European Archives of Oto-Rhino-Laryngology (2019) 276:2259–2265
https://doi.org/10.1007/s00405-019-05458-w

RHINOLOGY

Current concepts in advanced sinonasal mucosal melanoma: a single institution experience

Christian M. Meerwein[1,4] · Martin Hüllner[2,4] · Ralph Braun[3,4] · Michael B. Soyka[1,4] · Grégoire B. Morand[1,4] · David Holzmann[1,4]

Received: 5 March 2019 / Accepted: 30 April 2019 / Published online: 16 May 2019

Abstract

Purpose To present outcome measures of sinonasal mucosal melanoma (SMM) patients with particular focus on current radiological and therapeutic options, especially in the non-curative setting (immunotherapy).

Methods Retrospective study on SMM patients treated at our institution between January 1992 and December 2018.

Results FDG-PET/MRI has emerged as the new hybrid imaging modality, addressing the need for high local tissue contrast in the paranasal sinuses and the skull base, while allowing for whole-body staging in search for distant metastases, including the brain. Primary treatment protocols consisted of tumor resection in 30/34 patients (88%), palliative radiation therapy (RT) in 3/34 patients (9%) and best supportive care therapy in 1/34 patient (3%). Of all the initially operated patients, 25/30 patients (83%) received adjuvant RT. A total of 9/34 patients (26%) was treated with immunotherapy after the previous combined therapy. For patients treated in curative intention, we observed a 1-year overall survival (OS) of 60% (18/30 patients) and a 3-year OS of 40% (12/30 patients). For patients treated with immunotherapy, median progression-free survival (PFS) was 5 months (IQR 0–13.75), with a maximum PFS of 16 months (combination of nivolumab and ipilimumab). However, there was no difference in OS in patients treated with immunotherapy vs. no immunotherapy (log rank 0.99).

Conclusions Sinonasal mucosal melanoma is a highly aggressive tumor, requiring multimodal therapy and developing a substantial incidence of distant metastases. The introduction of FDG-PET/MRI offers new possibilities in the radiological assessment of the tumor and immunotherapy has altered the management in the non-curative setting, resulting in a substantial progression-free survival in selected cases.

Keywords Sinonasal · Mucosal · Melanoma · FDG-PET/CT · FDG-PET/MRI · Immunotherapy · Radiology

Introduction

Sinonasal mucosal melanoma (SMM) accounts for approximately 7% of all sinonasal malignancies, and for 4–10% of all head and neck melanomas [1–3]. Despite multimodal treatment strategies, SMM remains a highly aggressive disease, with a 5-year survival rate ranging between 20 and 50%, and a peak of recurrence at approximately 1 year after initial diagnosis [2, 4, 5]. Radiological assessment consists of cross-sectional imaging, such as computed tomography (CT), magnetic resonance imaging (MRI) and (18F) fluoro-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT (FDG-PET/CT). MRI must supplement CT whenever an infiltration of the orbit or the skull base is suggested. In recent years, FDG-PET/MRI, has emerged as a new hybrid imaging modality suitable for oncologic staging. FDG-PET/MRI may simultaneously address the need for high local tissue contrast in the paranasal sinuses and skull base while allowing for whole-body staging in search for distant metastases (DM), including the brain [6, 7]. The cornerstones of treatment consist of surgical tumor resection followed by radiation therapy (RT) [1, 4]. The outcome heavily depends on the location of the tumor epicenter,

✉ Christian M. Meerwein
christian.meerwein@usz.ch

1 Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Zurich, Frauenklinikstrasse 24, 8091 Zurich, Switzerland

2 Department of Nuclear Medicine, University Hospital Zurich, Zurich, Switzerland

3 Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

4 University of Zurich, Zurich, Switzerland

infiltration of adjacent structures, such as skull base or orbit, and the incidence of DM [1, 8].

Since DM is the most common cause of treatment failure, potent systemic treatment options are required [8, 9]. Here, traditional chemotherapeutic regimens, such as dacarbazine-based protocols or temozolomide with cisplatin have continuously been replaced by immunotherapy [10, 11]. For example, both ipilimumab, an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) fully human monoclonal antibody, and nivolumab, an anti-programmed death 1 (PD-1) agent, were shown to improve overall survival (OS) in advanced melanoma, alone or in combination [12–14].

In context of the above-mentioned issues and based on two previous reports of our cohort, the aim of this study is to present the updated outcome measures of these patients with a particular focus on current radiological and therapeutic options [1, 15].

