



# Sinonasal Mucosal Melanoma: A Population-based Comparison of the EUROCARE and SEER Registries

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## Abstract

**Introduction** Sinonasal melanomas are rare tumors with no comparative survival studies between Europe and the US.

**Objective** To provide a population-based survival analysis between the two continents.

**Methods** The European Cancer Registry (EUROCARE) and the United States Surveillance, Epidemiology, and End Results (SEER) databases were queried to identify patients diagnosed with sinonasal melanoma between 2000 and 2007. Relative survival (RS) data were grouped by age, gender, geographic region, extent of disease, and treatment modality.

**Results** A total of 1,294 cases were identified between 2000 and 2007 (935 from EUROCAR-5 and 359 from SEER). Females were most commonly identified in Europe (56.4%) and in the US (54.9%). Patients over the age of 65 years comprised the greatest proportion of patients in Europe (70%) and in the US (71%). By region, Southern Europe had the highest 5-year RS (31.6%, 95% confidence interval [CI] = [21.3–42.5%]), and Eastern Europe the lowest (16.5%, [7.5–28.5%]). The aggregate European 5-year RS was 25.4% [21.8–29.1%] and the U.S. was (29.7%, [23.6–36%]).

**Conclusions** Although increasing in incidence, sinonasal melanomas remain rare. Women were more commonly affected. The most common age group was those older than 65 years, although age did not confer a prognostic value. The most common subsite was the nasal cavity followed by the maxillary sinus. Five-year RS was similar between continents with an inverse relationship between extent of disease and survival. The treatment of choice throughout Europe and the US remains primarily surgical.

## Keywords

- SEER program
- melanoma
- registries

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## Introduction

Mucosal melanoma is a group of malignant neoplasms that arise from the melanocytes of mucous membranes. They can originate in the mucous membranes of the nasal cavity, paranasal sinuses, oral cavity, esophagus, anus, and urogenital tract.<sup>1</sup> On the other hand, cutaneous melanoma is a group of neoplasms arising from melanocytes in the basal layer of the epidermis. Mucosal melanomas of the head and neck are much rarer than cutaneous melanomas, representing less than 1% of all melanomas.<sup>2</sup>

In Europe and in the United States (US), the head and neck are the most common sites for mucosal melanomas.<sup>1</sup> They represent 40.6% of mucosal melanomas in Europe and 55.4% of mucosal melanomas in the US.<sup>1</sup> Among head and neck mucosal melanomas, the sinonasal tract is the most common site in both populations.<sup>2,3</sup> Sinonasal mucosal melanomas (SNMMs) usually present with nonspecific signs and symptoms like epistaxis, facial pain, nasal discharge, and obstruction.<sup>3</sup> Advanced stage tumors may present with more severe signs and symptoms, like skin ulceration, ophthalmoplegia, and exophthalmos.<sup>3</sup>

The pathogenesis of mucosal melanomas, as opposed to cutaneous melanomas, is poorly understood.<sup>3</sup> Genetic mutations in mucosal melanoma were found to be different from those observed in cutaneous melanomas. Compared with cutaneous melanomas, mutations in the proto-oncogene BRAF are much rarer in mucous melanomas and found only in 5% of the cases.<sup>3</sup> The difference in the underlying genetic mutations means that mucosal melanomas may be an entirely different entity compared with their cutaneous counterparts.

In general, surgical treatment is the main modality of treatment for mucosal melanomas of the head and neck despite the lack of randomized trials supporting the surgical approach.<sup>3</sup> Postoperative radiotherapy is recommended for most patients, and primary radiotherapy is recommended for patients who decline surgery or have inoperable tumors.<sup>3</sup>

The prognosis of head and neck mucosal melanomas is usually poor due to the high rates of relapse.<sup>3</sup> Studies have shown that many factors influence the prognosis such as degree of pigmentation, gender, and the presence of distant metastasis.<sup>3</sup>

## Objective

In the present study, we attempted to determine if geographical location, anatomical subsite, extent of disease (EoD), and treatment modality also affect survival rates of SNMMs. We used the European population-based cancer registry (EUROCARE) database to report the survival rates for SNMMs in Europe between 2000 and 2007. We, then, compared the survival rates among European regions to determine if there are significant differences among them. Finally, the European survival rates were compared with the US survival rates obtained from the United States' Surveillance, Epidemiology, and End Results (SEER) database.

