Received: 6 July 2019 | Revised: 31 August 2019 | Accepted: 18 September 2019

DOI: 10.1002/lio2.317

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Survival benefits from concomitant chemoradiotherapy before radical surgery in stage IVA sinonasal mucosal melanoma?

Anna Hafström MD, PhD[1,2] | Eva Brun MD, PhD[2,3] | Simon Persson MD[2] | Johanna Sjövall MD, PhD[1,2] | Peter Wahlberg MD, PhD[1,2] | Lennart Greiff MD, PhD[1,2]

[1]Department of ORL, Head & Neck Surgery, Skåne University Hospital, Lund, Sweden

[2]Department of Clinical Sciences, Lund University, Lund, Sweden

[3]Department of Oncology, Skåne University Hospital, Lund, Sweden

Correspondence
Anna Hafström, Department of ORL, Head & Neck Surgery Skåne University Hospital, SE-221 85 Lund, Sweden.
Email: anna.hafstrom@skane.se

Funding information
Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse; Stiftelsen Acta Otolaryngologica

Abstract

Background: The aim of the study was to review a local treatment protocol for sinonasal mucosal melanoma (SNMM) focusing on triple modality treatment (TMT), that is, neoadjuvant concomitant chemoradiotherapy (CRT) and surgery.

Methods: In a retrospective design, data on clinical presentation, treatment, and survival were retrieved for 22 consecutive patients from a tertiary referral center.

Results: The mean overall survival (OS) for all patients (3 stage III, 16 stage IVA, and 3 stage IVB) was 62 months, and the 5-year OS rate 50%. Four of the 22 patients received treatment with palliative intention. Of the 18 patients who received treatment with curative intention, patients with stage IVA disease who received TMT (n = 10) had a 5-year OS of 70% and 10-year OS of 20%. The median disease-free survival for these patients was 51 months compared with 9 months for stage IVA not receiving TMT (n = 4).

Conclusion: A seemingly favorable survival outcome for a disease with characteristically poor prognosis was observed. The lead finding was a high survival rate (70% 5-year OS) for stage IVA patients who received neoadjuvant TMT. The observations suggest the possibility that patients with advanced SNMM (stage IVA) might benefit from concomitant CRT before surgery by delaying the onset of local recurrences and distant metastases.

Level of Evidence: Level 4, case series (with or without comparison).

KEYWORDS

adjuvant treatment, concomitant chemoradiotherapy, head and neck cancer, mucosal melanoma, sinonasal cancer

1 | INTRODUCTION

Primary sinonasal mucosal melanoma (SNMM) is a rare disease with an incidence of 0.2-1 per million.[1,2] It is more aggressive than its cutaneous counterpart and has a proclivity to metastasize to distant sites.[3] Patients are usually diagnosed at advanced stages, partly reflecting nonspecific presenting symptoms, that is, nasal obstruction and bloody nasal discharge.[4,5] Age, gender, histology, stage, and location (nasal vs paranasal) have been suggested as prognostic factors, but their clinical significance have not been consistently demonstrated.[6] The prognosis for patients with SNMM is dismal and 5-year overall survival (OS) ranges from 20% to 40%.[4,5,7-17] Thus, more effective treatment strategies are needed, but owing to the low incidence of SNMM such regimes have been difficult to develop.[18]

Parts of the results in this study was presented at the Scandinavian Society for Head and Neck Oncology (SSHNO) May 2018 in Kuopio, Finland, and at the Nordic Melanoma Meeting September 2018 in Copenhagen, Denmark.

There is no clear consensus on the optimal management of SNMM, although the primary treatment modality is generally considered to be wide surgical excision. Radiation therapy (RT) is sometimes used in the postoperative adjuvant setting to improve locoregional control.[4,6,19-23] According to US guidelines, adjuvant postoperative RT should be considered for stage III disease and is recommended for stage IVA after surgery, but in Australia postoperative RT is recommended only after nonradical surgery.[3]

SNMM has a high risk of hematogenous spread, and despite radical surgery of the primary tumor, the majority of patients are ultimately diagnosed with distant metastases (many within the first year after diagnosis) and most SNMM patients succumb to distant metastatic disease.[4,17,21,24-27] This may suggest that covert micro metastases are present at the time of diagnosis or around the time of the treatment.[28,29] Arguably, the high rate of distant metastases advocates that other treatment algorithms than postoperative radiotherapy could be more efficacious in this disease. Thus, adjuvant chemotherapy is an additional treatment option.[18,30,31] The efficacy of this treatment is, however, unclear and available information is mostly derived from observational studies.[18] A possible benefit from adjuvant chemotherapy is supported by results of a meta-analysis of 423 patients from 39 studies by Gore et al. Patients who received bimodal treatment that included chemotherapy or immunotherapy or both in addition to surgery had a significantly better survival rate than those who received single modality treatment, that is, surgery or chemotherapy alone.[18] Furthermore, a retrospective study from South Korea which included 32 head and neck mucosal melanoma (MM) and a prospective study from China (189 MM, whereof 86 head and neck MM) indicated survival benefits from adjuvant chemotherapy in patients with head and neck MM.[30,31]

