radiotherapy), mitoses (<10 vs ≥10 per HPF), and surgical margins (positive vs. negative) as the independent variables. Patients with T4b tumors or metastasis and those undergoing palliative treatment were excluded. The variable profile was defined according to MSS using the Classification and Regression Tree (CRT) method. Variables to generate the regression tree included the T category, N category, treatment, and mitoses. CRT analysis splits the data into segments that are as homogeneous as possible regarding the dependent variable. The MSS according to the variable profile was calculated using the Kaplan–Meier method. Differences in survival rates were compared using the log-rank test.

All statistical testing was two-tailed. Alpha was set to 0.05 for significance. All statistical analyses were made using STATA software v.16.1 (StataCorp, TX, USA).

## Results

### Characteristics of the patients

Fifty patients were included in the study, 27 (54.0%) from Hospital Clínic de Barcelona (HCB) and 23 (46.0%) from Hospital de

Table 1. Characteristics of the study cohort by hospital.

| Characteristics | Hospital Clínic de Barcelona | Hospital de la Santa Creu i Sant Pau | p-Value |
|---|---|---|---|
| Age (years) | | | 0.455 |
| Media (SD) | 69.2 (2.6) | 71.9 (2.3) | |
| Sex | | | 0.982 |
| Female, N (%) | 14 (51.9) | 12 (52.2) | |
| Tumor location, N (%) | | | 0.586 |
| Nasal cavity | 12 (44.4) | 12 (52.2) | |
| Paranasal sinuses | 15 (55.6) | 11 (47.8) | |
| T category, N (%) | | | *0.034 |
| T3 | 11 (40.7) | 11 (47.8) | |
| T4a | 14 (51.9) | 5 (21.7) | |
| T4b | 2 (7.4) | 7 (30.4) | |
| N category, N (%) | | | 0.318 |
| N0 | 22 (81.5) | 21 (91.3) | |
| N1 | 5 (18.5) | 2 (8.7) | |
| M category, N (%) | | | 0.124 |
| M0 | 22 (81.5) | 22 (95.7) | |
| M1 | 5 (18.5) | 1 (4.4) | |
| Stage, N (%) | | | 0.137 |
| III | 11 (40.7) | 11 (47.8) | |
| IVa | 9 (33.3) | 5 (21.7) | |
| IVb | 2 (7.4) | 6 (26.1) | |
| IVc | 5 (18.5) | 1 (4.4) | |
| Treatment, N (%) | | | *<0.001 |
| Surgery | 19 (70.4) | 2 (8.7) | |
| Surgery and RT | 3 (11.1) | 17 (73.9) | |
| Palliative | 5 (18.5) | 4 (17.4) | |
| Surgical approach, N (%) | | | 0.436 |
| Endoscopic | 14 (53.9) | 8 (42.1) | |
| Open | 12 (46.2) | 11 (57.9) | |

SD, standard deviation; RT, radiotherapy. Stage using American Joint Committee on Cancer (AJCC) Staging Mucosal Melanoma of the Head and Neck, 8th edition. *, Differences were considered statistically significant at $p < 0.05$.

la Santa Creu i Sant Pau (HSCSP). The age of the patients ranged from 40 to 95 years old (mean= 70.4, SD= 12.5) and the male/female ratio was 1:1.1 (Table 1). The median follow-up was 39.6 months (IQR= 78.5).

The median of time from diagnosis to first treatment was 30 days (IQR= 45). The period of treatment was categorized in 1984-2006, 2007-2014 and 2015-2020 considering the introduction of endoscopic surgical techniques for the second period, and the introduction of ICI therapy for SNMM in the third.

