Diplomarbeit

Sinonasal Mucosal Melanoma: Therapeutic Strategies and Survival for a rare Disease Entity

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Graz, 18.02.2019 *Markus Pomberger e.h.*

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Abstract

Introduction:

Sinonasal mucosal melanoma (SNMM) is a rare disease entity comprising 0.4% to 1.3% of all melanomas. Surgery with free margins has been the primary treatment over decades. Neither the addition of radiotherapy nor chemotherapy could significantly improve outcome rates of this devastating malignancy. This study presents all cases with Sinonasal Mucosal Melanoma treated at the Medical University of Graz and shows treatment and outcome of these patients and summarizes current literature for treatment options and outcomes.

Methods:

A retrospective patient chart review of all patients diagnosed with SNMM and treated at the Department of Otorhinolaryngology at the Medical University of Graz from 2001 to 2017 were included. Twelve patients were identified, and patient charts were searched for treatment and outcome data.

For the literature review, PubMed was systematically searched for articles meeting the following criteria: English or German language and full text articles available, patient data not dating back 1990, patient number over 10, treatment data including surgery and radiotherapy and overall survival outcome data.

Results:

Six patients were female, and 6 patients were over 65 years old. Out of 12 patients, 9 received endoscopic surgery. Main symptoms were Epistaxis and nasal obstruction. Six patients received adjuvant radiotherapy, and 3 patients received additional chemotherapy. One patient received adjuvant immunotherapy. Three patients, who did not undergo surgery, received chemoradiotherapy, radiotherapy alone, and chemotherapy alone, respectively. At the time of diagnosis 2 patients had distant metastases, 4 patients developed distant metastases during the course of the disease. Mean overall survival (OS) was 30,6 months, 3- and 5-year-OS was 25%, and 18.2%, respectively.

Conclusions:

Unspecific symptoms and hidden anatomic locations lead to delayed diagnosis and increased rates of metastatic spread. Distant metastasis is the main treatment failure in SNMM. Surgery with free margins remains the primary treatment for SNMM. The oncological efficacy of endoscopic resection seems to be similar to external approaches. Adjuvant radiotherapy might improve local control in individual cases, yet efficient

systemic therapy is needed to improve outcome rates. To evaluate and define more effective targeted treatment options and improve outcome rates, homogenous data and prospective multicentric analysis is needed.

Zusammenfassung

Einführung:
Primäre Melanome der sinunasalen Schleimhäute (SNMM) sind äußerst selten und umfassen 0,4 bis 1,3% aller Melanome. Die operative Entfernung mit freiem Resektionsrand war über Jahrzehnte die Standardtherapie. Weder adjuvante Strahlen- noch Chemotherapien konnten zu einer signifikanten Verbesserung dieses aggressiven Malignoms führen. Diese Arbeit erfasst alle Fälle von sinunasalen Melanomen, die an der Medizinischen Universität Graz behandelt wurden, führt deren Charakteristika, Behandlungen und Überlebenszeiten an und soll einen Überblick über derzeitige Behandlungsmöglichkeiten und Resultate in der Literatur geben.

Methoden:
Für die retrospektive Aufarbeitung der PatientInnen wurden alle PatientInnen herangezogen, bei welchen ein sinunasales Melanom an der Hals-Nasen-Ohren-Universitätsklinik Graz, im Zeitraum von 2001 bis 2017, diagnostiziert und behandelt wurde. Zwölf PatientInnen wurden identifiziert und die PatientInnenakte wurden nach relevanten InformationInnen durchsucht.
Für die systematische Übersichtsarbeit wurde in PubMed nach Artikeln gesucht, die folgende Kriterien erfüllen: englische oder deutsche Sprache und Volltextartikel verfügbar, PatientInnendaten nicht älter als/vor dem Jahr 1990, PatientInnenanzahl über 10, Behandlungsdaten inklusive Operation und Strahlentherapie sowie Angaben zur Gesamtüberlebenszeit.

Ergebnisse:
Von den 12 an der HNO-Universitätsklinik behandelten PatientInnen waren 6 weiblich und 6 PatientenInnen über 65 Jahre alt. Die Hauptsymptome waren Epistaxis und nasale Obstruktion. Neun PatientInnen wurden operiert, alle davon endoskopisch. Sechs PatientInnen erhielten eine adjuvante Strahlentherapie und 3 PatientInnen erhielten eine zusätzliche Chemotherapie. Ein Patient erhielt eine adjuvante Immuntherapie. Drei PatientInnen wurden ausschließlich operativ behandelt. Die übrigen 3 PatientInnen, die keiner Operation unterzogen wurden, erhielten jeweils nur Chemoradiotherapie, Radiotherapie sowie Chemotherapie. Zum Zeitpunkt der Diagnose hatten 2 PatientInnen Fernmetastasen, 4 PatientInnen entwickelten im Verlauf der Erkrankung Fernmetastasen. Das durchschnittliche/mediane Gesamtüberleben betrug 30,6 Monate, die 3- und die 5-Jahres-Überlebensrate war 25% bzw. 18,2%.

Schlussfolgerungen:

Die unspezifische Symptomatik und die versteckte anatomische Lage führen zu einer verzögerten Diagnosestellung und in weiterer Folge zu einer erhöhten Wahrscheinlichkeit der Entstehung von Fernmetastasen, die der Hauptgrund für das Therapieversagen bei der Behandlung von SNMM sind. Eine Operation mit freiem Resektionsrand ist nach wie vor die Standardbehandlung von SNMM. Die onkologische Effizienz der endoskopischen Resektion scheint der einer offenen Resektion des Tumors gleichwertig zu sein. Eine adjuvante Strahlentherapie kann die lokale Tumorkontrolle in Einzelfällen verbessern, jedoch ist zur Erhöhung der Überlebensraten eine effiziente systemische Therapie notwendig. Prospektive, multizentrische Studien mit einer höheren Zahl an PatientInnen und homogener Datenerfassung sind notwendig, um bestehende Behandlungsmöglichkeiten evaluieren und verbessern zu können.

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Abbreviations

A6	AJCC 6th Edition Staging System of the Nasal Cavity and Paranasal Sinuses
A7	AJCC 7th Edition Staging System for Mucosal Melanoma of the Head and Neck
ACCS	Accessory Sinus
B	Ballantyne Staging System
CA7	AJCC 7th Edition Clinical Staging
CBDCA	Carboplatin
CRT	Chemoradiotherapy
CSF	Cerebrospinal Fluid
CT	Chemotherapy
CT	Computer Tomography
DSS	Disease Free Survival
DTIC	Dacarbazine
EA	Endoscopic Assisted Resection
EB	Ethmoidal Bone
ER	Endoscopic Resection
ES	Ethmoidal Sinus
FESS	Functional Endoscopic Sinus Surgery
FS	Frontal Sinus
Gy	Gray
HDI	High Dose Interleukin
IR	Incidence Rate
IT	Immunotherapy
LN	Lymph Node
LNW	Lateral Nasal Wall
MRI	Magnetic Resonance Imaging
MS	Maxillary Sinus
n/a	Not Available/ Not Applicable
na	Not Assessed
NC	Nasal Cavity
NCDB	National Cancer Data Base

NCT	Neoadjuvant Chemotherapy
ND	Neck Dissection
NEC	Nasoethmoidal Complex
NF	Nasal Fossa
NLC	Nasolacrimal Duct
NPX	Nasopharynx
NS	Nasal Sinus
NV	Nasal Vestibule
OR	Open Resection
OR	Open Resection
OS	Overall Survival
Pal	Palliative Therapy
PET	Positron Emission Tomography
PNS	Paranasal Sinuses
RFS	Recurrence Free Survival
RT	Radiotherapy
S	Surgery
SB	Skull Base
SER	Sphenoethmoidal Recess
SNMM	Sinonasal Mucosal Melanoma
SS	Sphenoid Sinus
ST	Systemic Therapy
Sys	Systemic Therapy not otherwise specified
UK	Unknown
WT	Wild-Type

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1 Introduction

Malignant mucosal melanoma of the nasal cavity and paranasal sinuses (SNMM), first described by Lucke in 1869, is a rare disease entity with an incidence of 0.02 – 0.2 cases per 100.000 per year (1-6) and a 5-year-survival-outcome of about 30% (7, 8). Since the 1990s various authors proposed the importance of adjuvant radiotherapy for better outcome rates (9). Despite technological advances and growing possibilities of treatment options for oncological patients in the last two decades, like enhanced visibility for endoscopic or combined surgeries, 3- dimensional radiation therapy or novel systemic therapies, local control and distant metastasis in patients with SNMM remain hard to handle and prognosis is poor (7, 10).

The aim of this study was to compare contemporary treatment methods and survival outcome in patients with SNMM, particularly patients who underwent endoscopic surgery alone and patients who received endoscopic surgery and adjuvant radiotherapy.

A literature review in PubMed was conducted summarizing data available in current literature together with the results of the present study. Studies to be included should meet following criteria:

- Patient number over 10,
- Patient data not dating back 1990,
- Comparison of endoscopic surgery alone versus endoscopic surgery and adjuvant radiotherapy and
- Survival outcome stratified for staging.

For these criteria no matching studies or articles were found, thus a comparison was not possible. To ensure comparability, including criteria and methods were changed to a narrative review of contemporary literature.