## Methods

We used the SEER and EUROCARE population-based databases to determine the frequency and 5-year relative survival (RS) rates. The SEER database covers ~ 28% of the US population and includes data from 18 states/metropolitan areas. Data are subject to rigorous quality control studies and various assessments. EUROCARE-5, the latest version of EUROCARE, contains data on cancers diagnosed between 2000 and 2007. It includes 116 registries from 30 different European countries and reports ~ 50% of new cancer diagnoses in the European population.<sup>4</sup> The percentage of the population covered for each European region varies and has been reported in previous studies.

### Tumor Selection

The *International Classification of Disease for Oncology 3* (ICD-O-3) morphological codes corresponding to melanomas (8720–8790), and the topographical codes corresponding to the nasal cavity and paranasal sinuses (C30.0, C31.0–C31.9) were used to select SUMM. Patients younger than 15 years old were excluded. All death certificate-only (DCO) patients were excluded. The data concerning the treatment modalities and extent of disease were not uniformly available in the EUROCARE registries; therefore, they were reported only for registries that had < 30% of unknown data. For Europe, registries with a percentage of unknown data < 30% for treatment and extent of disease (EoD) were selected. The nine registries that had adequate EoD information were Austria; Estonia; Finland; Cracow, in Poland; Slovakia; Slovenia; Basque Country, in Spain; and Geneva and St. Gallen, in Switzerland. The 14 registries that had adequate treatment information were the Bulgaria; Estonia; Finland; Brandenburg; Saxony and Mecklenburg-Vorpommern, in Germany; Alto Adige and Biella, in Italy; Latvia; Norway; Kielce, in Poland; Slovakia; Navarra, in Spain; and England registries.

The EoD was classified based on the EUROCARE definitions: localized (confined to the site of origin), regional (the tumor has spread locally to the immediately adjacent tissue and/or to regional lymph nodes), metastatic (the tumor has spread to distant organs), and unknown.<sup>5</sup>

Subgroup analyses were performed by geographical region, age, gender, anatomical subsite of the tumor (nasal cavity; maxillary, sphenoid, ethmoid, frontal, overlapping, and accessory sinus NOS), extent of disease (localized, regional, or distant) and treatment modality (surgery and radiotherapy, surgery only, radiotherapy only, or neither).

The expected cumulative survival (ECS) was calculated through the Ederer II method while the overall survival (OS) was calculated through the actuarial method. Finally, the relative survival (RS) was calculated by dividing OS by the ECS.

According to the policies of the institutional review board (IRB), this study did not require IRB approval since the EUROCARE and the SEER databases do not contain patient identifying information.

## Results

A total of 1,294 cases of sinonasal melanoma were identified from both databases between the years 2000 and 2007 (935 from EUROCARE-5 and 359 from SEER). Demographic distributions are displayed in ►Table 1. By age group, patients aged 65 years and older represented the highest proportion of cases amongst all regions (70% of cases in Europe and 71% in the United States). More cases involved females in both Europe and the United States (56.4% and 54.9% respectively). The nasal cavity and the maxillary sinus were the most commonly involved subsites in Europe (83.4% and 7.3% respectively). A similar trend was observed in the United States, with 65.2% of cases found primarily in the nasal cavity versus 15.9% in the maxillary sinuses.

The 5-year relative survival rates are demonstrated in ►Fig. 1. Overall, European survival rates were comparable the United States (25.4% [21.8–29.1%] and 29.7% [23.6–36%], respectively). Within Europe, the southern countries demonstrated the highest rate at 31.6% (21.3–42.5%), while the eastern countries displayed the worst survival at 16.5% (7.5–28.5%).

Demographic distributions for all geographic regions are listed in ►Table 2. Survival ranged widely between age groups and locations. In Europe, overall, patients aged 55 to 64 years and 65 to 74 years had the best survival, at 30.1%, while those over the age of 75 years demonstrated the worst 5-year survival, at 19.6% (14.1–25.8%). In the United States, patients aged 15 to 44 years displayed the best survival, at

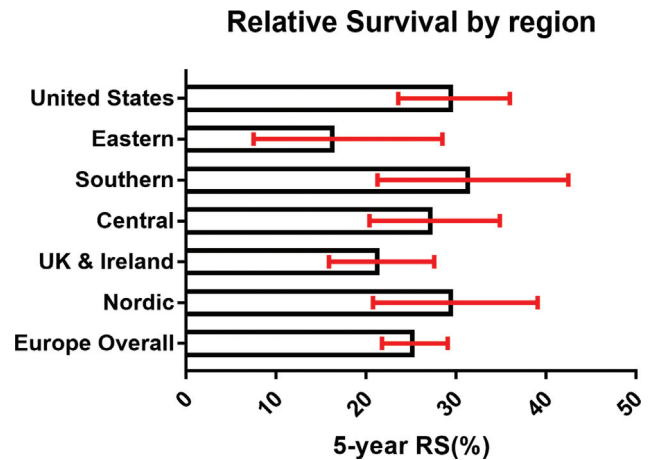


Fig. 1 5-year relative survival by region.