All patients were evaluated by an oncologic committee in both centers. There were no differences by stage in both hospitals with $\chi^2= 5.5$ ($p= 0.137$), nor in Kaplan-Meier survival analyses by Hospital for MSS ($p= 0.126$) (Figure 1). However, there were differences in the decision of the oncologic board when considering adjuvant RT. In the HCB, 19 (70.4%) patients underwent surgery, and 3 (11.1%) went through adjuvant RT and 5 (18.5%) received palliative treatment. Patients staged T3 and T4a without multifocality were considered resectable and underwent extended surgery. Tumor debulking was considered for those in which, due to the tumor's extension, the resection would imply a high morbidity. In contrast, HSCSP, with 2 (8.7%) patients receiving only surgery, 17 (73.9%) undergoing adjuvant RT and 4 (17.4%) palliative treatment, focused on less morbid surgery and adjuvant RT in all patients although the resection margins

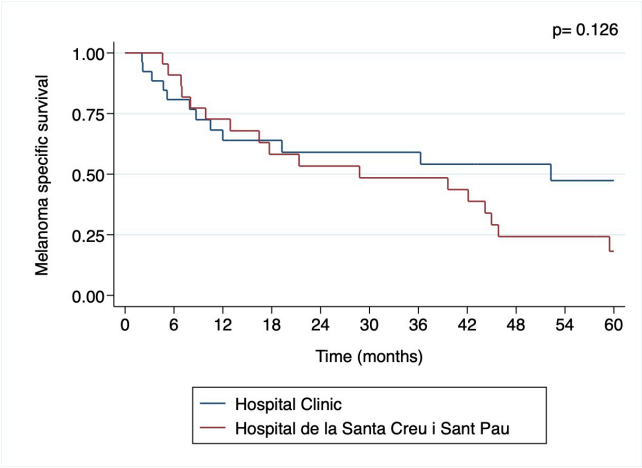


Figure 1. Kaplan-Meier survival analyses of the entire cohort grouped by Hospital. 5-year melanoma-specific survival. * p < 0.05, statistically significant.

were negative having into account the aggressiveness of these tumors. The median Gy (gray) dose reached was 53 (IQR= 10) with a mean of 30 fractions (IQR= 8). Hypofractionated radiation therapy was administered until 2011, when intensity-modulated radiation therapy (IMRT) was introduced.

Seventeen (34.0%) preoperative PET/CT were performed with a tumor SUV (Standard uptake value) mean of 13.3 (SD=8.9).

Targeted next generation sequencing (NGS) using Oncomine 22 or Target/DX Focus comprehensive assay were performed in 12 patients being *N-RAS* the most frequent mutation identified with 4 (33.3%), 2 (16.7%) for *C-KIT*, and 1 (8.3%) for each of *MYC, PIK3CA, K-RAS*, and *MET*. The *BRAF* V600 mutation was ruled out in 23 patients by either NGS or RT-PCR (cobas 4800 *BRAF* V600 mutation test). Due to the limited number of patients, the prognostic value of PET avidity and mutational spectra could not be assessed.

The characteristics of the study cohort, including univariate analysis data of MSS, are described in Table 2. Homogeneous distribution was found for age, sex, tumor location, T, and M with no differences for MSS.

Statistically significant differences were found for staging, N category, treatment period, surgical margins and first-line of treatment. Nevertheless, in multivariate analysis by treatment period, staging, N and treatment, the treatment periods do not show any differences (p= 0.963).

Since the introduction of ICI by Clinical trials 12 (24.0%) patients have received treatment during the progression of their disease (8 Nivolumab, 2 Ipilimumab, and 2 Pembrolizumab).

### Pathological characteristics of the sample

Histological confirmation of mucosal melanoma was obtained in all patients. The melanin absence/presence ratio was 1:2, and the most frequent cellularity was epithelioid. Ulceration was present in over 90% of the cohort. On the contrary, there were few findings of perineural invasion. Surgical Margins were analyzed and categorized by positive (30.4%), negative (32.6%) or not evaluable (37%). The summary of the histological description is shown in Table 3.