Methods

Study design

This study received ethical approval from the relevant authorities (ID: KEK 2016-00162). We retrospectively assessed all patients treated for SMM at the department of otorhinolaryngology/head and neck surgery at the University Hospital Zurich (Zurich, Switzerland) between January 1992 and December 2018. Patients with documented statement of unwillingness to contribute personal health-related data to any study were not included. According to our institution's policy, all included patients had initially been discussed in a multidisciplinary tumor board. This study is a follow-up of previously reported data of our cohort in 2010 and 2015 [1, 15].

Staging and therapy

For staging, all patients underwent systematic nasal endoscopy, CT and MRI of the paranasal sinuses. From 2001 on, all patients underwent hybrid FDG-PET/CT or FDG-PET/MRI, the latter being available at our institution since 2013. Before 2001, the imaging workup to rule out DM consisted of abdominal sonography and chest X-ray. All tumors were staged according to the seventh edition of the American Joint Committee on Cancer/Union Internationale Contre le Cancer [16]. Histopathological workup included a next-generation sequencing with an Oncomine Focus Assay (Life Technologies/Thermo Fisher Scientific, Germany) with mutation and amplification analysis for the most common genetic alterations in melanoma patients (e.g., NRAS, KIT, KRAS, BRAF, KIT, MYC).

In a curative intent, primary therapy consisted of surgical tumor resection, done either via transnasal endoscopic, via combined endoscopic skull base or purely craniofacial (external) approaches. Adjuvant RT was administered in all cases except for small isolated tumors in the most anterior portion of the nasal cavity or in case of DM at the time of scheduled RT. Postoperatively, all patients were followed with systematic nasal endoscopy every 2 months and MRI examination every 6 months. The first MRI examination was conducted 3 months after the end of the primary treatment protocol along with the first post-therapeutic FDG-PET/CT or FDG-PET/MRI (if scanned from 2001 on). Loco-regional disease persistence or DM after initial treatment were treated according to the multidisciplinary tumor board decision and included re-operation, classical chemotherapy, immunotherapy, tumor debulking to improve nasal breathing or control tumor bleeding, palliative RT, intralesional interferon-alpha 2a therapy (Roferon©, Roche, Switzerland; 3 Mio. Units per injection) or best supportive care.

Variables and statistical analysis

Data were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) if appropriate. Overall survival was defined from initial diagnosis to the date of death of all causes and included only patients with primary curative treatment intention ($n=30$). Disease-free survival (DFS) was defined from the end of complete primary treatment until relapse (any site) or death of all causes and included only patients, who reached a complete clinical and radiological remission at the end of primary treatment ($n=19$). Kaplan–Meier estimates with calculation of log-rank statistics were performed to present overall survival and DFS, to compare OS for different T categories (cT3a/cT4a vs. cT4b) and for macroscopic clinical and/or radiological residual vs. no-residual disease after curative-intended treatment protocols. In the setting of immunotherapy, progression-free survival (PFS) was defined from the beginning of immunotherapy until the first documented clinical or radiological progression of disease. When comparing OS of patients treated with vs. without immunotherapy, we included only patients with primary curative treatment intention ($n=30$). The end of follow-up was December 2018. Descriptive statistics were made using SPSS for Windows 25.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient, tumor and treatment characteristics

A total of 34 patients with SMM was included. The median age was 72 years (IQR 63–78), and the cohort consisted of 15 males (44%) and 19 females (56%). Initial clinical T classification was cT3 ($n=18$, 53%), cT4a ($n=7$, 21%) and cT4b ($n=9$, 26%). Local tumor extension at initial presentation

included orbital involvement in 10/34 (29%) patients and dural infiltration in 9/34 (26%) patients. Of note, all nine patients with dural infiltration at initial presentation showed simultaneous orbital infiltration (cT4b). The tumor origin was the nasal cavity or the nasal septum in 29/34 (85%) patients, and the paranasal sinuses in 5/34 (15%) patients. In 26/34 patients (76%) we observed a unilocular endonasal tumor at initial presentation, while in 8/34 patients (24%), systematic nasal endoscopy after nasal decongestion revealed multilocular tumor manifestation. Initial clinical nodal classification was cN0 in 32/34 patients (94%) and cN + in 2/34 patients (6%). Initial staging revealed distant metastases in 2/34 patients (6%). Primary treatment protocols consisted of primary tumor resection in 30/34 patients (88%), palliative RT in 3/34 patients (9%) and best supportive care therapy in 1/34 patient (3%). The initial surgical approach was transnasal endoscopic approach in 17/30 patients (57%), combined endoscopic skull base in 6/30 patients (20%), a lateral rhinotomy approach in 4/30 patients (13%) and a transfacial-subcranial approach in 3/30 patients (10%). Of all initially operated thirty patients, 25/30 patients (83%) received adjuvant RT.