53.6% (26.4–74.7%), while those aged 45 to 54 years demonstrated the worst, at 20.4% (6.3–40.1%). No statistically significant disparities between males and females were seen in Europe, overall, or the United States.

When grouped by subsite, the nasal cavity, overall, provided the best prognosis in Europe (27.9% [23.9–32.2%]) and in the United States (33.3% [25.4–41.4%]); however, with no statistically significant difference between the two continents. The sphenoid sinus had the highest survival in Southern Europe (50.4% [0.6–91.4%]), although the validity of these data are questionable given the large confidence interval.

Table 1 Demographic and subsite distribution by European region and United States

N (%)	Europe Overall	Nordic	UK & Ireland	Central	Southern	Eastern	United States
Total	935 (100)	166 (100)	342 (100)	252 (100)	106 (100)	69 (100)	359 (100)
Age groups							
15–44 years	26 (23)	3 (2)	5 (2)	7 (3)	6 (6)	5 (7)	15(4)
45–54 years	77 (8)	17 (10)	25 (7)	23 (9)	7 (7)	5 (7)	26 (7)
55–64 years	177 (19)	29 (18)	63 (18)	44 (18)	22 (21)	19 (28)	63 (18)
65–74 years	236 (25)	45 (27)	80 (23)	69 (27)	23 (22)	19 (28)	77 (21)
75+ years	419 (45)	72 (43)	169 (49)	109 (43)	48 (45)	21 (30)	178 (50)
Gender							
Male	408 (44)	67 (40)	155 (45)	108 (43)	54 (51)	24 (35)	162 (45)
Female	527 (56)	99 (60)	187 (55)	144 (57)	52 (50)	45 (65)	197 (55)
Subsite							
Nasal cavity	780 (83)	135 (81)	305 (89)	195 (77)	94 (89)	51 (74)	234 (65)
Maxillary sinus	68 (7)	12 (7)	19 (6)	25 (10)	5 (5)	7 (10)	57 (16)
Sphenoid sinus	2 (0.2)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	29 (8)
Ethmoid sinus	32 (3)	6 (4)	15 (4)	8 (3)	2 (2)	1 (1)	2 (1)
Frontal sinus	5 (1)	0 (0)	2 (1)	3 (1)	0 (0)	0 (0)	8 (2)
Overlapping lesion†	15 (2)	1 (1)	0 (0)	7 (3)	2 (2)	5 (7)	9 (3)
Accessory sinus, NOS	33 (4)	12 (7)	1 (0.3)	14 (6)	1 (1)	5 (7)	20 (6)

Abbreviation: NOS, not otherwise specified.

†= of accessory sinus.

**Table 2** Relative survival by demographics and subsite

5-year RS (LL-UL)	Europe overall	Nordic	UK & Ireland	Central	Southern	Eastern	United States
Overall	30% (21–39%)	22% (16–28%)	27% (20–35%)	32% (21–43%)	17% (8–29%)	30% (24–36%)	22% (16–28%)
Age							
15–44 years	28% (11–48%)	67% (5–95%)	30% (1–72%)	19% (1–56%)	n.e.	0%	54% (26–75%)
45–54 years	26% (15–38%)	25% (7–50%)	23% (7–44%)	28% (10–50%)	39% (6–72%)	31% (1–73%)	20% (6–40%)
55–64 years	30% (23–38%)	38% (20–56%)	31% (19–44%)	28% (14–43%)	25% (9–45%)	n.e.	
65–74 years	30% (23–38%)	20% (8–36%)	30% (18–44%)	39% (25–54%)	34% (13–55%)	15% (3–38%)	22% (13–34%)
75+ years	20% (14–26%)	33% (17–51%)	11% (5–19%)	20% (10–34%)	30% (14–48%)	13% (2–34%)	31% (21–42%)
Gender							
Male	22% (17–27%)	16% (6–29%)	20% (12–29%)	28% (18–39%)	26% (13–41%)	n.e.	27% (19–37%)
Female	29% (24–34%)	39% (26–50%)	23% (15–31%)	27% (17–37%)	37% (22–52%)	21% (9–35%)	31% (23–40%)
subsite							
Nasal cavity	28% (24–32%)	35% (25–46%)	23% (17–29%)	31% (23–40%)	33% (22–45%)	20% (9–34%)	33% (25–41%)
Maxillary sinus	12% (4–24%)	19% (3–46%)	n.e.	10% (1–32%)	n.e.	n.e.	29% (14–45%)
Sphenoid sinus	50% (1–91%)	n.e.	n.e.	n.e.	50% (0.6–91%)	n.e.	18% (4–40%)
Ethmoid sinus	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
Frontal sinus	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	16% (1–50%)
Overlapping lesion	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
Accessory sinus, NOS	21% (6–41%)	n.e.	n.e.	35% (8–64%)	n.e.	n.e.	30% (9–55%)

Abbreviations: n.e., not estimable; NOS, not otherwise specified; RS, relative survival.