Mitoses are a known prognostic factor in cutaneous melanoma. To date, there is no consensus on the guidelines that should be delivered in the mucosal melanomas' reports. We categorized the mitoses by 10 or more mitoses per high-power fields (HPF) based on the SNMM experience published by Moreno et al. in the MD Anderson Cancer Center [18]. Thickness was excluded

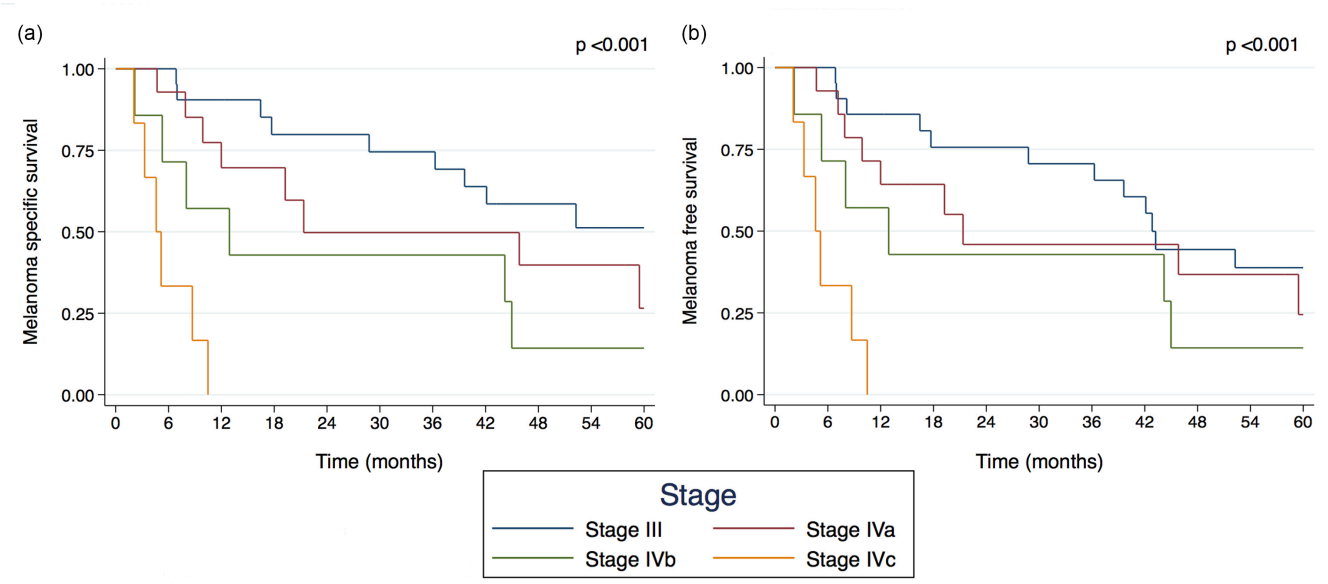


Figure 2. Kaplan-Meier survival analyses of the entire cohort grouped by stage. (a) 5-year melanoma-specific survival; (b) 5-year melanoma-free survival. * p < 0.05, statistically significant.

Table 2. Characteristics of the study cohort including univariate analysis data of disease-specific survival.

