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Case report

Radiotherapy alone as a method of treatment for sinonasal mucosal melanoma: A report based on six cases and a review of current opinion

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ABSTRACT

Objectives: Radiotherapy in patients with sinonasal mucosal melanoma (SNMM) was given as alternative treatment to surgery in cases with advanced, inoperable tumors or those not eligible for surgery. We presented the outcomes for patients with SNMM treated with radiotherapy alone.

Material and methods: The retrospective review of 6 consecutive SNMM (nasal cavity – 4 pts. and paranasal sinus – 2 pts.) patients (3 males and 3 females at mean age 64 years) treated between 2008 and 2016 was presented. The stage of disease was: T3 (1 pt.), T4a (3 pts.), T4b (2 pts.); with N0 and M0 in all patients. All patients underwent definitive primary photon radiotherapy (IMRT) alone; dose 66–72 Gy was delivered in 22–24 fractions given in 5 fractions (3 Gy) a week.

Results: The complete remission was observed in all our patients but only one patient survived 5 years without disease. Five patients died due to multiple distant metastases; two of those patients developed associated local recurrence 7–8 months after radiotherapy.

Conclusion: SNMM has a poor prognosis due to its high metastatic potential. Based on our numerically small report and data from literature we concluded that primary radiotherapy alone assured complete remission and even 5-year disease-free survival in only a few individual patients.

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1. Introduction

Sinonasal mucosal melanoma (SNMM) is a rare tumor that accounts for 0.7–1% of all malignant melanomas, approximately 4% of all sinonasal tumors and 8–10% of melanomas occurring in the head and neck (HNMM).^{1–6}

The prognosis for patients with HNMM is currently poor; the 5-year overall survival rate ranges between 8 and 45% of cases, and is usually less than 30%.^{2,3,7–11} HNMM is characterized by relatively frequent local recurrences (26–85%) and distant metastases (18–68%).^{2,9,11–14} Primary surgery, aimed at removing the tumor within the margin of healthy tissue, is the treatment of choice for such patients.^{4–7,9,13,15} Unfortunately, radical procedures are often difficult, mainly due to the dissemination of HNMM, its frequent multi-focal character and complex anatomy in the surgical field associated with the close proximity of numerous critical structures with important functions.^{4,5,10,13,16} If the procedure is not micro- or macroscopically radical, the widely accepted approach is the use of postoperative radiotherapy.^{4,5,7,14,17,18} In patients who are not eligible for primary surgical treatment, primary definitive or palliative radiotherapy is applied.^{4,5,14,17–22}

The objective of our study was to present the outcomes of SNMM patients treated with primary radiotherapy alone, and analyse current views on the role of external radiotherapy as a definitive treatment modality for HNMM.

2. Methods

The study focused solely on SNMM patients who had undergone definitive primary radiotherapy at the Maria Skłodowska-Curie Institute – Oncology Center in Krakow between 2008 and 2016. Patients were referred to our Department of Radiotherapy from Otorhinolaryngology Clinics, either because their cancer was inoperable or they had refused surgery. The extent of the disease was evaluated on the basis of local, thoraco-abdominal and brain CT and head and neck MRIs in all patients, scintigraphy in 2 patients and PET-scan in 4 patients. TNM staging was based on the 7th edition of the AJCC (American Joint Committee on Cancer 2010) classification of SNMM.²³ The radiotherapy toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Weekly follow-ups continued until acute toxicity was easily manageable. To confirm local control, MRI and/or PET-CT was performed every 3–6 months following the end of radiotherapy, and distant metastases were assessed by CT and for PET-CT. The overall survival time was calculated from the start of the treatment to the date of death or last confirmed date of survival.

3. Results

3.1. Patients

We presented six consecutive SNMM patients treated with primary radiotherapy alone; their characteristics are listed in Table 1.

Three males and 3 females were treated. The mean age was 64 years (range, 56–72 years). One patient was diagnosed as stage T3, 3 patients T4a, and 2 patients T4b, according to the 7th edition of the AJCC classification. No cervical lymph node or distant metastases were observed in the initial radiotherapy (N0, M0). Four patients were diagnosed with nasal cavity melanomas (2-T4a N0M0 inferior turbinate, and 2-T4bN0M0 nasal cavity without further anatomic details, because of the advanced state of the disease), one patient had ethmoid sinus melanoma and another sphenoidal sinus melanoma. All the patients reported nasal obstruction and/or epistaxis; one patient reported visual impairment. In four patients the tumour was inoperable, while the other two refused surgery.

Five patients had 3 positive melanocyte markers (S100 protein, HMB-45, and Melan-A); one patient had two positive makers (S100 and HMB 45). Ulceration was observed in 2 patients, and necrosis in one.