Immunotherapy was administered to 9/34 patients (26%) due to loco-regional tumor persistence/recurrence or DM after curative-intended combined therapy. Table 1 provides a detailed overview of subjects and immunotherapy characteristics. In a palliative setting, classical chemotherapy was administered to 4/34 patients (12%) and 5/34 patients (15%) were treated with palliative RT. One patient with a mutilating SMM and infiltration of the skin was treated with intralesional interferon-alpha 2a in addition to palliative RT. This combination lead to a temporary stagnation of tumor growth for 6 weeks.

Follow-up, outcome

The median follow-up duration was 16.5 months (IQR 8–59). At the last follow-up, 8/34 patients (24%) were alive and free of disease, 12/34 patients (35%) were alive with metastatic disease and 14/34 (41%) patients had died from their disease. For patients treated in curative intent, we observed a 1-year overall survival (OS) of 60% (18/30 patients) and a 3-year OS of 40% (12/30 patients) (Fig. 1). Survival estimates stratified by residual vs. no-residual disease after curative-intended treatment revealed a significant worse OS for patients with macroscopic clinical and/or radiological tumor persistence (Fig. 2, log rank = 0.000). When comparing initial clinical T classification cT3/cT4a vs. T4b, we found a robust difference in favor of cT3/cT4a patients, although not significant (log rank = 0.08). Of all 30 patients, who were treated in curative intent, 11/30 (37%) patients showed macroscopic clinical and/or radiological residual disease or progressive disease after completion of the initial treatment protocol. For the other 19 patients, the median disease-free survival (DFS) was 21 months (IQR 9–69), with development of local recurrence

Table 1 Patients that underwent immunotherapy

Age at start of IT	Prior therapy	State of disease at start of IT	Genetic alterations	Protocol	Initial response to IT	PFS after start of IT (months)	Side effects attributed to IT
74	Operation, RT	RD, MD	KRAS und MYC amplification, KRAS mutation	Ipilimumab/ nivolumab (4 ×) Nivolumab (18 ×)	Complete response	13	Thyreoiditis, hepatitis, arthritis, nephritis, rash
72	Operation, RT	LD	MYC amplification	Ipilimumab/ nivolumab (3 ×) Nivolumab (3 ×)	Complete response	8	Dermatitis, enteritis, colitis, hepatitis
73	Operation, RT	MD LD	–	Pembrolizumab	Lost follow-up	NA	Lost follow-up
72	Operation, BT	LD, RD	–	Ipilimumab (4 ×) Pembrolizumab (17 ×)	Stable disease	16	Not applicable (IT at other hospital)
77	Operation, RT	MD LD	–	Ipilimumab (4 ×)	Progressive disease	0	Hypophysitis
69	Operation, RT	LD		Ipilimumab (4 ×)	Progressive disease	2	Not applicable
79	Operation RT	MD	NRAS mutation	Ipilimumab (8 ×)	Progressive disease	0	Hypophysitis
60	Operation, RT, CT	MD, LD	–	Ipilimumab	Partial response	14	Colitis
55	Operation, RT	MD	BRAF mutation	Vemurafenib	Progressive disease	0	Not applicable

Of note: 1) All side effects could be managed conservatively. 2) Vemurafenib is a BRAF-inhibitor and can not be attributed to classical immunotherapy

BT brachytherapy, *CT* chemotherapy, *DM* distant metastases, *IT* immunotherapy, *LD* local disease, *MD* metastatic disease, *PFS* progression free survival, *RD* regional disease, *RT* radiation therapy

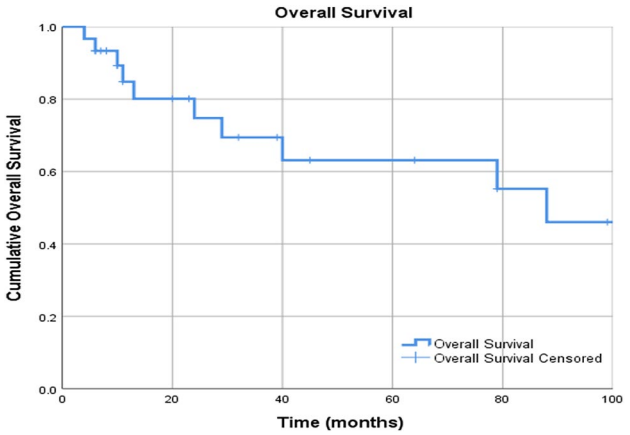

Fig. 1 Overall survival estimates for all patients treated in curative intention ($n=30$)