| Characteristics | Num. Patients (%) | Melanoma-Specific Survival % (95% CI) | p-Value |
|---|---|---|---|
| Age (years) | | | 0.478 |
| <70 | 24 (48.0) | 37.5 (21.2-57.3) | |
| ≥ 70 | 26 (52.0) | 28.0 (14.3-47.6) | |
| Sex | | | 0.755 |
| Male | 24 (48.0) | 30.4 (15.6-50.9) | |
| Female | 26 (52.0) | 34.6 (19.4-53.8) | |
| Tumor location | | | 0.478 |
| Nasal cavity | 24 (48.0) | 37.5 (21.2-57.3) | |
| Paranasal sinuses | 26 (52.0) | 28.0 (14.3-47.6) | |
| T category | | | 0.063 |
| T3 | 22 (44.0) | 45.5 (26.9-65.3) | |
| T4a | 19 (38.0) | 31.6 (15.4-54.0) | |
| T4b | 9 (18.0) | 0 (0.0-32.4) | |
| N category | | | *0.047 |
| N0 | 43 (86.0) | 38.1 (25.0-53.2) | |
| N1 | 7 (14.0) | 0 (0.0-35.4) | |
| M category | | | 0.069 |
| M0 | 44 (88.0) | 37.2 (24.4-52.1) | |
| M1 | 6 (12.0) | 0 (0.0-39.0) | |
| Stage | | | *0.035 |
| III | 21 (42.9) | 45.5 (26.9-65.3) | |
| IVa | 14 (28.6) | 42.9 (21.4-67.4) | |
| IVb | 8 (16.3) | 0 (0.0-35.4) | |
| IVc | 6 (12.2) | 0 (0.0-39.0) | |
| Treatment | | | *0.001 |
| Surgery | 21 (42.0) | 61.9 (40.9-79.2) | |
| Surgery and RT | 20 (40.0) | 15.0 (5.2-36.0) | |
| Palliative | 9 (18.0) | 0 (0.0-32.4) | |
| Surgical approach | | | 0.092 |
| Endoscopic | 22 (48.9) | 45.5 (26.9-65.3) | |
| Open | 23 (51.1) | 21.7 (9.7-41.9) | |
| Surgical Margins | | | *<0.001 |
| Negative | 15 (32.6) | 80.0 (54.8-93.0) | |
| Positive | 14 (30.4) | 21.4 (7.6-47.6) | |
| Non-evaluable | 17 (37.0) | 5.9 (1.0-27.0) | |
| Treatment period | | | *0.002 |
| 1984-2006 | 18 (36.0) | 11.1 (3.1-32.8) | |
| 2007-2014 | 17 (34.0) | 25.0 (10.2-49.5) | |
| 2015-2020 | 15 (30.0) | 66.7 (41.7-84.8) | |

CI, confidence interval; RT, radiotherapy. Stage using American Joint Committee on Cancer (AJCC) Staging Mucosal Melanoma of the Head and Neck, 8th edition. *, Differences were considered statistically significant at $p < 0.05$.

from our prognostic analyses because the real and confident thickness is difficult to determine since in these patients the samples are often fractionated [19].

Table 3. Summary of the histological description of the sample.

| Characteristics | Num. Patients (%) |
|---|---|
| Melanin presence | 21 (65.6) |
| Ulceration | 27 (93.1) |
| Perineural invasion | 1 (3.5) |
| Lymphovascular invasion | 15 (51.7) |
| Mitoses ≥ 10 HPF | 9 (31.0) |
| Tumor thickness ≥ 5 mm | 14 (58.3) |
| Cellularity | |
| Epithelioid | 19 (59.4) |
| Fusiform | 7 (21.9) |
| Others | 6 (18.7) |
| Surgical Margins | |
| Negative | 15 (32.6) |
| Positive | 14 (30.4) |
| Unknown / Not evaluable | 17 (37.0) |

HPF, high power fields; mm, millimeters.

### Survival analyses of the patients

All patients (from all AJCC stages, including IVc) were included for Kaplan-Meier survival analyses.

Overall survival at 3-years was 49.8% (95%CI= 34.5-63.3), and 26.1% (95%CI= 13.5-40.6) at 5-years. Melanoma-specific survival at 3-years was 51.2% (95%CI= 35.7-64.8), and 29.5% (95%CI= 15.9-44.5) at 5-years (Figure 2A). Finally, Melanoma-free survival at 3-years was 48.5% (95%CI= 33.5-62.0), and 24.9% (95%CI= 13.0-38.7) at 5-years (Figure 2B). Locoregional recurrence was present in 23 (46.0%) patients, and distant metastasis in 18 (36.0%). The median of time to locoregional recurrence was 23.0 months (IQR= 23.7), and 13.9 months (IQR= 21.1) for distant metastasis. We found no significant differences in Kaplan-Meier survival analyses by staging for locoregional-free survival and distant metastasis-free survival (p= 0.942 and p= 0.363, respectively) (Figure 3).