The literature concerning the benefit of neoadjuvant CRT treatment for SNMM is very sparse, with the exception of, for example, Amit et al. They did not find any benefits for patients with SNMM treated with either neoadjuvant or adjuvant chemotherapy. They examined 152 patients with SNMM treated with either surgery alone (n = 57), surgery with postoperative RT (n = 73), surgery with postoperative CRT (n = 8), or induction CRT followed by surgery and postoperative RT (n = 14), respectively, and reported 39%, 42%, 47%, and 27% 5-year OS.[29]

The lack of convincing data from literature about the benefits for patients with SNMM treated with either neoadjuvant or adjuvant chemotherapy, together with the finding that distant metastasis is the most common cause of treatment failure, highlights the importance of revisiting the current therapeutic approach to SNMM.[17] Our referral center has, since the 1990s, opted for a "triple modality treatment" (TMT) approach, that is, concomitant chemoradiotherapy (CRT) before surgery for patients treated with curative intention after having observed that concomitant cisplatin and accelerated hyperfractionated RT before surgery appeared to be effective in patients with locally advanced SNMM.[32]

The aim of this retrospective study was to describe outcome data for a population-based cohort of consecutive patients with SNMM from southern Sweden where the majority of patients treated with curative intention received concomitant CRT prior to surgical recetion, that is, TMT. We report a seemingly favorable outcome for patients receiving TMT compared with the literature.

2 | METHODS

We retrospectively reviewed medical records of all consecutive patients diagnosed with a SNMM in Southern Sweden and seen at Skåne University Hospital, Lund, a tertiary referral center, between 1 January 2001 and 31 December 2014, where treatment recommendation with curative or palliative intent was presented by a multidisciplinary tumor board (MTB). Ethical approval for the study was granted from the regional Ethical Review Board (2018/745). Data retrieved comprised age, gender, histology, stage and location, as well as diagnosis date, date of onset, WHO performance status, and Charlson/Deyo comorbidity index.[33] All patients were retrospectively restaged according to the 7th TNM edition of the International Union Against Cancer.[34] Available clinical information including radiological findings and intraoperative observations were used for staging purposes and to confirm the primary tumor site and extension. Data were gathered from the pathology report, including immunohistochemistry status (S-100, HMB-45, and Melan-A). Treatment data were collected including type and date of surgical resection, RT or CRT, or combinations thereof if applicable. Surgery was considered nonradical if a specimen did not have free margins according to the histopathology report, given that the margin was true, that is, not toward another tumor specimen. Also recorded was followed up, that is, recurrence date and localization, date of death, or last follow-up. Exclusion criteria was earlier SNMM.

Patient characteristics were described with summary statistics. Patients had routine follow-up controls every 3rd to 6th month until death or till 31 December 2018. Disease-free survival (DFS) was measured as the time from the end of primary treatment to the date of documented recurrence or death from any cause. We also assessed local and distant metastasis relapse-free survival (RFS), also measured as the time from the end of primary treatment to the date of documented recurrence or death from any cause. Surviving patients still recurrence-free and/or alive at the date of their last routine follow-up were censored on that date. OS was measured from date of diagnosis to the date of death from any cause. Standard Kaplan-Meier estimates of the censored DFS and OS distributions were computed using SPSS 24.0. The difference between survival curves was assessed by the log-rank test. Because of the small number of patients involved in the study, a multivariate analysis was not performed.

3 | RESULTS

A total of 22 SNMM patients were identified, 12 women and 10 men (median age 68 years, range 51-83). The 5- and 10-year OS rate was 50% and 19%, respectively. Patients with lower stage disease had better survival than higher stage disease ($P < .001$).

3.1 | Patients treated with curative intention

Eighteen patients, 11 women and 7 men (median age 68 years, range 51-83), met the inclusion criteria for treatment with curative intention as recommended by the MTB, that is, had locoregional contained disease and had undergone at least surgical resection with curative intent. Three patients presented with stage III disease, 14 stage IVA, and 1 stage IVB. Patient and treatment characteristics are summarized in Table 1. Presenting symptoms had a median duration of 3 months (range 0-12), the most common being nasal obstruction and epistaxis. All patients had a performance status of 0 according to WHO and the median Charlson/Deyo combined comorbidity index (CCI) was 4.5 (range 2-7).[33] The primary tumor was located in the nasal cavity for 11 (61%) patients. Seven patients (39%) had primary tumors with paranasal location, all involving the maxillary sinus, 2 also the nasopharynx, 3 also the orbital floor, and 2 also the skull base (Table 1). Most tumors (56%) were amelanotic and all featured positive immunohistochemistry stains for S-100, Melan-A, and/or HMB-45.

All 18 patients underwent surgery as part of their primary treatment. The type of surgery ranged from endoscopic surgery (n = 1) to open transfacial maxillectomies (n = 17) which included a craniofacial resection for one patient. Clear surgical margins was achieved in 94% of the cases. Thus, according to the histopathological reports and the discussions at the MTB conference, the surgery was considered as not radical for only one patient. This patient received postoperative RT and was then in remission for 20 months before being diagnosed with liver metastases.