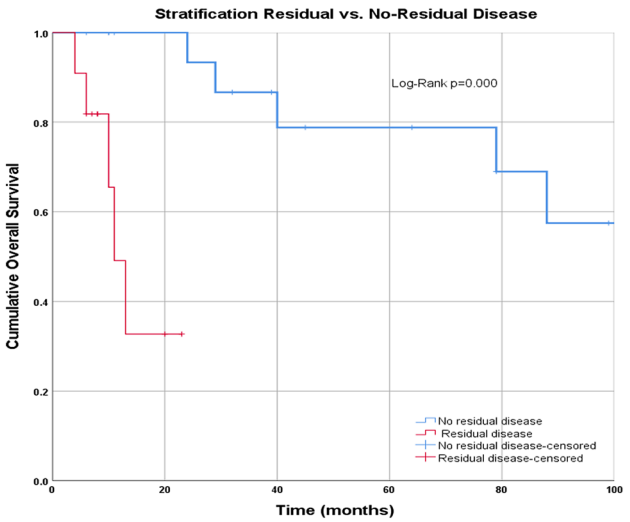

Fig. 2 Overall survival estimates for all patients treated in curative intention ($n=30$) stratified by residual vs. no-residual disease after primary treatment protocols

in 6/19 patients (32%), DM in 5/19 patients (26%) patients and both local recurrence and DM in 2/19 patients (11%) (Fig. 3). For patients treated with immunotherapy, the median progression-free survival (PFS) was 5 months (IQR 0–13.75), with a maximum PFS of 16 months (table 1). However, there was no difference in OS in patients treated with immunotherapy vs. no immunotherapy (log rank 0.99).

Discussion

Sinonasal mucosal melanoma is a highly aggressive neoplasm, typically originating from the nasal cavity or—less frequently—from the paranasal sinuses [1, 17]. At the time

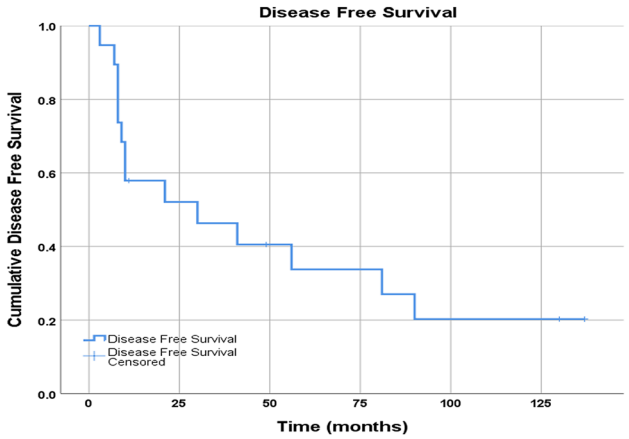

Fig. 3 Disease-free survival estimates after initial treatment protocols for all patients, who reached complete tumor remission ($n=19$)

of initial diagnosis, the tumor is usually locally advanced, shows a multilocular distribution pattern in approximately 25% of all patients and involves pivotal anatomic structures, such as the orbit or the skull base [1, 15, 18]. Those key structures are particularly affected by tumors arising from the ethmoid or maxillary sinus [1]. The presence of both regional and DM at initial diagnosis was rare (2/34 patients each, 6%) in our cohort, which is in line with previous reports [18]. However, DM are known to be the most common cause of subsequent treatment failure [8]. Apart from advanced local tumor extension with dural or orbital involvement and the presence of DM at initial diagnosis, macroscopic tumor persistence after curative-intended primary treatment is a known and strong prognosticator of worse outcome, which was confirmed in our study [1, 15, 18].

The probably most sophisticated cross-sectional imaging modality for initial staging and restaging is FDG-PET/MRI, since it provides detailed anatomical and metabolic information on the loco-regional tumor extent and can assess DM, including brain metastases, in one single examination. Buchbender et al. [19] even postulated FDG-PET/MRI to become a "1-stop-shop whole-body N- and M-staging tool" in melanoma high-risk patients. Besides the lower radiation exposure owing to the absence of CT, FDG-PET/MR has some particular advantages compared to the traditional approach consisting of separately acquired FDG-PET/CT and MRI. A retrospective co-registration of FDG-PET/CT and MR images is often hindered by a different patient positioning, which—particularly in the head and neck—is due to radiofrequency surface coils that are positioned around the head and neck of the patient for MRI, but are absent in PET/CT. Such might lead to a "mismatch" of FDG uptake on retrospectively fused images. When comparing FDG-PET/CT with