### Univariate and multivariate cox regression analyses

To evaluate prognostic factors in patients treated with curative intention, patients with T4b tumors or metastasis, and those with palliative treatment have been excluded of the analyses. The univariate and multivariate Cox proportional hazards model found as survival predictors the treatment, and the mitoses (Table 4).

### Classification and regression tree for melanoma-specific survival

Subsequently, we aimed to analyze the effects of the different prognostic factors found in the univariate analyses on the MSS. Classification and regression tree for MSS by T, N, treatment and mitoses and showed three profiles of patients, being those that underwent surgery and less than 10 HPF mitoses the ones with the best prognosis compared to those with more than 10 mitoses or adjuvant radiotherapy (Figure 4A). Herewith, we presented the Kaplan-Meier according to the categorized patient profiles with significant differences for profile 1 (Surgery and mitoses <10 HPF) with a 5-year MSS rate of 74.1% (95%CI= 28.9-93.0) compared to the other profiles of patients (profile 2 and 3) for whom 5-year MSS rate was 24.7% (95%CI= 8.0-46.3) (Figure 4B).

Table 4. Prognostic factors of melanoma specific survival in univariate and multivariate cox regression analyses [1].

| Variables | Categories | HR | 95% CI | p-Value |
|---|---|---|---|---|
| **Univariate Model** | | | | |
| T category[2] | T3 vs. T4a | 1.7 | 0.7-4.3 | 0.281 |
| N category[2] | N0 vs. N1 | 17.2 | 2.8-104.2 | *0.002 |
| Treatment | Surgery vs. Surgery and RT | 3.9 | 1.4-11-0 | *0.010 |
| Mitoses | <10 vs. ≥ 10 HPF | 5.9 | 1.4-24.5 | *0.014 |
| Surgical Margins | Positive vs. Negative | 1.8 | 1.0-3.0 | *0.045 |
| **Multivariate Models** | | | | |
| N category | N0 vs. N1 | 10.2 | 0.4-302.4 | 0.178 |
| First line treatment | Surgery vs. Surgery and RT | 10.9 | 1.2-101.0 | *0.036 |
| Mitoses | <10 vs. ≥ 10 HPF | 8.26 | 1.1-64.7 | *0.044 |
| Surgical Margins | Positive vs Negative | 2.4 | 0.6-0.6 | 0.231 |

Dependent variable: Melanoma specific survival. Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; HPF, high power fields. * $p < 0.05$, statistically significant. [1] Patients with T4b tumors or metastasis and those with palliative treatment have been excluded. [2] T and N category using American Joint Committee on Cancer (AJCC) Staging Mucosal Melanoma of the Head and Neck, 8th edition.