This study in the first part reviews all cases with Sinonasal Mucosal Melanoma treated at the Medical University of Graz and shows treatment and outcome of these patients. Furthermore, a literature review of patient series starting from the 1990s should give an overview over the treatment options and outcomes in international comparison.

1.1 Epidemiology

Mucosal melanomas are a very rare entity comprising 0.4% - 1.3% of all melanomas (1, 2). About 40-55% of mucosal melanomas arise in the head and neck, the rest originates in female genitals, anal/rectal tract and urinary tract (1, 11). Of all mucosal melanomas of the head and neck a percentage of 60 -72% are of sinonasal origin (2, 12). Comprising less than 1% of all melanomas, the sinonasal mucosal melanoma has an approximate incidence of 0.02 – 0.2 cases per 100.000 per year (1-6).

Although some reports found modest (e.g. Mendenhall(13)) or significant (e.g. Khademi(14)) male preponderances, the great majority of studies with smaller and larger patient numbers show that there is a fairly equal gender distribution of about 45% male and 55% female patients (2-4, 12, 15, 16). SNMM has been found at all ages but primarily affects older age groups, with an increase of incidence between fifty and seventy years (2, 5, 12, 16).

In 2012, Marcus et al (12) published a retrospective analysis of the National Cancer Institute's Surveillance, Epidemiology and End Results database about the "Rising Incidence of Mucosal Melanoma of the Head and Neck in the US" (n=452). Interestingly, they found that from 1987 to 2009 the age-adjusted incidence rates (IR) in mucosal melanoma of the nasal cavity increased significantly with a total percentage change of about 103% and annual percentage change of 2.7%. While there was no significant change for male patients over the study period (PC 35.2%, APC 1%, $p < 0.3$), IR for female patients increased significantly by a total PC of 45% and APC of 3.4% ($p < 0.01$). In accordance to most other reports, they found a slight predominance of female patients compared to male patients, 52.4% to 47.6%, respectively (12).

1.2 Etiopathogenesis

Melanocytes are dendritic cells that derive from the neural crest. They are found mostly in the epidermis of the skin, but also in numerous other locations. These locations include the eye and the mucosal membranes (17). Melanocytes are known to migrate to mucosal tissue. More frequently they migrate to ectodermal derived mucosa than to endodermal derived mucosa. This means that they are more frequently found in the oral and nasal cavities than in the pharynx, larynx, tracheobronchial tree or the mucosa of the digestive

system. This fact might explain the lower frequency of melanomas in the areas of endodermal derived mucosa (18).
The function of melanocytes as pigment cells for UV protection in the skin and eye are well understood, yet their role in mucosal membranes remains uncertain. There are theories suggesting antimicrobial and immunological functions, as melanocytes could have phagocytic, antigen-presenting and cytokine-producing features (17).
There is still some controversy about the development of mucosal melanomas and risk factors remain to be identified (17-19).
Occupational exposure to formaldehyde was described as possible risk factor for SNMM but did not meet a wide response in the literature (20, 21). Also, the attempt to find viruses as an etiological factor failed up to now. No connection was found between human papilloma viruses, human herpes viruses, and polyomavirus and the etiopathogenesis of mucosal melanoma (17).

1.3 Pathology

1.3.1 Macroscopy

Most common location for SNMM in literature is the nasal cavity, specifically the nasal septum and the turbinates, followed by the nasal cavity in combination with the paranasal sinuses (21). An overview of reported locations in the present literature review is shown in Figure 4. Macroscopically SNMM typically appear as a polypoid mass with or without pigmentation and a size ranging from 0.3 to 7 cm (10, 14, 21-23). The tumors are frequently ulcerated and may present in an unspecific variety of appearances such as brownish, black, reddish, crimson, grey-white or even amelanotic imitating other tumors (17, 21, 24).

1.3.2 Microscopy

Sinonasal mucosal melanoma mostly presents with an intact overlying respiratory surface epithelium. There are several different growth patterns found in SNMM with the most common being of solid, spindled, polypoid, discohesive, pseudopapillary and peritheliomatous architecture. The cytomorphologic appearance of the tumor cells is most frequently of an undifferentiated nature with small to medium cells but also pagetoid, epithelioid, spindled and rhabdoid cells are commonly identified. Several of these

morphologic features can appear in one tumor. In most tumors atypical mitotic figures are present. Melanin pigmentation is not necessarily found in all tumors (21, 25).

1.3.3 Immunohistochemical markers

Given the unspecific clinical presentation and the variable macroscopic and microscopic appearances of SNMM immunohistochemical markers are often essential for diagnosis. The immunohistochemical profile of SNMM is equal to cutaneous melanomas (21, 26). Several melanoma-associated markers like protein S-100, HMB-45, melan-A, tyrosinase, vimentin and MITF are being used to support diagnosis of melanoma, yet the distribution of reactive markers varies in these tumors (17, 21, 24, 27). A panel of markers including protein S-100, HMB-45 and tyrosinase is recommended to accurately diagnose SNMM (21, 27).

1.4 Clinical presentation

Initial symptoms of SNMM are very unspecific and often misleading. The major symptoms are nasal obstruction and epistaxis either occurring alone or combined. Nasal obstruction occurs unilaterally and can be associated with symptoms like rhinorrhea, facial pressure or pain (24, 25). Patients often ignore these unspecific symptoms at first which results in delayed diagnosis in a remarkable number of patients (5, 20). In a study with 115 SNMM patients, Thompson et al found that patients who had nasal obstruction alone, suffered worse prognosis compared to patients who initially presented with epistaxis (21). Late symptoms include nasal deformity, exophthalmos, ophthalmoplegia causing diplopia, and epiphora (20, 24).

1.4.1 Metastasis

Due to unspecific symptoms and delayed clinical presentation of SNMM, diagnosis is frequently made in advanced stages (24, 28).

Regional Metastasis

Only about 5 % of patients with SNMM have lymph node metastasis at the time of initial presentation. However, patients with distant metastasis would frequently develop regional metastases in the course of the disease and numbers would rise up to 40% (21, 24).

Distant Metastasis

While only 10 to 15% of patients with SNMM initially present with distant metastasis, it has been shown that 40 to 70% of these patients develop distant metastases during the disease, thus being the main treatment failure in SNMM (7, 13, 19, 29). The most common sites of distant metastases are lung, liver, bone and brain (19, 24, 30). These findings indicate either an early hematogenous spread of the disease, or the existence of micrometastases at the time of diagnosis, or both, underlining the importance of early resection with free margins and effective systemic therapy (7, 31).

Martin et al recommend complete systemic staging with MRI of the brain, CT-scans or alternatively PET-scans for every patient with SNMM, to optimally define possible distant metastases prior to treatment (30).

1.5 Staging

Several staging systems have been proposed and modified for mucosal melanoma to categorize the disease and be able to name prognostic values and preferable treatment modalities.

In 1970 Ballantyne(32) proposed a staging system for malignant melanoma of the head and neck which considered 3 stages: local disease (without extent or size), nodal metastasis and distant metastasis.

This system was modified by Prasad et al (33) in 2004 for staging primary mucosal melanomas of the head and neck, splitting up stage I into 3 levels of microstaging: Level 1 – in situ, Level 2 – invasion up to lamina propria, Level 3 – deep tissue invasion (34).

In 2003, Thompson et al. proposed a staging system for primary mucosal melanomas of the Sinonasal tract and nasopharynx, according to a study with 115 patients with SNMM analyzing prognostic factors, with 3 stages, the first 2 stages describing anatomic location (T1 – single site, T2 – more than 1 site) and the third stage describing the presence of regional(N) or distant metastasis(M) (21).

In 2002, the American Joint Committee on Cancer published its 6th edition of TNM-classification, including a chapter for malignancies in the nasal cavity and paranasal sinuses (Table 1).

Within that system, staging of the primary tumor is different for two major anatomic sites:

- maxillary sinus

- nasal cavity and ethmoid sinus

Microstaging is divided for each group from T1 (limited to mucosa at one subsite) to T4 (invasion of surrounding structures like orbital apex, dura, brain, nasopharynx) according to typical local spread.
Although regional lymph node spread is relatively uncommon, a classification from N0 – N3 was established, including size, location and number of affected lymph nodes (35).

Considering the highly aggressive behavior of malignant mucosal melanomas there was a complete change in the approach of classifying these tumors. In 2010, a new chapter for mucosal melanomas of the head and neck was established in the 7th edition of the AJCC-Staging-System (Table 2).
T1 and T2 stages of the primary tumor were discarded and lesions limited to the mucosa are classified as T3 lesions. T4a and T4b lesions are moderately advanced and very advanced. Also, the classifications of lymph node involvement were set to N0 (not present) and N1 (present), without any further characterization of afflicted lymph nodes, due to lack of prognostic value (36). Considering this renewal, all patients with nodal disease now advance to stage IV disease.
In December 2016 the new UICC 8th edition staging system has been published. That new system had no significant updates in respect to mucosal melanoma staging. Still T1 and T2, as well as precise N0 characterization, stay omitted due to aggressive growth and the rarity of lymph node metastases and their negligible prognostic value in SNMM.
Below tables give an overview of the AJCC classification systems from 2002 (Table 1) and from 2010 (Table 2).