FDG–PET/MRI in head and neck cancer, Kuhn et al. [20] showed that FDG-PET/MRI better differentiates tumor tissue from entrapped mucus in sinonasal cavities, that perineural spread can be assessed more accurately using PET/MRI, and that even bony structures, such as the skull base, can be assessed with FDG-PET/MRI with similar accuracy as with CT. A second recent study addressing the initial staging of head and neck tumors found FDG-PET/MRI to yield at least equal diagnostic accuracy as FDG-PET/CT, with additional advantage in soft-tissue contrast, which is of particular importance for the assessment of dural or orbital involvement [7]. Besides one single examination, FDG-PET/MRI has also advantages over two separate scans in terms of overall scanning time, patient throughput and potentially also with regard to costs (depending on local reimbursement policies) [21]. Today, still an important limitation of FDG-PET/MRI is its comparably low availability to the general population, since these scanners are concentrated in Western countries and in academic centers. However, this might change in the next decade (besides, SMM patients are typically treated at larger academic centers). Taking all arguments into account, FDG-PET/MRI has the potential to replace the traditional combination of FDG-PET/CT and MRI in SMM patients.

Depending on the local tumor extent, we opted for a primary surgical, transnasal endoscopic approach in 30/34 patients [1, 22]. However, a substantial dural or orbital involvement may still require a subcranial approach in selected patients, which was the case in 3/30 patients in our cohort. The pursuit of clear surgical margins, which can be challenging to obtain in multilocular disease, and which usually causes high morbidity, needs to be balanced against its disadvantages [15, 18]. A subtotal tumor resection with targeted, adjuvant RT may be preferable in many patients, particularly since a wide surgical resection does not necessarily decrease the rate of distant metastases or improve overall survival [23, 24].

In line with other reports, the majority of our surgically treated patients (35/30 patients, 83%) received adjuvant RT, which was shown to improve loco-regional control but not OS [17, 25]. In the further course of the disease, 7/34 patients (21%) developed regional metastases, and 14/34 patients (41%) DM. This resulted in a 1-year OS of 60% (18/34 patients) and a 3-year OS of 40% (12/34 patients). Previous series reported a 3-year OS ranging between 36 and 43% [18, 26, 17].

While the use of immunotherapy is well documented for advanced, non-mucosal melanomas, there is less evidence for mucosal melanomas, particularly for SMM [27, 28]. Similar to non-mucosal melanoma, a combination of nivolumab and ipilimumab seems to have greater efficacy than either agent alone [28]. In our cohort, immunotherapy was administered to 9/34 patients (26%) between 2012 and 2018, resulting in a median progression-free survival (PFS) of 5 months (IQR 0–13.75), with a maximum PFS of 16 months. Prior to immunotherapy, all nine patients had undergone multimodal treatment protocols and restaging showed DM in 6/9 patients and local tumor persistence in 3/9 patients. Molecular genetic analysis of the primary tumor was performed in all nine subjects and revealed genetic mutations in three patients and amplification of the MYC gene in two patients (Table 1). It is well known that BRAF mutation is very rare in mucosal melanoma (0–3%), while conversely, NRAS mutation and cMYC gene amplification are more common in mucosal melanomas and were identified as independent predictors of poor prognosis [29–31]. In our series, two patients were treated with a combination of ipilimumab and nivolumab [12]. Interestingly, a 74-year-old male patient with regional recurrence and liver and bone metastases showed complete response of all metastases, resulting in a PFS of 13 months until today (Fig. 4). Another 75-year-old female patient with an extended stage T4b tumor involving the orbit and dura showed complete response without any evidence of DM, resulting in a PFS of 8 months (Fig. 5). Another six patients were treated with ipilimumab alone and/or PD-1—checkpoint inhibitor

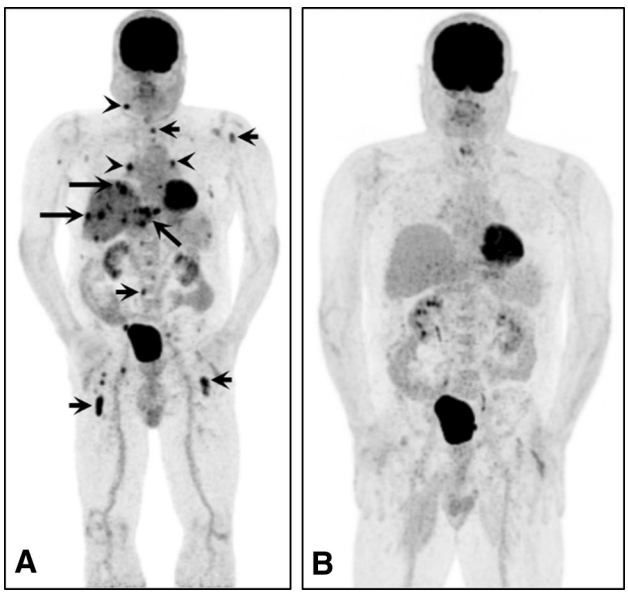

Fig. 4 74-year-old man with sinonasal mucosal melanoma. After the initial curatively intended therapy (transnasal endoscopic tumor resection + adjuvant radiation therapy), the patient developed multiple FDG-avid metastases. The coronal maximum intensity projection (MIP) FDG-PET image **a** shows multiple metastases in the liver (long arrows), multiple bone metastases (arrowheads), and lymph node metastases (short arrows) in the neck and in both pulmonary hili. Nine months later and after immunotherapy with ipilimumab and nivolumab, the coronal FDG-PET MIP image **b** shows complete response of all metastases