TMT, that is, preoperative concomitant CRT before surgery was only considered for patients with stage IVA and IVB tumors. Thus, 10 of 14 patients with stage IVA disease and 1 patient with stage IVB disease received neoadjuvant TMT. One patient with stage IVA disease received concomitant CRT after radical endoscopic surgery, that is, also TMT, but not neoadjuvant. Exclusion criteria for chemotherapy were inadequate renal function, severe cardiac or other comorbidity, or unacceptable risk of peri/postoperative morbidity or mortality. Intensity-modulated RT was administered 5 days weekly as part of the curatively intended combined treatment. In the neoadjuvant TMT regimen, the RT was hyperfractionated (1.5 Gy twice daily) to a dose of 51 to 66 Gy depending on adjacent vital structures and administered 5 days weekly. Cisplatin was administered concomitantly in weekly doses (40 mg/m^2). In addition, one

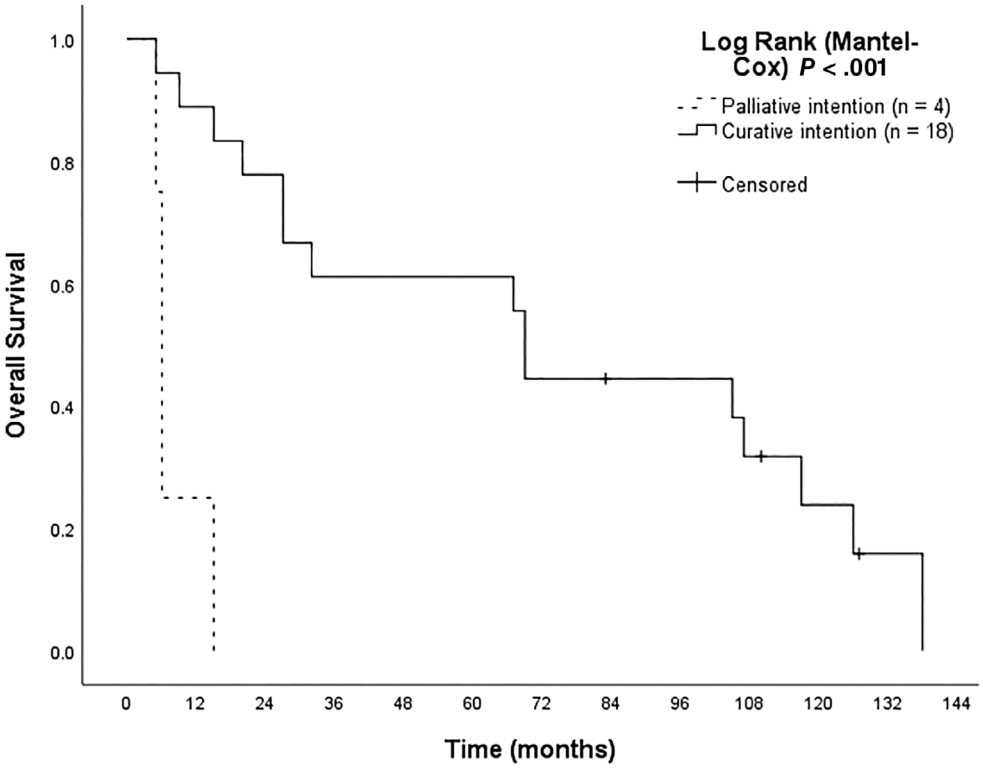
TABLE 1 Tumor and treatment characteristics of the entire cohort of sinonasal mucosal melanoma (SNMM) patients (n = 22)

Year of diagnosis	Gender and age	Stage	Primary tumor site and extension	Treatment intention	OS (months)	DFS (months)	First recurrence and survival outcome
2004	M 57	III	NC	Cur: S	32	27	M DOD
2009	M 67	III	NC	Cur: S	110	51	T Alive
2011	F 64	III	NC	Cur: S + RT	83	80	NED Alive
2001	M 71	IVA	NC: CP	Cur: CRT + S	107	76	T DOD
2001	F 83	IVA	PN: MS	Cur: S + RT	20	11[a]	M DOD
2002	F 78	IVA	NC	Cur: CRT + S	126	120	M DOD
2002	F 63	IVA	NC: MS/CP/NPH	Cur: CRT + S	117	109	T + M DOD
2003	F 77	IVA	NC: Palate	Cur: CRT + S	69	51	M DOD
2004	F 51	IVA	NC	Cur: CRT + S	27	14	M DOD
2005	F 71	IVA	NC	Cur: S	138	5	T DOD
2005	F 64	IVA	PN: MS/Premaxilla	Cur: CRT + S	9	3	M DOD
2006	F 69	IVA	NC: O	Cur: CRT + S	27	11	M DOD
2007	M 58	IVA	NC	Cur: S + RT	15	5	T + M DOD
2007	M 54	IVA	PN: NC/MS/ES/NPH/OF	Cur: CRT + S	67	17	M DOD
2008	M 78	IVA	NC	Cur: CRT + S	127	126	NED Alive
2009	F 60	IVA	NC	Cur: S + CRT	105	14	T DOD
2011	F 69	IVA	PN: NC/MS/Premaxilla	Cur: CRT + S	69	62	M DOD
2002	M 75	IVB	PN:NC/NPH/MS/ES/FS/SB	Cur: CRT + S	5	1	NED DID[b]
2001	F 75	IVB	PN: MS/ES/FS/O/SB	Pall: S + RT	6	0	NA DOD
2004	M 78	IVA	PN: MS/OF	Pall: RT	5	0	NA DOD
2005	M 61	IVA	NC: O	Pall: S	15	0	NA DOD
2014	F 61	IVB	PN: MS/ES/FS/O/SB	Pall: CRT	6	0	NA DOD

Abbreviations: CP, cribriform plate; CRT, concomitant chemoradiotherapy; Cur, curative; DFS, disease free survival; ES, ethmoid sinus, F, female; FS, frontal sinus; M, male; MS, maxillary sinus; NC, nasal cavity; NPH, nasopharynx; O, orbit; OF, orbital floor; OS, overall survival; PN, paranasal cavity; Pall, palliative; RT, radiotherapy; S, surgery; SB, skull base; *First recurrence*: DOD, dead of disease; DID, dead in disease; M, distant metastasis; N, nodal; NA, not applicable; NED, no evidence of disease; T, local.