**Table 3** Distribution and relative survival by extent of disease, and treatment modality

	Europe		United States	
	N (%)	5-year RS (LL-UL)	N (%)	5-year RS (LL-UL)
Extent of disease (†)				
Localized	30 (25)	44% (22–64%)	92 (33)	43% (30–54%)
Regional	26 (22)	22% (7–42%)	98 (36)	30% (20–41%)
Distant	28 (24)	5% (0.3–20%)	63 (23)	7% (2–16%)
Unknown	34 (29)	32% (14–52%)	23 (8)	33% (15–53%)
Treatment modality (‡)				
Surgery + RT	109 (25)	15% (8–25%)	125 (45)	33% (24–43%)
RT	34 (8)	n.e.	28 (10)	17% (5–35%)
Surgery	106 (24)	36% (25–47%)	96 (35)	34% (23–46%)
No surgery or radiation	54 (12)	23% (10–39%)	20 (7)	6% (0.4–25%)
Unknown	134 (31)	17% (10–26%)	7 (3)	15% (0.7–48%)

Abbreviations: n.e., not estimable; RS, relative survival; RT radiationtherapy. .

Lastly, survival was categorized by EoD and treatment modality, as visualized in ►Table 3. Localized tumors demonstrated the best 5-year RS, calculated at 43.9% (22–63.9%) for Europe, and 42.7% (30.4–54.4%) for the United States. Patients presenting with metastasis displayed the worst prognosis, with only 4.9% (0.3–20.1%) of patients surviving after 5 years in Europe, as compared to 7.3% (2.3–16.1%) in the United States. Patients receiving surgery only demonstrated the highest survival in both continents. Between geographic regions, however, no statistical differences in survival were identified.

## Discussion

Sinonasal melanomas are uncommon entities that have been historically difficult to study due to their rarity in the population. Since previous studies have mostly consisted of case reports or case series in single institutions, population-based studies have enabled clinicians to better assess the clinicopathologic behavior of sinonasal melanoma with large, cross-institutionalized datasets.<sup>6,7</sup> Although European cancer registries have reported survival for many head and neck cancers, the present study represents the first report and comparison of survival for sinonasal melanomas between Europe and the United States.<sup>6,8–10</sup>

In general, melanoma is not uncommon. There are roughly 83,000 new cases per year in the United States, with ~1% arising from mucosal surfaces (around 800 cases per year).<sup>11–13</sup> Of those, ~ 55% occur in the head and neck, with the sinonasal cavities accounting for 66 to 80.3% of cases.<sup>10,14–17</sup> The overall incidence of SNMM has been estimated at 0.5 to 0.71/million people per year.<sup>10,17</sup> Despite this being a rare tumor, studies have shown that the incidence of nasal cavity melanoma increased in the United States from 1987 to 2009. With an overall annual percentage change of 2.4%, these represent a growing clinical problem.<sup>18</sup> Another study by Marcus et al. demonstrated an overall decrease in sinonasal malignancies from 1960 to 2010, yet

a rise in SNMM.<sup>18</sup> Curiously, there is an inverse relationship between geographical areas of malignant mucosal and cutaneous melanoma.<sup>16</sup>

Across Europe and the United States, the nasal cavity was the most common subsite for SNMM. This has been well supported in prior studies.<sup>16,18</sup> Interestingly, the United States had a smaller proportion of nasal cavity primaries (65.2% versus 83.4%), and a larger proportion of maxillary cavity primaries (15.9% versus 7.3%) when compared with Europe. Ethmoid sinus melanomas were the third most common site in Europe, while sphenoid melanomas were the third most common site in the United States. Sphenoid melanomas were only reported in Southern Europe, possibly explaining its low incidence in Europe.