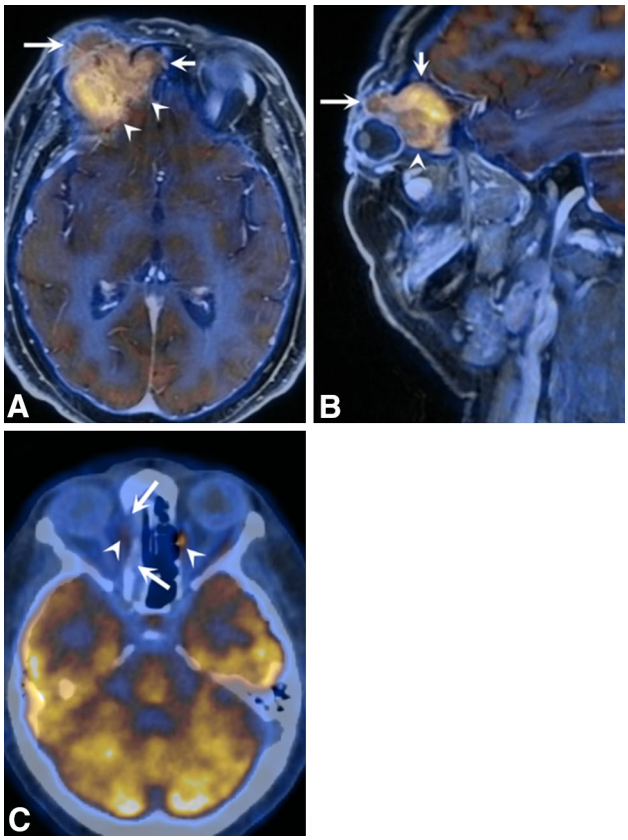

Fig. 5 72-year-old woman with extended T4b sinonasal mucosal melanoma. Axial T1-weighted fat-suppressed contrast-enhanced FDG-PET/MR image **a** shows a moderately FDG-avid tumor (SUV_{max} 7.9) that infiltrates the right-sided fronto-ethmoid recess (short arrow), the supraorbital subcutaneous adipose tissue (long arrow) and the dura of the anterior fossa (arrowheads). Sagittal FDG-PET/MR image **b** shows also infiltration of the fronto-ethmoid recess (short arrow) and the supraorbital subcutaneous adipose tissue (long arrow), along with intraconal extension into the right-sided orbit (arrowhead), causing deformation of the eyeball and exophthalmos. Four months later, after surgical resection, adjuvant radiation therapy and immunotherapy with nivolumab and ipilimumab, the axial (**c**) and sagittal (**d**) FDG-PET/CT images show complete remission of the tumor. An FDG-negative osseous defect persists in the right-sided lamina papyracea and middle ethmoid air cells (arrows). Faint physiological FDG uptake of bilateral extraconal muscles (arrowheads) is seen

pembrolizumab (Table 1). Of these six subjects, one 72-year-old woman showed stable local and regional disease with a PFS of 16 months under serial therapy with ipilimumab and pembrolizumab. Furthermore, a PFS of 14 months with partial response to local and distant disease was observed in a 60-year-old male patient. However, on the other hand, progressive disease was seen in the other four patients under immunotherapy, with three patients receiving ipilimumab alone and one patient vemurafenib, a BRAF-inhibitor. Overall survival was not different in patients treated with immunotherapy compared to no immunotherapy. However, studies on larger populations are needed to profoundly answer the question, if (1) immunotherapy increases PFS compared to conventional therapeutic options in the non-curative setting, and (2), if an increased PFS translates into a higher OS.

Conclusion

We confirmed SMM to be highly aggressive, requiring multimodal therapy and developing a substantial incidence of DM during follow-up. The introduction of FDG-PET/MRI offers new possibilities in the radiological assessment of the tumor and immunotherapy has altered the management in the non-curative setting, resulting in a substantial PFS in selected cases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants/ethical approval retrospective studies This retrospective study received ethical approval from the relevant authorities (ID: KEK 2016-00162).