[a]Surgical nonradicality but received postoperative RT and was in local remission after that.

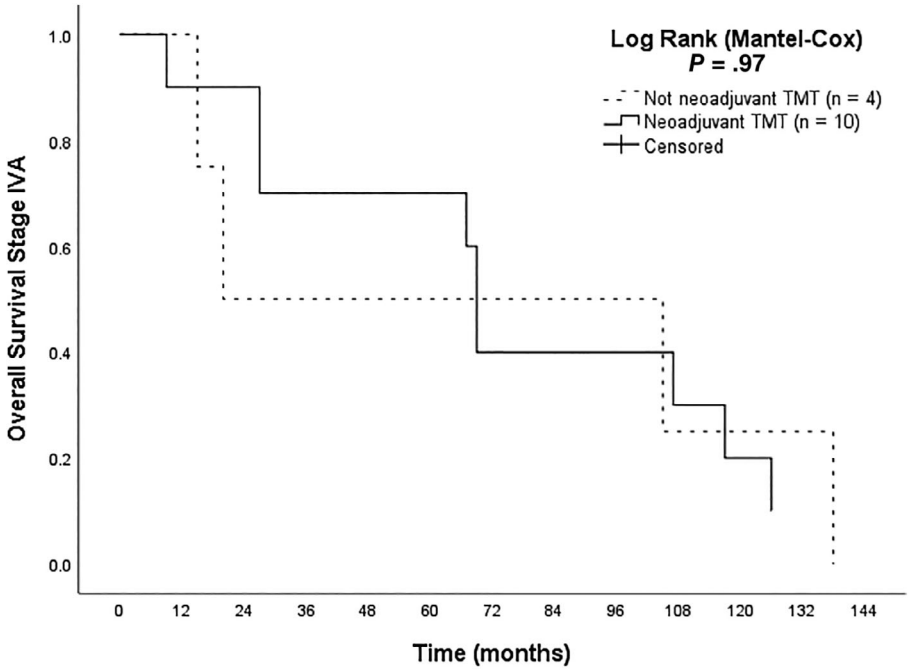
[b]Dies of unknown reasons 1 month after radical surgery.



Numbers at risk (OS)

Months	0	12	24	60	96	120
Palliative	4	1	0	0	0	0
Curative	18	16	14	11	7	3
Events	0	5	3	3	4	4

FIGURE 1 Kaplan-Meier curve depicting overall survival (OS) proportion from initial diagnosis to death for the entire cohort (n = 22). All except three patients died during the follow-up period (all except one from sinonasal mucosal melanoma [SNMM]). The numbers at risk and events are shown in a separate table beneath the figure



Numbers at risk (OS)

Months	0	12	24	60	96	120
Neoadjuvant TMT	10	9	9	7	4	2
Not TMT	4	4	2	2	2	1
Events	0	1	2	2	3	3

FIGURE 2 Kaplan-Meier curve depicting overall survival (OS) proportion from initial diagnosis to death for 14 patients with stage IVA disease treated with curative intention. Ten patients had triple modality treatment (TMT) which included preoperative concomitant chemoradiotherapy and surgery whereas four patients did not. The numbers at risk and events are shown in a separate table beneath the figure

TABLE 2 OS and DFS for stage IVA patients treated with curative intention (n = 14)

		OS (months)			DFS (months)		
Treatment	N	Mean ± STD	Median	95% CI lower to upper bound	Mean ± STD	Median	95% CI lower to upper bound
Not TMT	4	69.5 ± 30.8	20	0.0-108.2	9.0 ± 2.1	6	0.1-11.9
TMT	10	74.5 ± 13.1	70	65.9-72.0	59.0 ± 14.3	51	0.0-120.7
All	14	73.9 ± 12.9	69	65.4-72.6	44.7 ± 11.9	14	6.7-21.3

Abbreviations: DFS, disease-free survival; OS, overall survival; TMT, neoadjuvant concomitant chemoradiotherapy and surgery.