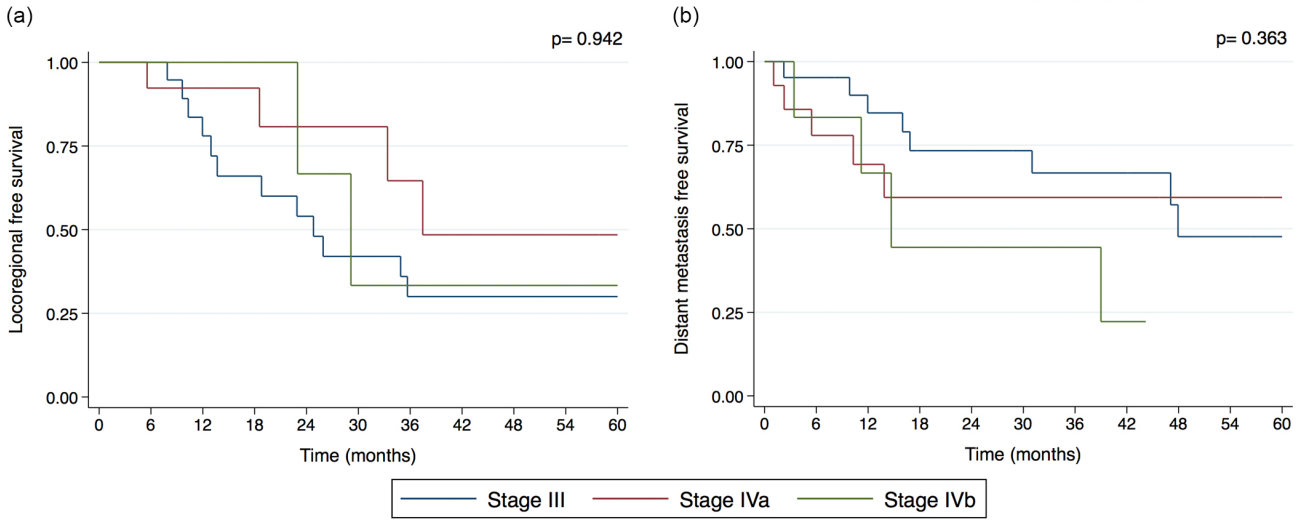


Figure 3. Kaplan-Meier survival analyses grouped by stage. (a) 5-year locoregional free survival; (b) 5-year distant metastasis free survival. * $p < 0.05$, statistically significant.

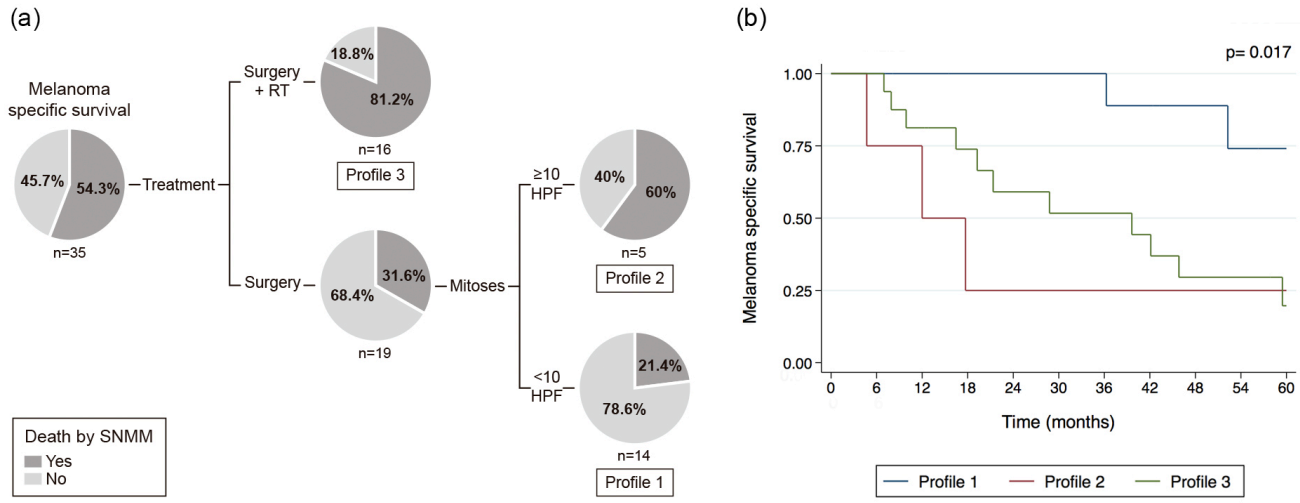


Figure 4. First line treatment and mitoses are associated with the melanoma-specific survival. (a) Classification and regression tree for melanoma-specific survival (MSS) rates based on the treatment and mitoses. Variables included were: T category, N category, treatment, and mitoses. Pie charts represent the proportion of patient death by disease. Yes includes patients dead by tumor, No those who were not dead at the last follow-up; (b) Kaplan-Meier survival analysis and log-rank showing MSS according to the categorized patient profiles. Abbreviations: SNMM, Sinonasal mucosal melanoma; RT, radiotherapy; 10 per HPF, high power fields. * Patients with T4b tumors or metastasis and those with palliative treatment have been excluded. **, Differences were considered statistically significant at $p < 0.05$.