Table 1. American Joint Committee on Cancer Staging System of the Nasal Cavity and Paranasal Sinuses, 6th Edition (2002)(35)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Maxillary Sinus	
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus
Nasal cavity and ethmoid sinus	
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor involving two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single, ipsilateral lymph node, _3 cm in greatest dimension
N2	
N2a	Metastasis in a single, ipsilateral lymph node, >3 cm and <6 cm
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm
N3	Metastasis in a lymph node >6 cm

Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage	
Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0 T1–T2, N1, M0
Stage IVA	T4a, N0/N1, M0 T1–T4a, N2, M0
Stage IVB	T4b, any N, M0 Any T, N3, M0
Stage IVC	Any T, Any N, M1

Table 2. American Joint Committee on Cancer Staging System for Mucosal Melanoma of the Head and Neck, 7th Edition (2010)(36)

Primary Tumor	
T3	Mucosal disease
T4a	Moderately advanced disease Tumor involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	N0 No regional lymph node metastases
N1	N1 Regional lymph node metastases present

Distant Metastasis	
M0	M0 No distant metastasis
M1	M1 Distant metastasis present

Stage	
Stage III	T3, N0, M0
Stage IVA	T4a, N0, M0 T3–T4a, N1, M0
Stage IVB	T4b, Any N, M0
Stage IVC	Any T, Any N, M1

1.6 Therapy

1.6.1 Multimodal Approach

As with other cancers, a multidisciplinary tumor board, consisting of a head and neck surgeon, radio-oncologist, medical oncologist and if necessary a neurosurgeon, should be involved to find the best multimodal approach (37, 38).

The primary treatment of sinonasal mucosal melanoma is surgical resection of the tumor. A wide resection to achieve clear margins should be the goal of every operation. In cases where free margins are obtained, patient outcome tends to be significantly better (39, 40).

Adjuvant treatments like radiotherapy and systemic therapy are frequently used, however there are no standardized treatment regimens and recommendations mostly emphasize treatment on a patient to patient basis (31).

Definitive radiotherapy or concomitant chemoradiotherapy are used in inoperable cases or as palliative therapy.

1.6.2 Surgery

External Approach

Traditionally, extensive sinonasal malignancies are managed via external approaches such as transfacial approach via lateral rhinotomy, Weber-Ferguson or midfacial degloving, or craniofacial (transcranial-transfacial) approach (37, 38, 41).

With open approaches an en-bloc excision of the tumor is possible, even for extensive tumor masses.

Although some authors underline the oncological importance of en-bloc resections, the number of comorbidities, surgical complications and mutilating outcomes including wound complications, long postoperative recovery times and external surgical scars, are relatively high compared to a minimal invasive approach.

Postoperative complications in about 50% of cases and postoperative mortality of about 4% have been reported.

Thus, minimal invasive alternatives to standard external approaches have been of peculiar interest in the last decades (41, 42).

Endoscopic Surgery

In the last decades, surgical approach of sinonasal malignancies has shifted from purely external approaches to a growing number of endoscopically assisted and purely endoscopic resections.(42)

Functional Endoscopic Sinus Surgery (FESS) is a minimal-invasive alternative to external approaches. Typical indications for FESS are chronic sinusitis with or without nasal polyps and epistaxis control, as well as ophthalmic procedures (e.g. orbital decompression) and CSF (cerebrospinal fluid) leak closures.

Also, nasal masses and tumors are resected endoscopically with increased frequency (40). In low grade tumor masses en-bloc resection is possible, for lager tumors piecemeal resections were found to have similar oncological efficacy compared to en bloc resections by external surgical techniques (41-43).

Before endoscopic surgery it is important to collect information regarding tumor size and surrounding structures with MRI for soft tissue and neural structures, CT-scan for bony invasions and endoscopic visualization (40, 42). Identification of the tumor origin plays an important role in selecting appropriate surgical techniques depending on the affected structures. If the tumor is small enough, an en-bloc resection is possible, otherwise the tumor mass is resected in a piecemeal fashion, debulking towards its origin (42, 44).

Limitations of sole endoscopic approaches are infiltration of nasal bones, extensive involvement of the frontal sinuses, extensive involvement of orbital structures or the lacrimal system, or involvement of the zygomatic recess or anterior wall of the maxillary sinus. Also, massive tumors infiltrating the dura or brain parenchyma should be an indication for a combined approach. If free surgical margins cannot be obtained by transnasal endoscopic resection, an external approach should be considered (42).

In unresectable tumors, however, endoscopic resection may be helpful for palliative treatment like providing sinonasal airway, controlling epistaxis or decompressing the orbit (40).

Patients undergoing endoscopic tumor resection, typically receive general anesthesia. Broad-spectrum prophylactic antibiotics are given preoperatively (44).

Overall complication rate of FESS is 0.5%, according to a retrospective study by Suzuki et al (45). Possible complications of endoscopic surgery are: bleeding, orbital hematoma or injury resulting in diplopia or blindness, craniospinal fluid leak and synechiae formation (40).

1.6.3 Radiotherapy

Radiotherapy (RT) is a commonly used adjuvant treatment option in SNMM.
Mostly used postoperatively, it is also applied alone in palliative settings or inoperable patients. Postoperative radiotherapy is applied to improve local control after surgical resections or with positive or uncertain margin status.
Optimal radiotherapeutic treatment schemes and actual oncologic efficacy for SNMM, however, remain controversial. Conventional fractionation schedules consist of around 50 Gy delivered in 20 fractions of 2.5 Gy (46).
In the past, melanoma cells were considered to be resistant to radiotherapy (47). Radiobiological studies of melanoma cells have shown wide variations of in vitro radio resistance and typical survival curves for melanoma cells suggesting a distinct ability for repair of sublethal DNA-damage.
The α/β ratio is a parameter for radiation sensitivity per fraction in specified tissues. The α/β values for melanomas of different anatomic origin vary widely, thus recommendations on ideal fractionation doses are difficult to define (46).
Novel radiotherapeutic treatment modalities like intensity modulated radiotherapy (IMRT), 3D conformal radiotherapy(3D-CRT) show improvement in limiting the volume of healthy tissue involvement to reduce complications (46).
Proton beam radiation shows better dose distribution than conventional X-ray irradiation with comparable results and better tolerability according to a phase II trial by Zenda et al (48).

1.6.4 Systemic Therapy

Systemic therapy is typically used in patients with nodal or distant metastatic disease and palliative patients. With a recurrence rate of about 50 % SNMM has a bad outcome despite surgical resections, adjuvant radiotherapy and chemotherapy (19, 49, 50).
Acceptable rates of local control can be reached by surgical resection with free margins and adjuvant radiotherapy, yet, given the high rate of distant metastases, systemic therapy seems to be of importance regarding overall survival outcome. As most studies regarding systemic therapy derive of analyzing the efficacy in cutaneous melanoma, there are no standardized treatment regimens for sinonasal mucosal melanoma (7, 46, 51).
Conventional chemotherapeutic agents do not seem to have satisfying impact on regional and distant metastases. Novel, targeted systemic therapies with monoclonal antibodies are

being discussed throughout recent literature and are believed to have better oncological efficacy and a lower rate of complications compared to standard chemotherapy (7).

Chemotherapy

A broad variety of chemotherapeutic agents such as dacarbazine, carboplatin, cisplatin, vindesine, temozolomide and trofosamide are being used either alone or in combination in cases of disseminated or palliative disease. Treatment regimens regarding chemotherapy differ widely throughout the literature, not exceeding response rates over 20% and without desired effects on outcome rates (25, 46, 52, 53).

Immunotherapeutic agents such as Bacillus Calmette-Guerin, interleukin-2 and interferon-alpha are repeatedly used in combination with chemotherapy in patients with mucosal melanomas. Typical combinations would be dacarbazine, cisplatin or tamoxifen with high dose IL-2 and IFN-alpha. Although promising response rates were observed in several studies an overall survival benefit could not be found (54).

Molecular Profile and Systemic therapy

Targeted therapies with monoclonal antibodies have already proven their effectiveness in cutaneous melanomas. Recently published studies have also shown positive effects of these novel agents in mucosal melanomas (55, 56).

As monoclonal antibodies target specific mutational aberrations of cutaneous melanomas it would seem that these agents would have effects on other types of melanomas as well. However, studies have shown that mutations of oncogenes vary in subgroups of melanoma and suggest that melanoma to be molecularly heterogenous disease (57).

For example, melanomas of the skin which are not exposed to chronic sun damage have significantly higher number of BRAF mutations than mucosal melanomas (58).

Comparing mucosal melanomas from different sites, there was a higher frequency of KIT mutations in vulvar melanomas. This suggest that the frequency of KIT mutations in mucosal melanomas varies at different anatomical sites (59). For SNMM specifically, Zebrary et al summarized reported frequencies of mutations in SNMM of five studies and found high variability between these studies: KIT 0-60%, NRAS 22-60% and BRAF 0-6% (58).

Several studies have reported promising effects of targeted therapy for patients with KIT mutant melanomas and NRAS mutant melanomas with imatinib and dasatinib, and MEK1/2 inhibitor, respectively. Due to the small number of SNMM, mutations in KIT,

NRAS and BRAF genes have not yet been quantified for this tumor (60-62). Further investigation is needed to assess the frequency of mutations in KIT, NRAS and BRAF genes in SNMM to improve novel treatments (58).