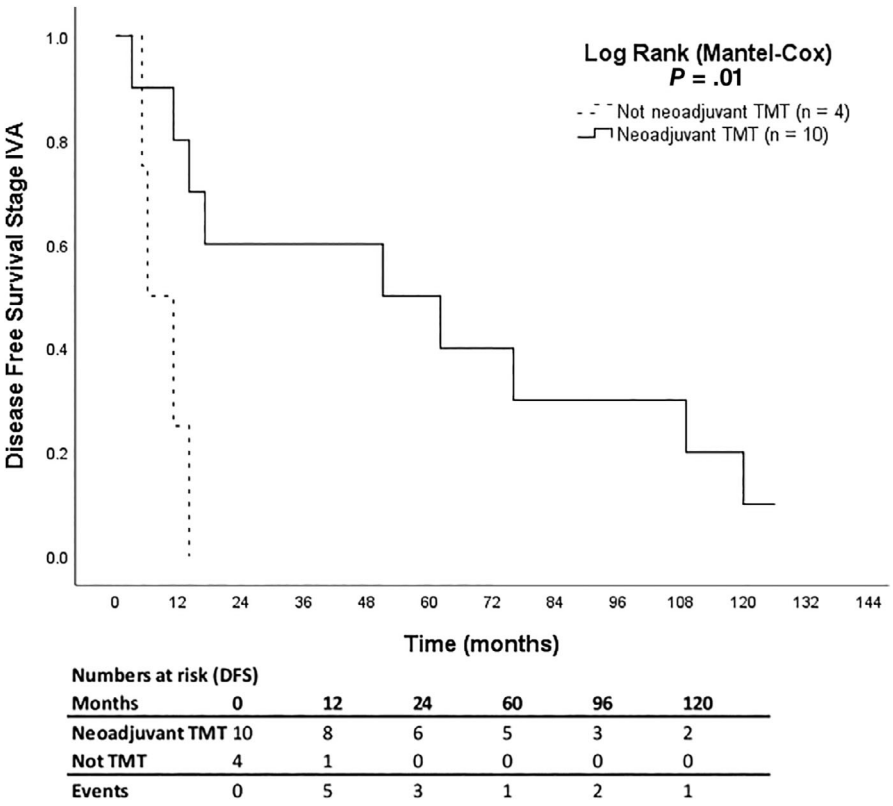


FIGURE 3 Kaplan-Meier curve depicting disease-free survival (DFS) proportion from end of primary treatment to first recurrence for 14 patients with stage IVA disease treated with curative intention. Ten patients had triple modality treatment (TMT) which included concomitant chemoradiotherapy and surgery and four patients did not. The numbers at risk and events are shown in a separate table beneath the figure

patient also administered 5-fluorouracil. At the discretion of the treating oncologist, some patients were judged inappropriate for chemotherapy.

Three patients (14%), two with stage III and one with stage IVA disease, were only treated with surgery, all with clear surgical margins. Three patients (14%), one with stage III and two with stage IVA disease, received double modality treatment, that is, surgery and postoperative RT (two after achieving clear surgical margins). When postoperative RT was administered, the doses were 45 to 66 Gy (1.5-3 Gy per fraction).

Patients were reviewed every 3 months with complete clinical examination including sinonasal endoscopy during the first 2 years and then at least every 6 months until last follow-up or death. The median follow-up duration of alive patients was 110 months (range 83-127) and no patient was lost to follow-up.

The median OS for patients treated with curative intention (n = 18) was 69 months (Figure 1). The 5-year OS rate was 61% and the 10-year OS 24%, without any correlation between given treatment and OS. The 5-year DFS rate was 33% and the 10-year DFS was 15%. Two of the patients in this cohort had no evidence of disease during long-term follow-up (Table 1). Of the initial recurrences, four patients recurred only locally, nine with single or multiple distant metastases, and two with local disease and distant metastases. Distant metastases were located in the lung (60%), brain (40%), liver (40%), other viscera (30%), bone (20%), and distant cutis (10%).

3.1.1 | Stage III (n = 3)

None of these patients had recurrences within 12 months and the median OS was 83 months (Table 1).

3.1.2 | Stage IVA (n = 14)

The median OS for the 10 patients with stage IVA disease who received neoadjuvant TMT was 69 months (5-year OS 70% and 10-year OS 20%) compared to median 20 months for those that did not receive this

treatment (n = 4) (Figure 2 and Table 2). The DFS for patients who received neoadjuvant TMT was significantly longer than for those that did not (P = .01) (Table 2 and Figure 3). All patients with stage IVA disease who did not receive neoadjuvant TMT had recurrences within 14 months, whereas only 3 of the 10 (30%) patients that received TMT did (Table 1). Stage IVA patients who received TMT had a mean local RFS of 99.7 months and a mean distant RFS of 66.4 months, whereas the corresponding numbers was 10.0 respective 8.5 months for stage IVA patients that did not receive TMT.

3.1.3 | Stage IVB (n = 1)

This patient with extensive tumor growth in the nasal and paranasal cavities, as well as the skull base, received neoadjuvant TMT. Unfortunately, he died for unknown reasons only 1 month after craniofacial extensive surgery after having being transferred back to the referring hospital (Table 1).

3.2 | Patients treated with palliative intention

Patients treated with palliative intention (n = 4) had very short survival (median OS 6 months) (Figure 1). The first patient had fast local tumor progression after nonradical debulking surgery and then received palliative RT, the second only received palliative RT because of second primary tumor in the lung, the third only nonradical surgery in the orbit because of choosing not to sacrifice the eye. The initial plan for the fourth patient was neoadjuvant TMT, but tumor progression with intracranial involvement inhibited the planned surgery (Table 1).