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Roth TN, Gengler C, Huber GF, Holzmann D (2010) Outcome of sinonasal melanoma: clinical experience and review of the literature. Head Neck 32(10):1385–1392. https://doi.org/10.1002/hed.21340
2. Bridger AG, Smee D, Baldwin MA, Kwok B, Bridger GP (2005) Experience with mucosal melanoma of the nose and paranasal sinuses. ANZ J Surg 75(4):192–197. https://doi.org/10.1111/j.1445-2197.2005.03343.x
3. Thompson LD, Wieneke JA, Miettinen M (2003) Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. Am J Surg Pathol 27(5):594–611
4. Mendenhall WM, Amdur RJ, Hinerman RW, Werning JW, Villaret DB, Mendenhall NP (2005) Head and neck mucosal melanoma. Am J Clin Oncol 28(6):626–630
5. Dauer EH, Lewis JE, Rohlinger AL, Weaver AL, Olsen KD (2008) Sinonasal melanoma: a clinicopathologic review of 61 cases. Otolaryngol Head Neck Surg 138(3):347–352. https://doi.org/10.1016/j.otohns.2007.12.013
6. Sekine T, Barbosa FG, Delso G, Burger IA, Stolzmann P, Ter Voert EE, Huber GF, Kollias SS, von Schulthess GK, Veit-Haibach P, Huellner MW (2017) Local resectability assessment of head and neck cancer: positron emission tomography/MRI versus positron emission tomography/CT. Head Neck 39(8):1550–1558. https://doi.org/10.1002/hed.24783
7. Sekine T, de Galiza Barbosa F, Kuhn FP, Burger IA, Stolzmann P, Huber GF, Kollias SS, von Schulthess GK, Veit-Haibach P, Huellner MW (2017) PET+MR versus PET/CT in the initial staging of head and neck cancer, using a trimodality PET/CT+MR