2 Materials und Methods

For the retrospective patient series, the electronic database of the Medical University of Graz "open MEDOCS" was used to identify all patients diagnosed or treated with Sinonasal Mucosal Melanoma at the Department of Otorhinolaryngology. Twelve patients were identified from 2001 to May 2017.

For patient data collection and retrospective analysis, approval of the institutional review board of the Medical University of Graz was obtained.

For the literature review, MEDLINE and PubMed central databases were searched with the terms "sinonasal" and "melanoma".

Studies with following including criteria were used for further analysis:

- English or German language and full text available,
- patient number over 10,
- patient data not dating back 1990,
- treatment including surgery and radiotherapy, and
- overall survival outcome data.

302 primary matches were found and 279 were excluded on basis of title and abstract.

23 studies were taken into full-text assessment.

Eighteen studies were chosen to be undertaken a narrative systematic review and are listed in Table 6Table 6.

Four studies have a significant overlap in patient data but were still taken into closer election because of some differently evaluated parameters (3, 25, 31, 63).

A structured systematic review or metanalysis with quantitative comparison outcomes such as survival, treatment modalities, surgery alone, surgery and radiotherapy, surgery and chemoradiotherapy and staging, could not be performed because the available data are not comparable to each other due to heterogeneity of data in the studies.

3 Results

3.1 Retrospective Analysis

Twelve patients were diagnosed with Sinonasal Mucosal Melanoma from 2001 to 2018 at the Department of Otorhinolaryngology of the Medical University of Graz. Mean age of all patients was 66.5 years, median age was 70 years (range, 43 to 88). There were 6 female and 6 male patients.

An overview of the results is given in Table 3 below.

Table 3. Overview of Results

Characteristic	**N° of Patients (%)**
Total N° of Patients	12 (100)
Sex	
Male	6 (50)
Female	6 (50)
Age	
<65	6(50)
>65	6(50)
Location	
Nasal cavity*	7 (58)
Paranasal sinuses**	2 (17)
Both	3 (25)
Principle Symptoms	
Epistaxis + nasal obstruction	7 (58)
Epistaxis only	2 (17)
Nasal obstruction only	1 (8)
Nasal/Orbital pressure	1 (8)
Collapse	1 (8)
Staging	
T3	7 (50)
T4a	2 (25)
T4b	3 (25)
Treatment	
Surgery only	2 (17)
Surgery + adjuvant radiotherapy	3 (25)
Surgery + adjuvant chemoradiotherapy	3 (25)
Surgery + immunotherapy	1 (8)
Radiotherapy + chemotherapy	1 (8)
Radiotherapy alone	1 (8)
Chemotherapy alone	1 (8)

**Nasal cavity includes: Nasal Vestibule and Atrium, Nasal Septum, Nasal Conchae and Sphenoethmoidal recess.*
***Paranasal Sinuses includes: Maxillary Sinus, Ethmoidal Sinus, Frontal Sinus, Sphenoidal Sinus.*

3.1.1 Location

In 6 cases the primary tumor site was the nasal cavity, in 1 case the paranasal sinuses and in 4 cases both, the nasal cavity and the paranasal sinuses. In one patient the primary tumor site was the nasal septum and ethmoid bone with infiltration of the skull base.
In cases confined to the nasal cavity the inferior and middle nasal concha, the nasal septum, and the sphenoethmoidal recess were involved.
In the case confined to the paranasal sinuses, the right ethmoidal and sphenoidal sinuses were involved with local destructive growth and invasion of bony structures.
In one patient the tumor involved the middle nasal concha and the frontal sinus and had infiltrated the orbit. One patient had a massive tumor mass involving the nasal cavity, maxillary sinus and skull base, infiltrating the orbit and the hard palate.
All tumor locations are listed in Table 5.

3.1.2 Symptoms

In 7 cases principal symptoms were epistaxis and nasal obstruction, in 2 cases nasal obstruction was the only symptom, 1 patient had nasal obstruction only, 1 patient had a feeling of pressure in the nasal cavity and left orbit, and 1 patient had a collapse due to severe metastatic progression of the principle tumor.

3.1.3 Staging

The AJCC 7th edition staging system for mucosal melanoma of the head and neck was used in this series. At the time of diagnosis 7 patients were staged T3, 2 patients T4a and 3 patients T4b.
Of those patients with T3 lesions, none had distant metastases, only one patient had positive lymph node metastasis located in submandibular lymph nodes, and in 3 patients lymph node involvement could not be excluded.
In patients with T4a lesions 1 did not show signs of locoregional or distant metastatic spread, while 1 patient had distant metastases in the lungs, pleura, adrenal gland, pancreas, and retroperitoneal soft tissue at the time of first staging. Of patients with T4b lesions one did not have locoregional or distant metastases, one had metastatic spread into the liver, and one patient showed metastases in lungs and liver.
Staging information for each patient is listed in Table 5.

3.1.4 Immunohistochemical Markers and Mutation Status

Diagnosis was confirmed by immunohistochemical markers in 9 cases. In 6 cases Melan A, Protein S-100 and HMB-45 showed positive immunohistochemical reaction. Melan A showed positive immunohistochemical reaction in all 9 cases, Protein S-100 in 8, HMB-45 in 6 cases and Tyrosinase and Vimentin, each in 1 case. In 2 cases information was unavailable because diagnosis was made in other institutions and in 1 case the immunohistochemical activity was not assessed.

To find out whether targeted treatment options are applicable, mutation status of BRAF, KIT and NRAS was assessed in several cases (Table 4). However, in all cases assessed, genetic analysis only brought up wild-type sequences and did not show mutant phenotypes.

Table 4. Immunohistochemical Markers and Mutation Status of all Patients

Patient	Immunohistochemical Reaction	BRAF	KIT	NRAS
1	na	na	na	na
2	Melan A, S-100	WT	WT	na
3	Melan A, S-100, HMB-45	na	na	na
4	Melan A, S-100	na	WT	na
5	Melan A, S-100, HMB-45	WT	WT	na
6	Not available	WT	WT	na
7	Melan A, HMB-45	na	WT	na
8	Melan A, S-100, HMB-45, Tyrosinase	na	na	na
9	Melan A, S-100, HMB-45	WT	WT	na
10	Melan A, S-100, HMB-45, Vimentin	WT	WT	WT
11	Not available	WT	WT	WT
12	Melan-A, S-100, HMB-45	WT	WT	WT

Abbreviations: na: Not Assessed; WT: Wild-Type.

3.1.5 Treatment

An overview of all patients is given in Table 5 below.

Nine out of 12 patients received endoscopic surgery. Two patients had revisional surgeries due to local recurrence, of these 1 patient had an open resection via midfacial degloving because of local destructive growth of the tumor. In 3 patients functional neck dissection was performed. Of those patients who had undergone surgery, 6 patients received adjuvant treatment. Three received radiotherapy, 3 received radiotherapy plus chemotherapy and 1 received Immunotherapy (Nivolumab + Ipilimumab). Two patients had surgery alone. Three patients who did not undergo surgery received radiotherapy plus chemotherapy, radiotherapy alone and chemotherapy alone, respectively. Chemotherapeutic agents used were dacarbazine, carboplatin and ixoten.

Table 5. Overview of all Patients

No	Age	Sex	Location	Staging	Surgery	RT	ST	ND	OS
1	54	f	NC	T3N0M0	FESS	yes	HDI, CBDCA	no	24
2	41	m	ES, SS	T3N0M0	FESS	yes	CBDCA	no	104,1
3	81	f	NC, NS, SER	T4aN0M0	FESS; revisional FESS	yes	no	no	9,2
4	83	f	NC, MS, ES, FS	T4aN0M1	no surgery	yes	DTIC	no	19,3
5	80	f	NC, NS, SER	T3N1M0	FESS	yes	no	no	11,5
6	79	m	NC, MS, SB, Ob, HP	T4bN0M0	no surgery	yes	no	no	22,1
7	82	f	NC, MS	T3NXM0	FESS	no	no	no	8,4
8	59	f	NC	T3NXM0	FESS; revisional OR, FESS	no	no	yes	88+
9	47	m	NC	T3N0M0	FESS	yes	no	yes + LN	55,8+
10	61	m	NC	T3NXM0	FESS	yes	DTIC	yes	14,2
11	88	m	NC, FS, Ob	T4bN0M1	no surgery	no	Ixoten	no	7,1
12	43	m	NS, EB, SB	T4bN0M1	FESS	no	Nivolumab+ Ipilimumab	no	9

Abbreviations: NC: Nasal Cavity; NS: Nasal Septum; SER: Sphenoethmoidal Recess; MS: Maxillary Sinus; ES: Ethmoidal Sinus; EB: Ethmoidal Bone; SS: Sphenoid Sinus FS: Frontal Sinus; Ob: Infiltration of Orbit; SB: Skull Base; HP: Hard Palate; FESS: Functional Endoscopic Sinus Surgery; OR: Open Resection; RT: Radiotherapy; ST: Systemic Therapy: HDI: High Dose Interleukin; CBDCA: Carboplatin; DTIC: Dacarbazine; ND: Neck Dissection; LN: submandibular Lymph Node; OS: Overall Survival [months].

3.1.6 Metastasis

Locoregional

At the time diagnosis, one patient had afflicted lymph nodes. Three patients developed lymph nodes metastases 2, 6 and 39 months after surgery.