3.2. Treatment

All patients were treated with definitive primary photon radiotherapy alone. Doses varying between 66 Gy and 72 Gy were delivered in 22–24 fractions (3 Gy), 5 fractions a week. Intensity modulated radiation therapy (IMRT) was applied. The gross tumor volume (GTV) was determined with CT, MR, and PET-CT. The clinical target volume (CTV) was defined as GTV + 5 mm margins, and the planning target volume (PTV) as CTV with the addition of 3–5 mm. The dose constraint for organs at risk (brain stem and optic nerves/chiasma) was 45 Gy.

3.3. Toxicity

The most common acute toxicities were dermatitis and mucositis, which were observed in all 6 of our patients, ranging from grades 1–2 in 5 patients and grade 3 grade in 1 patient. Conjunctivitis grades 1–2 was observed in 2 patients and middle ear inflammation grade 2 in 1 patient.

The most common late adverse event was chronic sinusitis grades 1–2, noted in all our patients. Watery eyes due to lacrimal duct obstruction grade 2 was observed in 2 patients (Nos. 2 and 6), ototoxicity grade 1 in other 2 patients (Nos. 1 and 3). Patient No. 5 had optic nerve toxicity, resulting in decreased visual acuity (grade 2), 23 months after radiotherapy. No late complications were observed in patient No. 4, alive after 5 years disease free.

3.4. Outcomes

Three months after radiotherapy complete remission of the tumor was observed in all our patients. One patient (T3N0M0) survived more than 5 years disease free. Five patients died due to multiple distant metastases; the mean survival time of these patients was 22.2 months (range, 8–52 months). Distant metastases were observed in the liver (4 patients), the lungs (3 patients) and the brain (2 patients); in two patients metastases were also located in the cervical lymph nodes. Two patients with metastases developed associated local recurrence – 7–8 months after radiotherapy. These patients who developed dis-

Table 1 – The characteristics of 6 patients treated with radiotherapy alone for sinonasal mucosal melanoma.

Patient	Year of treatment	Gender	Age (yrs)	Site of primary	TNM	Outcome
1	2008	F	72	Ethmoid sinus	T4aN0M0	Died after 52 months, no local recurrence, with multiple metastases
2	2010	M	59	Nasal cavity	T4bN0M0	Died after 8 months, with local recurrence and multiple distant metastases
3	2010	F	67	Nasal cavity	T4aN0M0	Died after 12 months, no local recurrence, with multiple metastases
4	2011	F	68	Sphenoidal sinus	T3N0M0	Alive above 5 years without disease
5	2014	M	64	Nasal cavity	T4aN0M0	Died after 28 months, no local recurrence, with multiple metastases
6	2016	M	56	Nasal cavity	T4bN0M0	Died after 11 months, with local recurrence and multiple distant metastases

F, female; M, male.

tant metastases received only supportive care therapy despite their performance status.

4. Discussion

4.1. Our material

The vast majority of SNMM patients receiving primary radiation therapy alone have advanced, inoperable tumors or are ineligible for surgery due to, e.g., their performance status or comorbidities; this group also includes patients who have not given their consent to surgical treatment.^{4,5,7,14,16,17,19–22,24–41}

Four of our patients had inoperable tumors while two refused surgery. As in our group, most studies report a similar incidence between male and female SNMM patients^{1,4,5,30,32}; some researchers observe a slight male predominance.^{5,8,25} All our patients were diagnosed over the age of 55, with a mean age of 64 years, which is consistent with the literature.^{2,5,8,27,28,30,32} The primary location was more frequently located in the nasal cavity (4 patients) than in the paranasal sinuses (2 patients), which is in line with most reports.^{6,8,17,19,21,27}

All our patients were treated with primary photon radiotherapy alone; doses ranging between 66 and 72 Gy were delivered in 22–24 fractions (3 Gy), 5 fractions a week. The IMRT technique was employed. The tumor was in complete remission in all our patients three months after such radiotherapy. The literature demonstrates that complete or partial local remission can be achieved with primary radiotherapy, even in patients with locally advanced SNMM, and in the case of individual patients the 3- or 5-year survival rates are also possible.^{24,28–32} One of our patients had more than 5-year disease-free survival; five other patients died due to multiple distant metastases with a mean survival time of 22.2 months. Two patients with distant metastases developed associated local recurrence, 7 and 8 months after radiotherapy.

Overall, the prognosis for patients with SNMM is currently poor; the overall 5-year survival rate ranges between 8 and 45% of all cases, and is usually less than 30%.^{4–8,12–14,16} The mean survival time for SNMM in the literature varies between 20 and 41.5 months.⁸ The SNMM is characterized by relatively frequent local recurrences (26–54%) and distant metastases (above 60%).^{4–6,14}