4 | DISCUSSION

In this retrospective analysis of 22 consecutive patients with SNMM (where also four patients who received palliative treatment intention were included), we observed a 50% 5-year OS, which seemingly is better than the 20%-40% OS rates reported previously.[4,5,7-17] Our lead finding was a particularly high survival rate in a cohort of 10 stage IVA SNMM treated with neoadjuvant TMT with curative intention: 5-year OS was 70% and 10-year OS 20%. The results warrant attention as they may suggest a favorable survival outcome for a disease with characteristically poor prognosis.

Cancer cells circulating in the blood represent a mechanism by which a tumor can metastasize, and trauma to a tumor, for example, caused by piecemeal resection, may increase their numbers.[35,36] Accordingly, it is established that cancer cell implantation can occur at sites remote from a primary tumor due to surgery.[37] The high rate of distant metastases in patients who succumb to SNMM, verified in this study, may of course reflect that covert micrometastases are present at the time of diagnosis, but a mechanism involving release of cancer cells into the blood caused by a surgery may also be considered.[28,29] An inferred hypothesis is that concomitant CRT before surgery for SNMM, that is, TMT, reduces the risk that circulating cancer cells produce metastases.[37] Neoadjuvant CRT may be particularly important in well-vascularized areas such as the sinonasal region where gross en bloc resection sometimes is not possible and piecemeal surgery is performed either with endoscopic or open transfacial approaches. The high 5-year OS rate (70%) observed in our study for patients with stage IVA disease who received neoadjuvant TMT with curative intention may reflect that this regimen indeed adjourns the establishment of metastases. In agreement, the fact that only one patient in this cohort suffered from local recurrence during the first 5 years of follow-up, represented by a 90% 5-year local RFS, is promising as local failure is considered to be a harbinger of metastatic disease.[24] However, all but two patients who received neoadjuvant TMT eventually succumbed to the melanoma disease, which suggests that this treatment regimen might merely have delayed the onset of metastatic disease.

There is a sparsity of literature on neoadjuvant CRT in SNMM.[29] In contrast to our findings, Amit et al did not find any benefits for patients with SNMM treated with neoadjuvant CRT.[29] In their study, 152 patients with SNMM were treated with either surgery alone, surgery with postoperative RT, surgery with postoperative CRT, or induction CRT followed by surgery and postoperative RT. They reported 5-year OS rate of only 27% for the last cohort which included 14 patients.[29] In our cohort, the 10 patients with stage IVA disease who received TMT with curative intention had a higher survival rate (5-year OS 70%). Because of the retrospective study design and the small number of subjects involved, our findings must be interpreted with caution. However, despite these drawbacks, the patient cohort consists of all consecutive patients diagnosed with SNMM in the referral region from 2001 through 2014. Thus, our findings suggest the potential that patients with advanced SNMM (stage IVA) may benefit from concomitant neoadjuvant CRT before surgery, but prospective studies are warranted.

Malignant melanoma is traditionally regarded as more resistant to RT than many other cancers and a reason may be that the disease features extremely effective sublethal repair mechanisms.[20] In addition, a particular challenge with regard to RT for SNMM is that the tumors are located in anatomical sites surrounded by important radiosensitive structures. There are several studies suggesting that adjuvant RT improves local control in SNMM,[4,6,19-21,26,38] whereas positive effects on survival has been observed infrequently.[8,39] In our study, the 5-year local control rate was 90% in the group of patients who received TMT. This outcome is similar to results reported by Yao et al who demonstrated that primary surgery in combination with postoperative RT plus/minus adjuvant chemotherapy yielded an overall 3-year local control rate of 92% in a cohort of 32 patients with SNMM treated with curative intention.[38] Their patients, however, had less advanced tumors (54% with T3 disease and 46% with T4a disease) than in our curative cohort (17% with T3 disease and 83% with T4a or T4b disease). Furthermore, more of their patients were diagnosed with distant metastasis within 3 years (60%) compared to 40% in our TMT cohort. These outcomes might infer the benefits of deploying a neoadjuvant TMT regimen.

Our results concur with the concept that RT reduces the risk of local recurrences. More than 80% of our patients received RT with curative intention, and only 26% of them had local recurrences as a first recurrence, compared to 66% of patients who did not receive RT. Furthermore, one might speculate that the hyperfractionated RT regimen used in the neoadjuvant setting benefitted the stage IVA patients in our cohort. The 70% 5-year OS for Stage IVA patients is unusually high compared to other studies where patients have received RT in an adjuvant postoperative setting.[4,8,18,39] The dose-fractionation schedule we used in TMT regimen, that is, 1.5 Gy twice daily, might have been beneficial regarding complications as hyper-fractionation is reported to lower the risk of late complications when radiation is delivered to structures such as the nasal cavity and paranasal sinuses.[19]

Thus, any SNMM therapy must entail aggressive local control with minimal toxicity to adjacent structures, and include systemic treatment. Additional studies are needed to assess the efficacy and toxicities associated with radiation dose escalation, particle beam radiation, and RT fractionation, and to determine the role of targeted therapies such as tyrosine kinase inhibitors in the adjuvant treatment of SNMM. Encouraging clinical responses to tyrosine kinase inhibitors in patients with advanced melanomas harboring genetic aberrations suggest that these agents may have an adjuvant and/or neoadjuvant role in SNMM. In addition, immunotherapy has shown promising results in patients with mucosal melanoma, albeit to a lesser extent than in patients with cutaneous melanoma.