Distant

Four patients developed distant metastasis 2, 10, 11 and 16 months after initial treatment. Affected organs were lungs in 4 cases, liver in 3 cases, retroperitoneal soft tissue in 2 cases, kidneys in 2 cases and in 2 cases bony structures in the thoracic and lumbar column and the femur. At the time of diagnosis 1 patient had liver metastasis, 1 patient had metastasis in lungs and liver, and 1 patient had distant metastasis in lungs and pleura, the adrenal gland, pancreas and peritoneum.

3.1.7 Survival:

As per April 2018, 2 patients are still alive at 88 (FESS + open revision via midfacial degloving + neck dissection + revisional FESS) and 51 (FESS + Radiotherapy + neck dissection and resection of functional lymph nodes) months. For all patients, including those who did not receive surgery, median overall survival (OS) was 16.7 months with a range from 7.1 to 104.1 months, while mean survival was 30,6 months. 1-year-OS was 58.3%, 3-year-OS was 25%, 5-year-OS was 18.2%. For patients who underwent surgical resection median OS was 14.2 months with a range from 7.1 to 104.1 months, while mean survival was 35,4 months, and 1-year-OS, 3-year-OS and 5-year-OS were 55.6%, 33.3%, and 22.2%, respectively. For 3 patients who did not receive surgery mean OS was 16.7 months, with 19, 22 and 7 months, respectively. (Figure 2)

Stratified by tumor stage, mean overall survival was 52.9, 14.3 and 12.7 months for T3, T4a and T4b, respectively. (Figure 3)

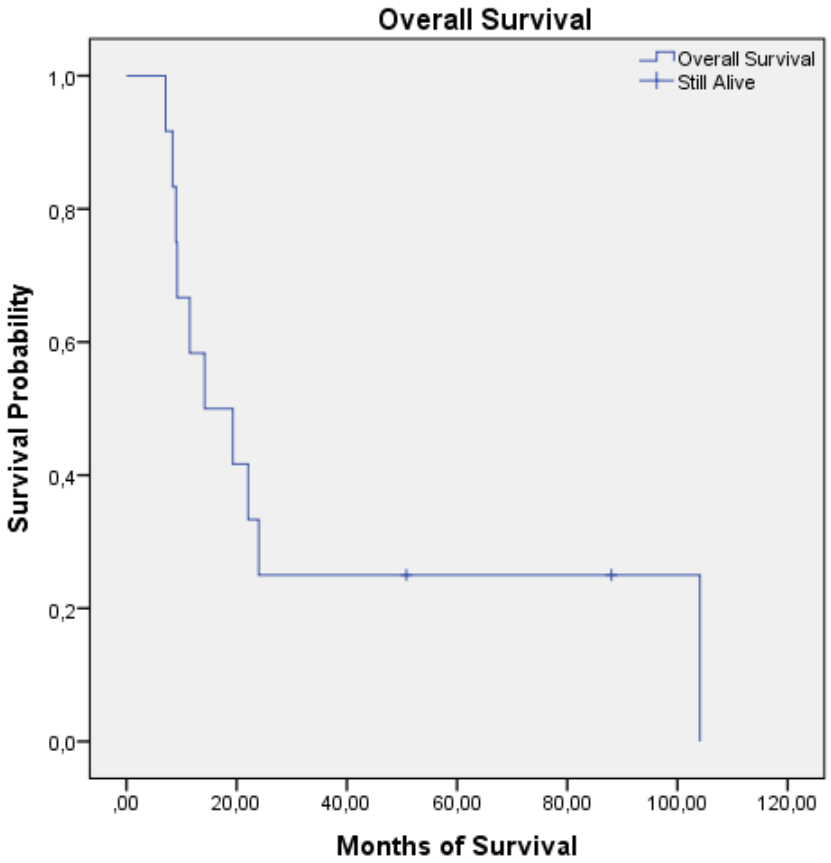

Figure 1. Overall Survival of Patients

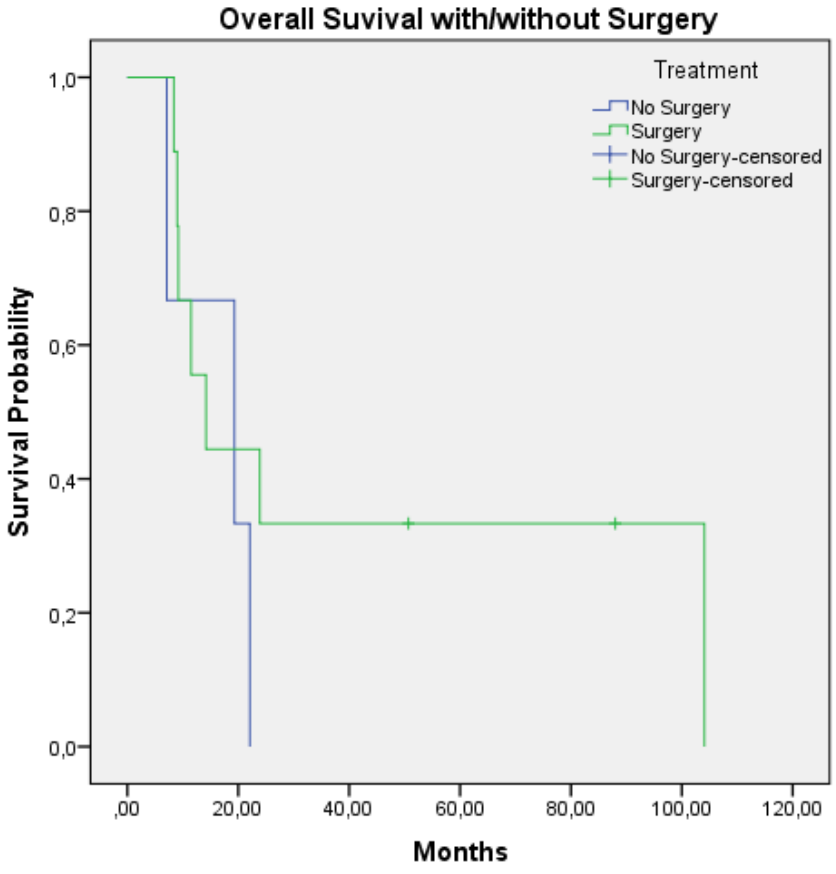

Figure 2. Overall Survival of Patients with and without Surgery

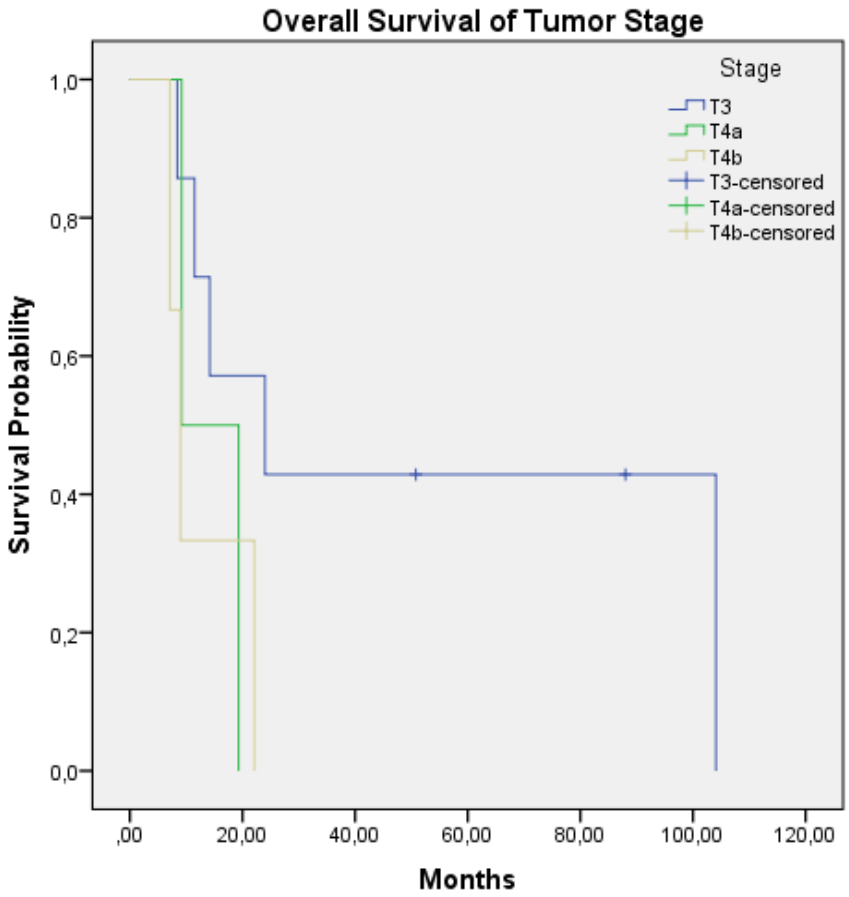

Figure 3. Overall Survival stratified for Tumor Stage

3.2 Literature Review

The results of the literature review are listed below in Table 6, including 18 articles and the results of the present series. Konuthula et al(3) and Ajmani et al(63), as well as Moreno et al(25) and Amit et al(31), each have overlapping sources of patient data from the National Cancer Data Base (NCDB) and the MD Anderson Cancer Center, respectively.