system. Clin Imaging 42:232–239. https://doi.org/10.1016/j.clinimag.2017.01.003
8. Amit M, Tam S, Abdelmeguid AS, Kupferman ME, Su SY, Raza SM, DeMonte F, Hanna EY (2018) Patterns of treatment failure in patients with sinonasal mucosal melanoma. Ann Surg Oncol 25(6):1723–1729. https://doi.org/10.1245/s10434-018-6465-y
9. Lund VJ, Howard DJ, Harding L, Wei WI (1999) Management options and survival in malignant melanoma of the sinonasal mucosa. Laryngoscope 109(2 Pt 1):208–211
10. Lian B, Si L, Cui C, Chi Z, Sheng X, Mao L, Li S, Kong Y, Tang B, Guo J (2013) Phase II randomized trial comparing high-dose IFN-alpha2b with temozolomide plus cisplatin as systemic adjuvant therapy for resected mucosal melanoma. Clin Cancer Res 19(16):4488–4498. https://doi.org/10.1158/1078-0432.CCR-13-0739
11. Atkins MB, Hsu J, Lee S, Cohen GI, Flaherty LE, Sosman JA, Sondak VK, Kirkwood JM, Eastern Cooperative Oncology G (2008) Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the eastern cooperative oncology group. J Clin Oncol 26(35):5748–5754. https://doi.org/10.1200/JCO.2008.17.5448
12. Larkin J, Hodi FS, Wolchok JD (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373(13):1270–1271. https://doi.org/10.1056/NEJMc1509660
13. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363(8):711–723. https://doi.org/10.1056/NEJMoa1003466
14. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, Smylie M, Dummer R, Hill A, Hogg D, Haanen J, Carlino MS, Bechter O, Maio M, Marquez-Rodas I, Guidoboni M, McArthur G, Lebbe C, Ascierto PA, Long GV, Cebon J, Sosman J, Postow MA, Callahan MK, Walker D, Rollin L, Bhore R, Hodi FS, Larkin J (2017) Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 377(14):1345–1356. https://doi.org/10.1056/NEJMoa1709684
15. Stanimirov Rossi O, Vital D, Soyka MB, Roth TN, Huber GF, Holzmann D (2015) Multilocular sinonasal malignant melanoma: a poor prognostic subgroup? Eur Arch Otorhinolaryngol 272(1):123–129. https://doi.org/10.1007/s00405-014-3098-z
16. Edge SB, Compton CC (2010) The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17(6):1471–1474. https://doi.org/10.1245/s10434-010-0985-4
17. Dréno M, Georges M, Espitalier F, Ferron C, Charnolé A, Dréno B, Malard O (2017) Sinonasal mucosal melanoma: a 44-case study and literature analysis. Eur Ann Otorhinolaryngol Head Neck Dis 134(4):237–242. https://doi.org/10.1016/j.anorl.2017.02.003
18. Sun CZ, Li QL, Hu ZD, Jiang YE, Song M, Yang AK (2014) Treatment and prognosis in sinonasal mucosal melanoma: a retrospective analysis of 65 patients from a single cancer center. Head Neck 36(5):675–681. https://doi.org/10.1002/hed.23355
19. Buchbender C, Heusner TA, Lauenstein TC, Bockisch A, Antoch G (2012) Oncologic PET/MRI, part 2: bone tumors soft-tissue tumors, melanoma, and lymphoma. J Nucl Med 53(8):1244–1252. https://doi.org/10.2967/jnumed.112.109306
20. Kuhn FP, Hullner M, Mader CE, Kastrinidis N, Huber GF, von Schulthess GK, Kollias S, Veit-Haibach P (2014) Contrast-enhanced PET/MR imaging versus contrast-enhanced PET/CT in head and neck cancer: how much MR information is needed? J Nucl Med 55(4):551–558. https://doi.org/10.2967/jnumed.113.125443
21. von Schulthess GK, Veit-Haibach P (2014) Workflow considerations in PET/MR Imaging. J Nucl Med 55(Supplement 2):19S–24S. https://doi.org/10.2967/jnumed.113.129239
22. Lund V, Howard DJ, Wei WI (2007) Endoscopic resection of malignant tumors of the nose and sinuses. Am J Rhinol 21(1):89–94
23. Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, Teitcher J, Panageas KS, Busam KJ, Chmielowski B, Lutzky J, Pavlick AC, Fusco A, Cane L, Takebe N, Vemula S, Bouvier N, Bastian BC, Schwartz GK (2011) KIT as a therapeutic target in metastatic melanoma. JAMA 305(22):2327–2334. https://doi.org/10.1001/jama.2011.746
24. Moreno MA, Hanna EY (2010) Management of mucosal melanomas of the head and neck: did we make any progress? Curr Opin Otolaryngol Head Neck Surg 18(2):101–106. https://doi.org/10.1097/MOO.0b013e3283374d31
25. Li W, Yu Y, Wang H, Yan A, Jiang X (2015) Evaluation of the prognostic impact of postoperative adjuvant radiotherapy on head and neck mucosal melanoma: a meta-analysis. BMC Cancer 15:758–758. https://doi.org/10.1186/s12885-015-1750-7
26. Lombardi D, Bottazzoli M, Turri-Zanoni M, Raffetti E, Villaret AB, Morassi ML, Ungari M, Vermi W, Battaglia P, Castelnuovo P, Facco C, Sessa F, Donato F, Nicolai P (2016) Sinonasal mucosal melanoma: a 12-year experience of 58 cases. Head Neck 38(Suppl 1):E1737–1745. https://doi.org/10.1002/hed.24309
27. Postow MA, Luke JJ, Bluth MJ, Ramaiya N, Panageas KS, Lawrence DP, Ibrahim N, Flaherty KT, Sullivan RJ, Ott PA, Callahan MK, Harding JJ, D'Angelo SP, Dickson MA, Schwartz GK, Chapman PB, Gnjatic S, Wolchok JD, Hodi FS, Carvajal RD (2013) Ipilimumab for patients with advanced mucosal melanoma. Oncologist 18(6):726–732. https://doi.org/10.1634/theoncologist.2012-0464
28. D'Angelo SP, Larkin J, Sosman JA, Lebbe C, Brady B, Neyns B, Schmidt H, Hassel JC, Hodi FS, Lorigan P, Savage KJ, Miller WH Jr, Mohr P, Marquez-Rodas I, Charles J, Kaatz M, Sznol M, Weber JS, Shoushtari AN, Ruisi M, Jiang J, Wolchok JD (2017) Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 35(2):226–235. https://doi.org/10.1200/JCO.2016.67.9258
29. Jakob JA, Bassett RL Jr, Ng CS, Curry JL, Joseph RW, Alvarado GC, Rohlfs ML, Richard J, Gershenwald JE, Kim KB, Lazar AJ, Hwu P, Davies MA (2012) NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer 118(16):4014–4023. https://doi.org/10.1002/cncr.26724
30. Lin X, Sun R, Zhao X, Zhu D, Zhao X, Gu Q, Dong X, Zhang D, Zhang Y, Li Y, Sun B (2017) C-myc overexpression drives melanoma metastasis by promoting vasculogenic mimicry via c-myc/snail/bax signaling. J Mol Med 95(1):53–67. https://doi.org/10.1007/s00109-016-1452-x**(Berl)**
31. Furney SJ, Turajlic S, Stamp G, Nohadani M, Carlisle A, Thomas JM, Hayes A, Strauss D, Gore M, van den Oord J, Larkin J, Marais R (2013) Genome sequencing of mucosal melanomas reveals that they are driven by distinct mechanisms from cutaneous melanoma. J Pathol 230(3):261–269. https://doi.org/10.1002/path.4204