In recent years, targeted therapies (ie, inhibitors of c-KIT, NRAS/MEK, BRAF, etc.) and immunotherapies (anti CTLA-4 and anti PD-1/PD-L1) have improved the outcome for patients with cutaneous melanomas.[40] These observations may offer hope also for patients with SNMM. For example, recent molecular findings suggest proto-oncogene KIT aberrations in MM, which may serve as an adjuvant therapeutic target for tyrosine kinase inhibitors.[6] Moreover, Postow et al reported durable responses to ipilimumab (targeting CTLA-4), although with low overall response rates, in a retrospective analysis of 33 patients with unresectable or metastatic SNMM.[41] Additionally, Mignard et al reported that immunotherapy significantly improved survival for patients with metastatic stage IIIC-IV MM. The median OS for 151 patients (39% head and neck) treated with anti-CTLA-4 or anti-PD-1 was significantly longer (16 months) than for 78 patients treated with chemotherapy including at least 1 cycle of carboplatin, fotemustine, dacarbazine, or temozolomide (9 months).[42] These aforementioned results and that the majority of our patients ultimately succumbed might suggest that all patients with SNMM should be offered neoadjuvant and/or adjuvant systemic oncological treatment. Also, because no patient with SNMM is staged lower than stage III, this is in accordance with the present adjuvant treatment protocols for patients with cutaneous malignant melanoma (≥stage III).

5 | CONCLUSION

We found a seemingly higher survival rate for SNMM patients treated with curative intention than reported in the literature. Our findings which should be interpreted with caution given the small number of patients in the study, suggest the potential that patients with advanced SNMM (stage IVA) may benefit from concomitant neoadjuvant CRT before surgery. The results emphasize a need for prospective studies with appropriate comparison groups focusing on adjuvant therapies before and/or after surgery for curatively intended treatments of SNMM.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ORCID

Anna Hafström https://orcid.org/0000-0002-6160-0347

REFERENCES

1. Marcus DM, Marcus RP, Prabhu RS, et al. Rising incidence of mucosal melanoma of the head and neck in the United States. *J Skin Cancer*. 2012;2012:231693.
2. Jangard M, Hansson J, Ragnarsson-Olding B. Primary sinonasal malignant melanoma: a nationwide study of the Swedish population, 1960-2000. *Rhinology*. 2013;51(1):22-30.
3. Pittaka M, Kardamakis D, Spyropoulou D. Comparison of international guidelines on mucosal melanoma of the head and neck: a comprehensive review of the role of radiation therapy. *In Vivo*. 2016;30(3):165-170.
4. Moreno MA, Roberts DB, Kupferman ME, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M.D. Anderson Cancer Center. *Cancer*. 2010;116(9):2215-2223.
5. Letievant JC, Poupart M, Ambrun A, Colin C, Pignat JC. Single-center retrospective series of fourteen patients with mucosal melanoma of the nasal cavity and paranasal sinuses. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2016;133(6):387-391.
6. Lazarev S, Gupta V, Hu K, Harrison LB, Bakst R. Mucosal melanoma of the head and neck: a systematic review of the literature. *Int J Radiat Oncol Biol Phys*. 2014;90(5):1108-1118.
7. Narasimhan K, Kucuk O, Lin HS, et al. Sinonasal mucosal melanoma: a 13-year experience at a single institution. *Skull Base*. 2009;19(4):255-262.
8. Gal TJ, Silver N, Huang B. Demographics and treatment trends in sinonasal mucosal melanoma. *Laryngoscope*. 2011;121(9):2026-2033.
9. Koivunen P, Back L, Pukkila M, et al. Accuracy of the current TNM classification in predicting survival in patients with sinonasal mucosal melanoma. *Laryngoscope*. 2012;122(8):1734-1738.
10. Lund VJ, Chisholm EJ, Howard DJ, Wei WI. Sinonasal malignant melanoma: an analysis of 115 cases assessing outcomes of surgery, postoperative radiotherapy and endoscopic resection. *Rhinology*. 2012;50(2):203-210.
11. Sun CZ, Li QL, Hu ZD, Jiang YE, Song M, Yang AK. Treatment and prognosis in sinonasal mucosal melanoma: a retrospective analysis of 65 patients from a single cancer center. *Head Neck*. 2014;36(5):675-681.
12. Elliot A, Jangard M, Marklund L, et al. Sinonasal malignancies in Sweden 1960-2010; a nationwide study of the Swedish population. *Rhinology*. 2015;53(1):75-80.
13. Lawaetz M, Birch-Johansen F, Friis S, et al. Primary mucosal melanoma of the head and neck in Denmark, 1982-2012: Demographic and clinical aspects. A retrospective DAHANCA study. *Acta Oncol*. 2016;55(8):1001-1008.
14. Samstein RM, Carvajal RD, Postow MA, et al. Localized sinonasal mucosal melanoma: outcomes and associations with stage, radiotherapy, and positron emission tomography response. *Head Neck*. 2016;38(9):1310-1317.