Table 6. Overview of Literature Review

Autor	Data	n°	Mean Age	Gender n (%)	Location n (%)	Staging n (%)	Treatment n (%)	Surgical approach	Margin status n (%)	5-year-OS [%]
Khademi et al. 2011(14)	1995 - 2005	18	65	M: 16 F: 2	NC: (62) ES (19) MS (19)	B: I: 8 II: 7 III: 3	S + RT: 18 CT: 5	n/a	n/a	23
Konuthula et al. 2017*(3)	2004 - 2010	695	69	M: 316 F: 379	NC: 470 PNS: 225	n/a	S: 206 S+RT: 271 S+CRT: 49 S+CT:29 RT: 42 CT: 21	n/a	neg: 300 pos: 127 UK: 268	21.7
Lombardi et al. 2016(39)	2003 - 2012	58	71	M: 21 F: 37	NEC: 51 MS: 6 FS: 1	A7: T3: 30 (52) T4a: 17 (29) T4b: 11(19)	S:42 S+RT: 13 S+CRT: 2 S+CT: 1	OR: 7 ER: 47 Both: 4	neg: 41 (71) pos: 17 (29)	29
Martin et al. 2004(30)	1991 - 2002	20	77	M: 8 F: 12	NC: 8 PNS:3 NC+PNS: 9	A6: T1: 3(15) T2: 6(30) T3: 3(15) T4: 8(40)	S: 2 S+RT: 15 S+CT: 1 RT: 2	n/a	n/a	2YOS: 23
Meng et al. 2014(64)	2000 - 2010	69	66	M: 37 F: 32	NC: 36 LNW: 19 MS: 21 ES: 18 NS: 4 SS: 4	CA7: III: 37 (54) IVA: 27 (39) IVB: 5 (7)	S: 27 S+RT: 24 S+RT+CT: 18	OR: 41 ER: 28	n/a	21.8
Moreno et al. 2010**(25)	1993 - 2004	58	63	M: 35 F: 23	LNW: 25 NS: 14 MS:11 ES: 5 SS: 1 NPX: 1 NV: 1	A6: T1: 16 (27) T2: 19 (33) T3: 12 (21) T4: 11 (19)	S: 25 S+RT: 31 RT: 2 Adj CT: 14 Adj IT:22	OR: 46 ER: 10	neg: 46 pos: 12	38.7
Narasimhan et al. 2009(22)	1995 - 2007	18	68	M: 8 F:10	NC: 6 (33) NS: 3 (17) MS: 12 (67)	A6: I: 2 (11) II: 2 (11) III: 4 (22) IV: 10 (56)	S: 18 Adj RT: 10 Adj CT: 10 Adj IT: 8	n/a	n/a	34
Roth et al. 2010(65)	1992 - 2007	25	71	M:8 F:17	NC: 11 NS: 4 MS:5 ES: 5	n/a	S: 11 S+RT: 7 S+CRT: 2 S+CT:1 RT: 3 NoT: 1	OR: 6 ER: 15	neg: 16 pos: 5	33
Samstein et al. 2016(23)	1998 - 2013	78	68	M: 38 (49) F:40 (51)	NC: 52 (67) PNS: 26 (33)	A7: T3: 39 T4a: 29 T4b: 8 UK: 2	S: 14 S+RT: 58 S+CRT: 6	n/a	neg: 30 pos: 24 UK: 24	31
Swegal et al. 2014(66)	1998 - 2012	25	67	M: 14 F:11	NC: 17 (68) PNS: 8 (32)	CA7: III: 9 (36) IVA: 6 (24) IVB: 8 (32) IVC: 2 (8)	S: 3 S + RT: 22 Adj Sys: 6	OR: 13 (52) ER: 12 (48)	neg: 14 (56)	2YOS: OR: 64% ER: 44%

Tajudeen et al. 2014(67)	1991 - 2011	14	64	M: 7 F: 7	NC: 11 PNS: 3	A6: T1: 6 (43) T2: 2 (14) T3: 0 (0) T4a: 6 (43)	S: 3 (21) S+RT: 8 (57) S+CRT: 2 (14) S + UK: 1 (7)	n/a	neg: 10 (71%) pos: 4 (29%)	35
Vandenhende et al. 2012(68)	1991 - 2008	25	68	M:12 F: 13	LNW: 11 (44) MS: 4 (16) NS: 5 (20) NF:1 (4) Other: 4(16)	A7: T3: 6 (24) T4a: 8 (32) T4b:11 (44) N1: 1	S: 80 S+RT: 15 RT: 1 Pal: 1	OR: 12 (52) ER: 11 (48)	neg: 20(80) pos: 5 (20)	3YOS: T3: 100 T4: 52
Won et al. 2015(10)	1994 - 2013	155	63	M: 81 F: 74	NC: 99 NS:54 MS:34 ES:28 FS: 6 SS: 6 SB: 6 Orbit: 9 NPX: 5 NLC: 3 Skin: 6	CA7: III: 67 IVA: 65 IVB: 9 IVC: 14	S: 48 S+RT: 54 S+Sys: 28 S+CRT: 11 UK: 14	OR: 63 incl ER:70	n/a	40.1
Yu et al. 2015(69)	1999 - 2013	29	62	M:18 F:11	LNW: 12 NS: 7 MS:5 ES: 5	A6: T1: (34) T2: (34) T3: (21) T4: (17)	S: 22 RT: 28 CT: 17	EA: 7 ER: 15	n/a	27.6
Huang et al. 2007(5)	1994 - 2005	15	69	M: 8 F:7	n/a	B: I: 14 II: 1	S+RT: 10 S+CRT: 3 CRT: 1 UK: 1	OR: 5 ER: 8	n/a	33
Ajmani et al. 2017*(63)	2004 - 2013	696	n/a	n/a	NC: (74.6) PNS: (25.4)	CA7: III: (49.5) IVA: (39.1) IVB: (11.4) UK: (24.3)	S: 305 S+RT: 399 RT incl adj CT	n/a	neg: (73)	24 S: 24.3 S+RT: 8.2
Amit et al. 2017**(31)	1991 - 2016	152	64	M: 65 F: 87	NC: 119 PNS: 32 UK: 1	A7: T3: 97 T4a: 54 T4b: 3	S: 57 S+RT: 73 S+CRT:8 S+RT+NCT: 14	n/a	n/a	41 S:39 S+RT: 41 S+CRT: 47 S+RT+NCT: 27
Gal et al. 2011(6)	2000 - 2007	304	n/a	M:133 F:171	NC: 199 MS: 46 ES:27 ACCS:32	CA7: III: 98 IVA: 77 IVB: 34 IVC:37 UK:58	S: 128 S+RT: 120 RT: 23 UK: 33	n/a	n/a	24.2
Present	2001 - 2017	12	67	M:6 F:6	NC: 7 PNS: 2 UK: 3	CA7: III: 6 IVA:2 IVB: 1 IVC: 3	S: 2 S+RT: 3 S+CRT: 3 S+IT: 1 Pal: 3	ER: 8 Incl ER: 1	n/a	18.2

Abbreviations: NC: Nasal Cavity; NS: Nasal Septum; NV: Nasal Vestibule; NF: Nasal Fossa; NEC: Nasoethmoidal Complex; LNW: Lateral Nasal Wall; MS: Maxillary Sinus; ES: Ethmoidal Sinus; FS: Frontal Sinus; SS: Sphenoid Sinus; ACCS: Accessory Sinus; PNS: Paranasal Sinuses; NPX: Nasopharynx; NLC: Nasolacrimal Duct; SB: Skull Base; UK: unknown; B: Ballantyne Staging System; A6: AJCC 6th edition staging of primary tumor; A7: AJCC 7th edition staging of primary tumor; CA7: AJCC 7th edition clinical staging; S: Surgery; RT: Radiotherapy; CRT: Chemoradiotherapy; CT: Chemotherapy; IT: Immunotherapy; Sys: Systemic Therapy not otherwise specified; NCT: Neoadjuvant Chemotherapy; Pal: Palliative Therapy; OR: Open Resection; ER: Endoscopic Resection; EA: Endoscopic Assisted Resection; OS: overall survival; n/a: not available/not applicable.

*Overlapping source of patient data: National Cancer Data Base

**Overlapping source of patient data: MD Anderson Cancer Center

4 Discussion

Sinonasal Mucosal Melanoma is a rare tumor entity with an average 5-year-OS rates not exceeding 35%. This has not changed in last decades, although treatment options in surgery, radiotherapy and systemic therapy have improved. Given the rarity of this tumor, its anatomically difficult location und its histopathological and immunohistochemical peculiarities, survival rates remain worse compared to cutaneous melanomas. Although some prognostic findings were made by several single- and multicentric studies, nationwide database reviews and meta-analyses discussing prognostic factors and treatment outcomes, there is still no consensus for a standard of treatment regarding adjuvant Therapy. The reasons for this might be the retrospective character of existing studies and their diversity in terms of patient selection, staging and treatment specific survival outcome, which makes bias-free comparison and analysis difficult.

Patient selection

In the present review, information about patient selection differs in numerous studies. While smaller, single-center case series have a limited number of cases and therefore have no specific inclusion criteria, multicentric and nationwide studies can afford more detailed inclusion criteria in terms of patient history, initial staging, curative and palliative treatment intent. Given these differences, statistical comparison and analysis would increase the probability of selection bias and decrease its scientific value.
As in other smaller single-center studies, the present series includes all patients with SNMM treated at our institution. Therefore, it also includes patients with metastatic spread at the beginning of treatment as well as palliative patients with impact on outcome rates.