A small disparity between genders was observed, with women having a higher incidence in both Europe and the United States (56.4% and 54.9%, respectively). Multiple studies have also cited this trend.<sup>9,18</sup> Conversely, Southern Europe had a 50.9% male predominance. This finding could be due to sample size, population demographics or another unmeasured factor. Survivability may also have a gender predilection. Previous studies have reported that being male carried a negative prognostic value, although our analysis failed to demonstrate any difference in the 5-year RS regarding gender.<sup>19,20</sup>

Sinonasal melanomas favor the elderly. Many studies have identified patients > 60 years old as the largest group affected.<sup>16,17</sup> Our analysis revealed that age > 65 comprised the vast majority of cases. Roughly 70% of all cases in Europe and the United States were > 65. Despite predominance in the elderly, age was not identified as a prognostic factor in either group.

The overall 5-year survival for sinonasal melanoma is poor. The mean 5-year survival is generally described to be no higher than 32%.<sup>9</sup> Comparison of the 5-year RS in the United States and Europe revealed similar results. When further broken down by subsite, variability in 5-year RS was observed.<sup>10,11,21</sup> Analyzing Europe as a whole, the 5-year



relative survival for melanoma of the nasal cavity was 27.9% versus 12.2% for the maxillary sinus. There was no 5-year RS difference in the United States regarding subsite in our analysis; however, previous studies on SNMM subsites in the United States have demonstrated differences in 5-year RS, with the best prognosis also being in the nasal cavity followed by the maxillary sinus.<sup>9,21</sup> Increased survival in the nasal cavity subgroup is attributed to earlier symptomology, leading to earlier diagnosis and easier surgical resection. This has been demonstrated consistently among many sinonasal cancers.<sup>22,23</sup>

Not surprisingly, local, regional and distant disease was correlated with 5-year RS in both Europe and the United States. In the United States, there was a drop in the 5-year RS as the extent of disease (EoD) increased (42.7%, 30.1%, and 7.3 for local, regional and distant involvement). European data displayed a similar trend, with 43.9% 5-year RS for local disease and 4.9% for distant disease. Regional disease data in Europe had widely overlapping confidence intervals, so it is unclear whether no difference exists or if more data are needed to demonstrate a trend similar to that of the United States. The EURO CARE EoD data had a large percentage of unknowns, which could have diluted the sample. Regardless, this is not unexpected as both sinonasal cancers and melanomas of all types carry a worse prognosis with advanced stage.<sup>9,24</sup>

Treatment for sinonasal melanoma remains primarily surgical. Endoscopic and open approaches have provided similar results with far less morbidity utilizing endoscopic techniques.<sup>9,11,14,19,20</sup> Surgery or combined surgery and radiotherapy have proven superior to radiation alone.<sup>10,21</sup> Chemotherapy has been largely unsuccessful, despite advances in identifying cellular markers (e.g., C-kit) and other targeted therapies.<sup>10,13,14</sup> In the United States, the 5-year RS of treatment with surgery and combination therapy were similar. Interestingly, surgical resection in Europe had a 35.6% 5-year RS, while combination therapy was just 15.3%. Perhaps, this difference in Europe was biased by addition of radiation in more advanced cases rather than an organic difference in the populations. It is also possible that this discrepancy is due to limited access to quality radiation treatment centers in certain areas in Europe, especially for the poorer countries in Eastern Europe. For example, it has been reported that Eastern European countries have a lower quality of healthcare when compared with western European countries and a larger reliance on tertiary care centers.<sup>25,26</sup>

The limitations of the present study include a lack of American Joint Committee on Cancer (AJCC) staging in the EURO CARE-5 database and inherent population differences captured by both databases. Europe was separated into sub-regions, which was inclusive of each country contained within that region, while the United States was represented as a single entity, thus ignoring individual differences in ethnicity and regional socioeconomic disparities. There were also a large number of patients in Europe with an unknown stage at diagnosis, which restricts our ability to draw conclusions about survival and treatment success. Another limiting factor of this study was our inclusion criteria, mainly regarding the

EURO CARE-5 database. Excluding all patients with either <30% completeness of data or death certificate only (DCO) restricted our ability to analyze all patients with sinonasal melanoma. Some contributing databases within Europe were incompletely represented due to these data criteria. With Europe being a diverse region, there are potential locoregional variations that could have been under or overestimated. Despite these factors, the diverse and broad sample provides insight into rare cancers such as SNMM.

## Conclusion

Although sinonasal melanomas are increasing in incidence, they remain a rare pathology. In both Europe and the United States, women were more commonly affected. Likewise, the most common age group was those > 65 years, although age did not confer a prognostic value. The most common subsite was the nasal cavity, followed by the maxillary sinus. Five-year RS was similar between continents, with an inverse relationship between EoD and survival. The treatment of choice throughout Europe and the United States remains primarily surgical.

### Compliance with Ethical Standards

This article does not contain any studies with human participants or animals.

### Conflict of Interests

The authors have no conflict of interests to declare.

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