15. Robin TP, Jones BL, Gordon OM, et al. A comprehensive comparative analysis of treatment modalities for sinonasal malignancies. *Cancer*. 2017;123(16):3040-3049.
16. Konuthula N, Khan MN, Parasher A, et al. The presentation and outcomes of mucosal melanoma in 695 patients. *Int Forum Allergy Rhinol*. 2017;7(1):99-105.
17. Amit M, Tam S, Abdelmeguid AS, et al. Patterns of treatment failure in patients with sinonasal mucosal melanoma. *Ann Surg Oncol*. 2018; 25:1723-1729.
18. Gore MR, Zanation AM. Survival in sinonasal melanoma: a meta-analysis. *J Neurol Surg B Skull Base*. 2012;73(3):157-162.
19. Benlyazid A, Thariat J, Temam S, et al. Postoperative radiotherapy in head and neck mucosal melanoma: a GETTEC study. *Arch Otolaryngol Head Neck Surg*. 2010;136(12):1219-1225.
20. Li W, Yu Y, Wang H, Yan A, Jiang X. Evaluation of the prognostic impact of postoperative adjuvant radiotherapy on head and neck mucosal melanoma: a meta-analysis. *BMC Cancer*. 2015;15:758.
21. Lopez F, Rodrigo JP, Cardesa A, et al. Update on primary head and neck mucosal melanoma. *Head Neck*. 2016;38(1):147-155.
22. Amit M, Na'ara S, Hanna EY. Contemporary treatment approaches to sinonasal mucosal melanoma. *Curr Oncol Rep*. 2018;20(2):10.
23. Amit M, Tam S, Abdelmeguid AS, et al. Approaches to regional lymph node metastasis in patients with head and neck mucosal melanoma. *Cancer*. 2018;124(3):514-520.
24. Manolidis S, Donald PJ. Malignant mucosal melanoma of the head and neck: review of the literature and report of 14 patients. *Cancer*. 1997;80(8):1373-1386.
25. Patel SG, Prasad ML, Escrig M, et al. Primary mucosal malignant melanoma of the head and neck. *Head Neck*. 2002;24(3):247-257.
26. Temam S, Mamelle G, Marandas P, et al. Postoperative radiotherapy for primary mucosal melanoma of the head and neck. *Cancer*. 2005; 103(2):313-319.
27. Cheng YF, Lai CC, Ho CY, Shu CH, Lin CZ. Toward a better understanding of sinonasal mucosal melanoma: clinical review of 23 cases. *J Chin Med Assoc*. 2007;70(1):24-29.
28. Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. *J Am Acad Dermatol*. 2007;56(5):828-834.
29. Amit M, Tam S, Abdelmeguid AS, et al. Role of adjuvant treatment in sinonasal mucosal melanoma. *J Neurol Surg B Skull Base*. 2017;78(6): 512-518.
30. Ahn HJ, Na II, Park YH, et al. Role of adjuvant chemotherapy in malignant mucosal melanoma of the head and neck. *Oral Oncol*. 2010;46(8):607-611.
31. Lian B, Si L, Cui C, et al. Phase II randomized trial comparing high-dose IFN-alpha2b with temozolomide plus cisplatin as systemic adjuvant therapy for resected mucosal melanoma. *Clin Cancer Res*. 2013; 19(16):4488-4498.
32. Albertsson M, Tennvall J, Andersson T, Biorklund A, Elner A, Johansson L. Malignant melanoma of the nasal cavity and nasopharynx treated with cisplatin and accelerated hyperfractionated radiation. *Melanoma Res*. 1992;2(2):101-104.
33. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.
34. UICC International Union Against Cancer. In: Sobin LH, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*. 7th ed. Hoboken, NJ: Wiley-Blackwell; 2010:309.
35. Clawson GA, Kimchi E, Patrick SD, et al. Circulating tumor cells in melanoma patients. *PLoS One*. 2012;7(7):e41052.
36. Labelle M, Hynes RO. The initial hours of metastasis: the importance of cooperative host-tumor cell interactions during hematogenous dissemination. *Cancer Discov*. 2012;2(12):1091-1099.
37. Cappell MS. Risk factors and risk reduction of malignant seeding of the percutaneous endoscopic gastrostomy track from pharyngoesophageal malignancy: a review of all 44 known reported cases. *Am J Gastroenterol*. 2007;102(6):1307-1311.
38. Yao JJ, Zhang F, Zhang GS, et al. Efficacy and safety of primary surgery with postoperative radiotherapy in head and neck mucosal melanoma: a single-arm phase II study. *Cancer Manag Res*. 2018;10:6985-6996.
39. Kingdom TT, Kaplan MJ. Mucosal melanoma of the nasal cavity and paranasal sinuses. *Head Neck*. 1995;17(3):184-189.
40. Ascierto PA, Accorona R, Botti G, et al. Mucosal melanoma of the head and neck. *Crit Rev Oncol Hematol*. 2017;112:136-152.
41. Postow MA, Luke JJ, Bluth MJ, et al. Ipilimumab for patients with advanced mucosal melanoma. *Oncologist*. 2013;18(6):726-732.
42. Mignard C, Deschamps Huvier A, Gillibert A, et al. Efficacy of immunotherapy in patients with metastatic mucosal or uveal melanoma. *J Oncol*. 2018;2018:1908065.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Hafström A, Brun E, Persson S, Sjövall J, Wahlberg P, Greiff L. Survival benefits from concomitant chemoradiotherapy before radical surgery in stage IVA sinonasal mucosal melanoma? *Laryngoscope Investigative Otolaryngology*. 2019;4:624–631. https://doi.org/10.1002/lio2.317