Principle Symptoms

Due to the anatomical location of the tumors, the lack of symptoms in lower stages might contribute to delayed diagnosis in advanced stages and the generally poor outcome rates. The vast majority of patients throughout the literature had either nasal obstruction or epistaxis or both as principle symptoms (5, 10, 14, 22, 25, 30, 39, 64, 65, 68, 69), which is in accordance to our patient series. Other symptoms reported were facial pain, facial pressure, recurrent rhinorrhea and ophthalmic symptoms like epiphora, diplopia and visual impairment (39).

Location

Several authors found evidence that the location of the primary tumor is an important prognostic factor. Tumors of the nasal cavity tend to have better prognosis in terms of RFS and OS, while patients with the primary tumor arising in the paranasal sinuses have worse outcome (3, 6, 10, 16, 23, 65). A possible cause for this divergence could be that paranasal sinus lesions might be diagnosed at a more advanced tumor stage than lesions in the nasal cavity due to their hidden anatomic location (2, 3, 6, 70). A delayed perception of symptoms in the paranasal sinuses can lead to a deferred time to first contact with a specialist and therefore a prolonged time to diagnosis, while the manifestation of symptoms in the nasal cavity might occur in an earlier stage which would result in earlier diagnosis and treatment (69). Also, epistaxis as a common symptom, indicates that SNMM is frequently diagnosed in an advanced tumor stage (65). Figure 4 shows an overview of the frequency of locations reported in reviewed articles. However, documentation of involved structures varies widely in reviewed studies. Some authors divide roughly into nasal cavity and paranasal sinuses for primary origin while others divide particularly into structures of the nasal cavity such as the lateral nasal wall or the nasal septum, or each one of the sinuses. Also, as bigger tumors involve more than one site, some authors enlist more than one location for one tumor.

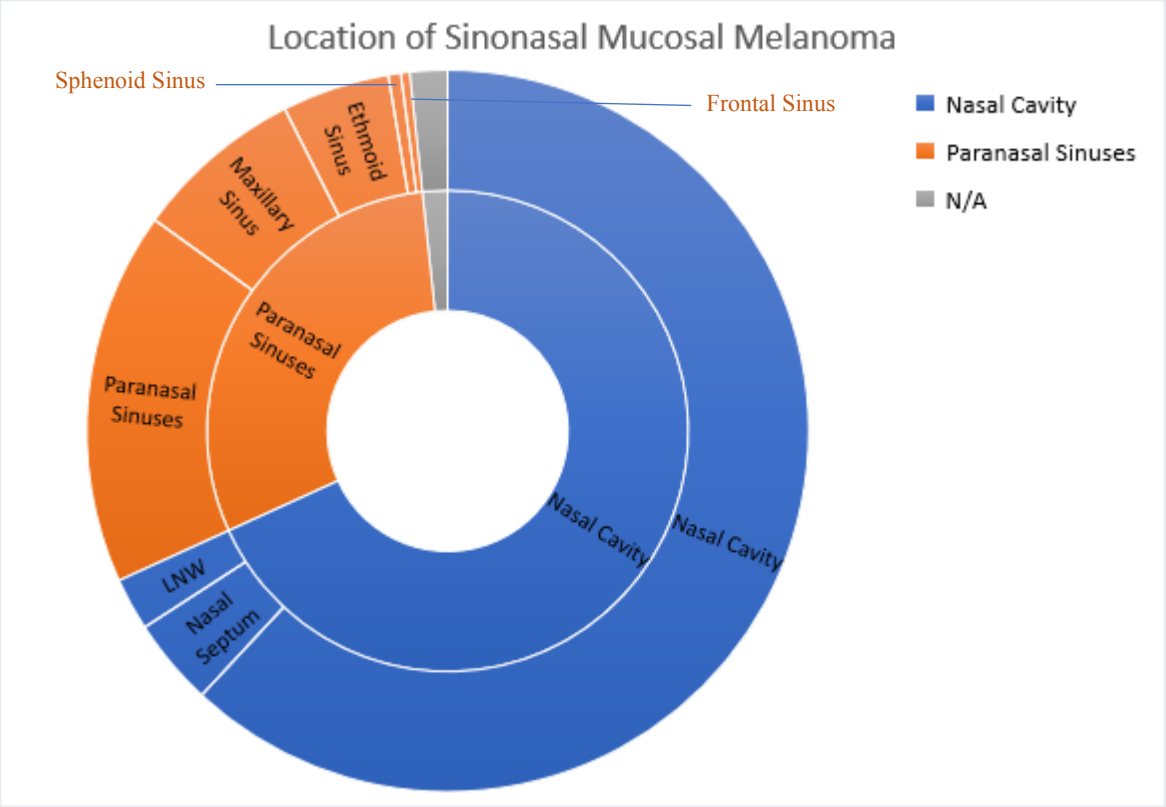

Figure 4. Primary Locations of SNMM as reported in the literature review. Excluding reports of Ajmani et al(63) and Moreno et al(25) due to overlapping patient data and excluding Huang et al(5) due to lack of information

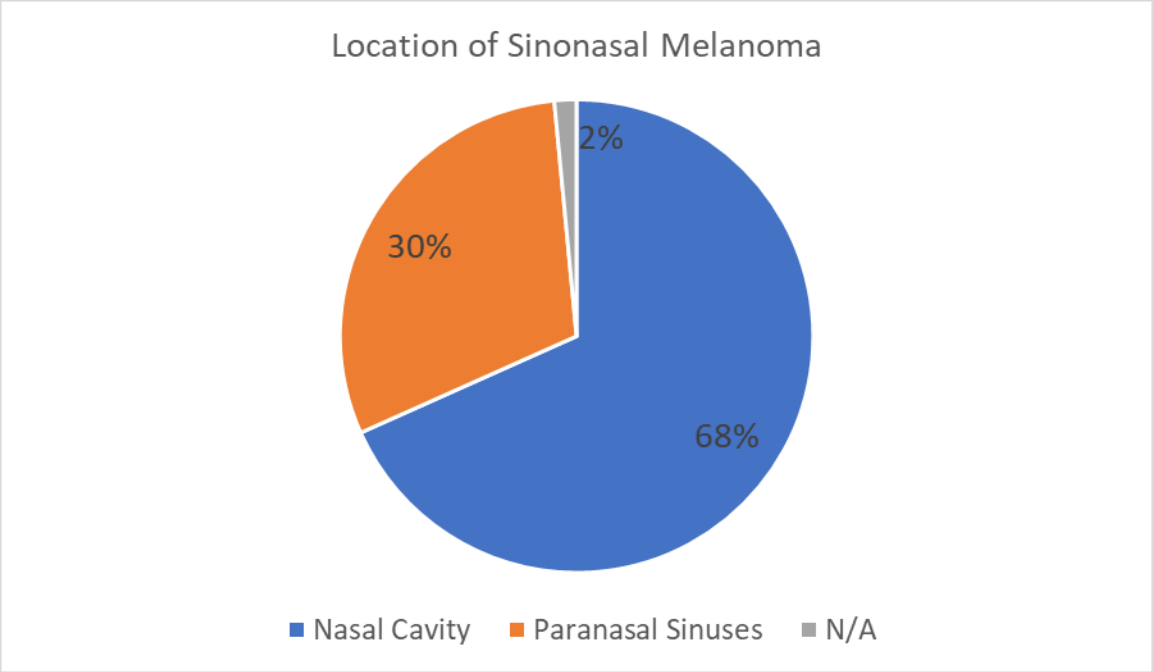

Figure 5. Percental Distribution of Primary Locations in SNMM

Prognostic factors

Numerous different prognostic factors for SNMM were found in literature. Patients with primary tumors arising the nasal cavity had better survival outcome than originating from any of the paranasal sinuses (3, 10, 23, 25, 31, 65, 67). Negative margins after resection also turned out to be a significant prognostic factor by many authors (3, 39, 63, 71). Interestingly, the level of melanin pigmentation was described as prognostic factor by Moreno et al and Yu et al (25, 69). Naturally, patients with advanced stages had worse outcome (6, 14, 23, 30, 39). Also, in the present series patients with T3 lesions tend to have better overall survival than patients with advanced tumors (Figure 3), yet there is no statistical significance due to the low population number.

Staging

There are still several different methods at use to stage SNMM which makes comparison of different series more difficult. The newest staging system of AJCC (7^{th} edition)(36) for malignant melanomas of the head and neck (mmTNM) was introduced in 2010. Although some authors argued that the former carTNM-system of 2002 (AJCC 6^{th})(35) has adequate prognostic value and is internationally better known(30), the mmTNM-system is used with increased regularity in newer series. Several studies have shown that the accuracy of this staging system regarding prognostic evaluation is equal or superior to others, especially in the staging of advanced tumors (4, 6, 72).