## Discussion

With a 5-year OS rate of 26.1% and 5-year MSS of 29.5%, our results confirm the poor prognosis widely described in literature on SNMM and match with the recent database published by Ganti et al. with 1874 SNMM patients with a 5-year overall survival of 24% [20]. Age and gender did not affect the prognosis in our cohort; similar results were obtained by Jangard et al., as well as in the multivariate analyses performed by Konuthula et al. (p=0.76) [5,21].

Flukes et al. evaluate the SNMM survival by comparing 3 periods of time: the first historical, the second marked by the introduction of endoscopic surgery and the third with the initiation of ICI therapies in their center [13]. We have replicated their analysis in our cohort. Although in the univariate analyses differences are seen in favor of recent years, these are not significant in the multivariate when correcting for stage.

Concerning the surgical approach, we found no differences in the univariate analysis. These findings are validated by studies comparing endoscopic versus open approaches, showing that, although endoscopy offers less morbidity, it has no effect on

survival [22,23].

Another sub-analysis to consider was the treatment period related to the introduction of ICI therapies. Although at present we have not seen differences in survival in our cohort, patients receiving these therapies have been in the light of Clinical Trials addressing advanced or metastatic mucosal melanomas. However, ICI has recently been approved as adjuvant therapy for cutaneous and mucosal melanomas [24]. Future analyses should be performed to assess whether the use of ICI as adjuvant therapy improves the prognosis of SNMM.

Contrary to what is mostly reported in the literature [20,25,26], we did not find prognostic differences due to tumor location. We believe this might be a classification bias since it is difficult to determine the real tumor extension and which of them exclusively involve the nasal cavity. Another hypothesis is that the tumor's location does not alter prognosis, as has been described by Manton et al. [27] this might be related to the extensive experience in the management of pathologies in the paranasal sinuses and skull base.

In accordance with the above, we did not find differences in locoregional recurrence for III versus IV stages (p=0.942), neither for distant metastasis (p=0.363). Locoregional recurrence was found in 46.0% of patients with a median time of 23.0 months. Distant metastases were found in 36.0% with a median time of 13.9 months. Similar survival rates were seen in patients with stages III and IVa, and catastrophic poor prognosis with no 5-year survival rates for IVb and IVc stages. These findings agree with those published by Amit et al. where, the presence of distant metastasis was the most common factor of treatment failure leading to a poor OS rate [15].

A Cox regression was performed to analyze which prognostic factors may imply a better survival in the cohort of patients with intention-to-cure, in those patients with T3 or T4a, N0 or N1 tumors. We found that the variables that most influenced the MSS were the N category at diagnosis, ≥ 10 mitoses per HPF, surgical margins and the treatment received. The profile of patients with better survival included those that underwent surgery with <10 mitoses per HPF, for which the 5-year MSS rate was 74.1% (95%CI= 28.9-93.0) with significant differences compared to the other profiles of patients for whom 5-year MSS rate was 24.7% (95%CI= 8.0-46.3).

The mitotic index has been a prognostic factor for cutaneous melanoma until the recent 8th edition of the AJCC when it was removed [28]. Concerning mucosal melanomas, Prasad et al. proposed a microstaging, based on the depth of invasion as histologic predictors of survival, however they did not include mitoses in their analyses [29]. Moreno et al. described that the presence of 10 or more mitosis per HPF appeared to be an outcome predictor that reached borderline statistical significance (P=0.0619) [18]. Furthermore, Amit et al. found a significantly higher rate of mitosis in mutated tumors compared to non-mutated (63% vs 31% had mitosis ≥1 mm-2 respectively, p=0.01). Nevertheless, in their univariate analysis comparing patients with and without detected mutations showed no association of mutation status with the OS, although no direct analysis of mitoses was performed [11]. Further studies are needed to elucidate the association of the mitotic index and the prognosis in SNMM together with establishing the cut-off point of mitosis per HPF that might be related to a worse OS.