4.2. Data from the literature

In 2004, Wada et al. summarized an analysis of 31 HNMM patients, 20 of whom were treated with primary radiotherapy alone and 11 were irradiated due to massive macroscopic residual lesions after surgery. Cobalt-60 telegamma therapy was the treatment used for 7 patients while 10 MeV photon irradiation was applied in 24 cases. The total radiation dose ranged from 32 to 64 Gy (median 50 Gy) and the fractionated dose varied between 1.5 and 13.8 Gy. In 17 cases, the fractionated dose was ≥ 3 Gy, while in the remaining 14 patients it ranged from 1.5 to 2.5 Gy. Full remission was achieved in 9 (29%) patients and partial remission in 18 (58%). The three-year overall survival was 33%. Local recurrences were noted in 13 (41.9%) patients and distant metastases in 11 (35.5%). In 10 patients irradiated due to massive gross residual tumors, local control was not observed. Patients irradiated with a fractionated dose ≥ 3 Gy had a statistically significantly higher rate of local regression. Late grade 3 and 4 complications, manifesting themselves in the form of mucosal necrosis and persistent bleeding, developed in 2 (6.5%) patients.¹⁹

In 2007, Combs et al. presented an analysis of 8 patients with SNMM irradiated with IMRT dose of 66 Gy and using conventional fractionation (1.8–2.2 Gy). The three-year overall survival rate was 75% and the 3-year local recurrence-free survival rate was 57.1%.³³

In 2008, Wagner et al. reported 4 patients irradiated with a dose of 69.2 Gy delivered twice daily in fractions of 1.2 Gy with a 6-h interval. Local control was observed in 1 (25%) patient.²⁵

In 2011 Thariat et al. analysed a group of 23 patients with SNMM and reported that definitive radiotherapy was proposed for two elderly patients in whom the extent of the disease hindered surgery. The radiotherapy protocol consisted of three series of 18 Gy doses (three fractions of 6 Gy each, every other day for 1 week) with scheduled 3-week treatment breaks. One patient achieved local disease control.¹⁸

In 2013, Ozyigit et al. presented the outcomes of 4 SNMM patients treated in 2007–2009 using a Cyber Knife. The therapy was delivered in doses of 30 Gy administered in 3 fractions or 35 Gy in 5 fractions. Full tumor regression was achieved in three patients for a period of 26 months. Partial regression was observed in 1 case. Two patients survived for 2 years with no signs of the disease. One patient developed complications in the form of hard palate perforation, which required surgical

intervention. In one patient, who died due to dissemination of the disease, necrosis had affected a fragment of the temporal lobe.²⁰

In 2015, Bourgeois and Singh reported 2 patients with SNMM who were irradiated in Roswell Park with a single dose of 15 Gy using IMRT. These were cases involving inoperable recurrent tumors after surgery, and the treatment was palliative. One patient survived 7 years without any signs of the disease and the other achieved remission but developed a local relapse, which along with distant metastases led to the patient's death.²²

Christopherson et al. (2015) used a dose of 45–70 Gy (conventional fractionation) and achieved local control in 2 out of 5 patients (40%) with SNMM.³⁴

It seems certain that primary radiotherapy in SNMM patients should at least be conducted using the IMRT technique.

4.3. Charged particle therapy

In recent years, numerous reports have addressed the use of proton and carbon ion radiotherapy in the case of patients with HNMM, mostly with SNMM.^{21,26,27,35–40}

Published results of carbon ion or proton radiotherapy used in with HNMM (especially with SNMM) showed that 5-year local control and overall survival averaged 52–83% and 51–58% respectively for proton radiotherapy, and 75–84% and 27–35%, respectively, for carbon ion radiotherapy.^{21,26,35,40}

In 2014, Patel et al. presented a systematic review and meta-analysis to compare the clinical outcomes of patients with paranasal sinus and nasal cavity malignant tumors and treated with charged particle therapy with those of individuals receiving photon therapy. Out of 41 studies, a total of 43 cohorts were identified; 30 cohorts were treated with photon therapy (1186 patients), whereas 13 received charged particle therapy (286 patients). Overall, 1472 patients were included (approximately 12% with SNMM). These studies suggest that charged particle therapy might be associated with better outcomes for malignant diseases of the nasal cavity and paranasal sinuses.³⁸

According to an Ordinance of the Polish Minister of Health, sinonasal mucosal melanoma has been one of indications for proton radiotherapy since 2016. At the time of writing, two patients received proton radiotherapy for SNMM at our Center. Mucosal reaction in grade 3 was observed in both, and skin reaction was 2 and 3 grade.

5. Conclusion

Primary radiotherapy is recommended as the standard option for SNMM patients with advanced, inoperable tumors or for those who do not qualify for surgery due to their poor performance status; this group also includes patients who did not consent to surgical treatment. Primary radiation therapy alone can be used as both radical and palliative treatment. It has been proven that primary radiotherapy offers the possibility not only of good palliation effects, but also, in individual cases, complete local remission with 3 or 5-year survival. Unfortunately, the prognosis for patients with SNMM remains poor

due to the strong metastatic potential of these tumors; survival might be improved by a combination of radiotherapy with effective neoadjuvant or adjuvant systemic treatment.

Conflict of interest

None declare.

Financial disclosure

None declare.

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