Surgery

Complete tumor excision is commonly accepted as standard treatment for patients with SNMM. Several studies have shown that survival is significantly better in patients with free surgical margins (3, 39, 71). Due to the complex anatomy of the sinonasal cavities near vital structures, and the tumors pattern of locally invasive and destructive growth, surgical resection with free margins is challenging and seems not possible in many cases (23, 25, 64, 68). Moreover, radical surgical procedures which often come with significant cosmetic and functional deficiencies do not seem to be justified when over 40% of the patients develop distant metastasis after achieving local control with surgery (20, 25, 31, 41). Because of the lack of prospective, randomized trials concerning SNMM it is not possible to collect data about the quality of life of patients who underwent different surgical approaches (73).

Most studies show similar outcomes in comparing open to endoscopic surgery. Amit et al showed, that the oncological efficacy of endoscopic surgery is similar to open surgery but with a potentially lower risk of morbidity (31).
Won et al demonstrated in their study over 155 patients, that local control rate and survival rate were significantly better when including an endoscopic surgical approach (10). In a series of Moreno et al, 2-year overall survival was significantly higher in patients who underwent an endoscopic resection. However, since an external approach tends to be used in higher staged tumors, the possibility of a selection bias cannot be excluded in these studies (25).
In a review of patients with local recurrence of SNMM, Ledderose et al. showed that there is no significant difference in survival time between open and endoscopic approach (41).
A multicentric study with 58 patients of Lombardi et al. concluded, that endoscopic resection was associated with better overall survival and that these findings would not comprise selection bias because there was no significant association between surgical approach, pT-staging, positive margins and need for adjuvant treatment (39). However, external or combined (endoscopic and external) approaches are still recommended as effective surgical options in SNMM massively infiltrating surrounding and bony structures (39, 43).
Advancements in endoscopic surgery may provide improved techniques for visualization of difficult anatomical circumstances to achieve negative margins in open and endoscopic resections (10, 63). Some authors emphasize that the surgeons experience with endoscopic surgery, a skilled team and adequate equipment are essential to attain free margins by endoscopic resection (10, 42, 66).

Adjuvant Therapy

Adjuvant Therapy in SNMM mostly consists of Radiotherapy, followed by Chemotherapy and infrequently Immunotherapy, also combined approaches are used. There still seems to be no uniform consensus about adjuvant treatment modalities and their outcome in the literature.

Radiotherapy

There is broad consistency in pointing out that adjuvant radiotherapy improves local control reducing local tumor recurrence rate but has no significant survival outcome (3, 10, 14, 23, 25, 29, 65, 68, 69, 74, 75). Yet, this finding was not confirmed in all studies,

suggesting that adjuvant radiotherapy had no positive impact either on local recurrence or overall survival (6, 49, 76).
A multivariate analysis, including age and stage, by Samstein et al. showed, that local recurrence free survival was greater in patients receiving adjuvant RT than not (5yOS 59% vs. 35%). 66% of patients who received adjuvant RT never recurred locally compared to 23% who did not. However, no difference was found in association with OS or DSS (23).
A connection between positive surgical margins, adjuvant radiotherapy, locoregional control or survival outcome could not be found by several authors (63, 66).

Information about radiation dose, fractionation and techniques is inconsistent and different radiation regimens have been presented. Moreno et al found improvement of locoregional control when a total dose of more than 54 Gy was emitted in a standard fractionation schedule (25). This radiation dose was confirmed by Yu et al and Wada et al (69, 75). Meng et al and Caspers et al found improvement of local control giving mean total dosages of 63.4 Gy and 64 Gy, respectively (64, 77). An even higher dosage above 70 Gy is suggested by Greenwalt et al to increase locoregional control (78).
In a recently published retrospective study of 152 patients treated at the MD Anderson Cancer Center, Houston, Texas, Amit el al described a standard scheme for radiation therapy using intensity modulated radiation therapy with a total dose of 60 to 70 Gy at 1.8 to 2 Gy per fraction over 6 to 7 weeks (31). Due to high radiation sensibility of melanoma cells and their concurrently high capacity to overcome sublethal DNA injuries, some authors have discussed the use of hypofractionation (>2.2 Gy) and high-dose per fraction (6-8 Gy) regimens (79, 80). In contrast to this argument, a prospective randomized trial by the Radiation Therapy and Oncology Group did not find any difference in survival comparing standard versus hypofractionated dose regimens in cutaneous melanoma (81). Likewise, other authors could confirm the lack of survival advantage or reduced recurrence rates between patients treated with standard fractionation and hypofractionation and therefore recommend conventional fractionation due to better tolerability (25, 31, 47, 82). Because of the heterogeneity of various studies, it is not always clear which was the prevailing argument for the use of higher dose fractions and since hypofractionation is commonly used in palliative cases, a selection bias cannot be excluded (46).
In a recent nationwide study by Ajmani et al, the addition of standard adjuvant therapy (RT and CRT) does not seem to offer a survival benefit except for advanced tumors staged IVB. They conclude, same as other authors, that due to the lack of survival benefit, the

added morbidity of radiation, radiotherapy should be prescribed individually and with caution (7, 63).

Radiation therapy still seems to be a point of controversy in the literature. The fact that many studies discussing this issue include all mucosal melanomas or even cutaneous melanomas, despite the histopathological differences of SNMM, MMHN and cutaneous melanomas, underlines the need of prospective, nationwide and international, homogeneous patient data to analyze outcomes and treatment options (39, 64).

Systemic Therapy

Systemic Therapy in Sinonasal Mucosal Melanoma does not seem to have the desired effects on survival outcome in advanced stages of the disease (25, 29, 46, 74). While regional lymph metastases are uncommon, distant metastases are one of the main treatment failures of SNMM. Classical chemotherapeutic agents like dacarbazine, or cisplatin-derivates do not seem to significantly impact SNMM, while other treatment approaches like novel immunotherapeutic agents are indicating better response rates and disease control rates for mucosal melanomas (25, 46, 83). On the other hand, Gore et al found, in a metanalysis on survival of SNMM, that particularly the combination of surgery and chemotherapy or Immunotherapy might increase survival in some patients (49). Due to the rarity of SNMM, most studies regarding novel systemic therapies cover subgroups of melanoma including cutaneous and mucosal melanomas.

According to Lian et al, the combination of temozolomide and cisplatin could provide a survival advantage in patients with mucosal melanoma (84).

Studies regarding the effectiveness of adjuvant biochemotherapy indicate, that the addition of Interleukin 2 and Interferon alpha-2 to chemotherapeutic agents like dacarbazine or carboplatin may not improve durable responses or survival outcome (3, 54, 84).

Gene expressions in mucosal melanomas like KIT, NRAS or BRAF might be of potential use for selective inhibitors. Although mutations of these gene expressions were found by other authors, only wild-type sequences were found in assessed tumors of the present series.

In a study by Hodi et al, patients with c-KIT mutations in advanced disease, were treated with the tyrosine kinase inhibitor imatinib and had a tumor response rate 54% and an overall disease control rate of 77% (85). Dummer et al demonstrated in a randomized phase III study of patients with advanced NRAS-mutation positive cutaneous melanoma,

that the MEK inhibitor binimetinib has superior overall response and disease control rates than dacarbazine (56).

Nivolumab and ipilimumab are immune checkpoint inhibitors. Nivolumab showed improved overall survival and better response rate versus dacarbazine in patients with BRAF wild-type melanoma in a phase III study by Robert et al (86). The combination of nivolumab and ipilimumab in patients with mucosal melanoma showed higher efficacy than either agent alone. The overall response rate of the combined treatment was 37%, in contrast to 23% and 8.3% with nivolumab and ipilimumab, respectively (55).

Thus, many authors emphasize the importance of novel systemic therapies in future investigations (8, 20, 31, 39).

5 Conclusion

Surgery with confirmed free margins remains the standard therapy for SNMM. With technological advances in terms of visualization and instruments, endoscopic resections do not seem to be inferior to external approaches. However, surgical approach ought to be chosen based on the probability to gain free margins. Adjuvant radiotherapy with a total radiation dose of 54 Gy or higher with standard fractionation schemes might be considered, if margin status cannot be assessed with certainty or complex anatomic circumstances of the primary tumor make a definite assertion difficult. Local recurrence and distant metastasis remain the main treatment failures in SNMM, even after achieving local control and R0 resections. Although standard chemotherapy does not seem to have satisfactory impact on SNMM, newer biological systemic agents like imatinib or the combination of ipilimumab plus nivolumab might improve overall survival of this fatal tumor. For further evaluation of effectiveness of these novel therapies it is important to consider the possibility of different genetic alterations between the tumor cells of cutaneous melanoma, mucosal melanoma, and particularly sinonasal mucosal melanoma. Therefore, it is necessary to investigate treatment modalities and outcomes distinctly for SNMM.
The number of different heterogenic single-centered or multi-centered case series and nationwide studies, all with a retrospective character, make reasonable comparison with useful statements regarding therapy options, including systemic therapy and survival outcome in SNMM difficult. Many authors in literature conclude similarly, that prospective multicentric studies are needed to reach higher patient numbers and improve scientific conclusions.
Beswick et al designed a multiinstitutional registry for patients with sinonasal malignancies, a web-based, secure database to prospectively collect data in cases diagnosed with Sinonasal malignancies. Seven American institutions were participating at the time of publication (87). This could be an incitement for further research of similar portals, especially in Europe.
In conclusion, early diagnosis, free surgical margins and effective systemic therapy are needed to improve survival outcome in sinonasal mucosal melanoma.

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