Concerning the treatment, Li et al. performed a meta-analysis of the prognostic impact of postoperative adjuvant RT concluding that RT was improving locoregional control without neither reducing the risk of distant metastasis nor finding differences in the OS [30]. In our cohort, those that underwent less extended surgery plus adjuvant RT had worst MSS compared to those that underwent radical surgery without adjuvant therapy. These findings should be analyzed with precaution because selection bias for more aggressive disease may be present among patients chosen for RT, although no differences were found by staging comparing patients with or without adjuvant RT. However, other variables that might have been considered, such as global patients' status, surgeon's appreciation of the intervention, ability to resect and to obtaining adequate margins, are difficult to analyze in a retrospective cohort.

Some authors have proposed moving away from radical surgery for patients with orbital or intracranial extension of the disease, arguing that the high rate of distant metastases does not justify a highly morbid surgery [13]. We agree with them considering the poor prognosis we found on T4b tumors. Nevertheless, our results showed that a wide surgical resection could improve overall survival in those T3 and T4a resectable tumors.

Following the same line, our patients with negative surgical margins showed better survival outcomes. These results are in accordance with Elsamna et al. [4] that analyzed the surgical margin status in SNMM, showing that negative surgical margins had better survival rates than positive ones, but no differences were found between positive surgical margins and patients without surgery, emphasizing the importance of patient selection and wide surgical resection to achieve a gross total tumor resection. However, real and reliable surgical margins are difficult to determine in endoscopic samples because the surgery often requires the resection of multiple separate samples. Samstein et al. exposed the difficulty in determining the margin status in SNMM, given the three- dimensional cavity and the complex resection near vital structures that may contribute to the variability in outcomes based on margin status [31]. Furthermore, Chiu et al. studied the accuracy of intraoperative frozen margins for SNMM explaining the difficulty in these tumors to obtain reliable margins due to their highly variable macroscopic and histological appearance, and the need for immunohistochemical staining to distinguish residual tumor cells from normal mucosal cells [19].

The limitations of our study are those of a retrospective study,

with the lack of accuracy of the data. However, we have gathered a cohort with no missing clinical data and in the histological analysis all the available samples were re-analyzed for the described variables. Despite this, there were samples that could not be retrieved.

We believe that it is essential to identify those profiles of patients who might benefit from more extended and aggressive surgery with adequate resection, to avoid radical surgery for those whose profile will not benefit from such a procedure. Further studies are needed to better identify patterns of disease and treatment failure to determine profiles of patients who might benefit from different treatment options.

## Conclusion

Sinonasal mucosal melanoma is an aggressive malignancy with a poor prognosis with a 5-year melanoma-specific survival of 29.5%, a 46% of locoregional recurrence rate with a median time of 23.0 months, and distant metastasis of 36% with a median time of 13.9 months. This systemic involvement of the disease encourages future studies on adjuvant ICI therapy to achieve improvements in survival.

The presence of 10 or more mitoses per HPF and treatment received were prognostic factors for survival in those patients with intention-to-cure (stages III and IVa). This analysis allowed us to find the patients with better survival profiles who would benefit from a wide surgical resection. We found a 5-year MSS rate of 74,1% in those that were N0, had a rate of <10 mitoses per HPF and underwent extended surgery. More studies will be needed to adequately define the patients' profiles that might benefit from different treatment options to increase the survival outcomes.

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## Authorship contribution

Conceptualization, MJR-L, CL and SPu; methodology, MJR-L, FXA-J; formal analysis, MJR-L, FXA-J; data curation, MJR-L, JRG-C, PC, SPo; writing-original draft preparation, MJR-L; writing-review and editing, CL, FXA-J, JRG-C, PC, AB, ML-C, AMA, MB, IA, JM; supervision, CL and SPu; project administration, CL and SPu. All authors have read and agreed to the published version of the manuscript.

## Conflict of interest

The authors declare no conflict of interest.

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