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Clinical patterns and outcomes of patients affected by primary malignant melanoma of the oral mucosa: A European multicenter retrospective chart review

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ABSTRACT

Introduction: The purpose of this European multicenter study was to describe and assess the characteristics, diagnosis, management, and recurrence of oral malignant melanoma at different European oral and maxillofacial surgery centers.

Materials and methods: This study was based on a systematic computer-assisted database that allowed the recording of data for all primary oral mucosal melanomas treated in the involved surgical units across Europe between January 1, 2003 and December 31, 2022. The following data were recorded for each patient: gender, age, site, TNM staging, metastases, symptoms, imaging features, histopathological features, treatment, complications, recurrence, follow up, and survival.

Results: A total of 29 patients (15 females, 14 males) with a primary oral mucosal malignant melanoma fulfilled the inclusion criteria. The mean age was 64.4 years. The most frequent primary site was the vestibular and crestal maxillary gum. Nineteen patients had been diagnosed with a T3 oral melanoma, nine patients with a T4a oral melanoma, and one patient with a T4b neoplasm. Three patients had distant metastases at diagnosis. Clinically, the most frequently observed clinical features were hyperpigmentation, nodular appearance, ulceration, and hemorrhage. Among the 27 surgical cases, radical/clear margins were obtained in 24 cases, non-radical/invaded margins were obtained in two cases, while in one case a non-specific result of margin positivity was found. The overall 2-year survival was 62%. The 2-year disease-free survival was 52%.

Conclusions: Oral mucosal melanoma is an aggressive and often asymptomatic malignancy. The overall long-term survival for patients with oral mucosal melanoma is poor, with a high rate of distant metastasis, independently

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from the performed treatment. Prevention and early diagnosis could be crucial to improving the disease-free survival of patients with oral mucosal melanomas.

1. Introduction

Oral malignant melanoma is an extremely rare tumor, representing 0.2–8.0% of all melanomas and 0.5% of all oral malignant neoplasms. Oral mucosal melanomas differ significantly from skin melanomas, both epidemiologically and genetically, with extremely lower survival rates compared with skin melanomas (Ascierto et al., 2017; Chae et al., 2020; Kuk et al., 2016).

Oral melanomas generally occur in the fifth decade, although they have been reported in patients between 20 and 80 years. They most frequently affect the palatal mucosa and the maxillary gingiva, followed by the mandibular gingiva, buccal mucosa, tongue, and floor of the mouth.

The etiopathogenesis of oral melanomas remains unknown, with hypothesized roles of chronic trauma (e.g. ill-fitting dentures), tobacco use, and environmental pollution (Meleti et al., 2007; Patrick et al., 2007; Rapidis et al., 2003).

The extremely low incidence of this malignant tumor has prevented consensus on an established protocol regarding treatment, with different combinations of surgery, radiotherapy, chemotherapy, and immunotherapy previously reported. Nevertheless, the extensive surgical resection of the tumor mass seems to represent the treatment of choice (Sääksjärvi et al., 2024; Sortino-Rachou et al., 2009; Tamura et al., 2024).

The prognosis for oral malignant melanoma is very poor, with a reported 5-year survival rate ranging between 5% and 20%. This low survival rate may be due to the histopathological characteristics, late diagnosis, or anatomical considerations that are associated with oral malignant melanomas (Tyrrell and Payne, 2018; Umeda et al., 2002).

Because of the rarity and low incidence of oral melanoma, large clinical case series are lacking, with most clinical information based on case reports.

The purpose of this European multicenter study was to describe and assess the characteristics, diagnosis, management, and recurrence of oral malignant melanoma at different European oral and maxillofacial surgery centers, in order to decrease the bias of patient selection, increase the size of the study population, and provide information about the current trends in oral melanoma management across Europe.

2. Materials and methods

This study was based on a systematic computer-assisted database that allowed the recording of data from all the treated oral mucosal melanomas from the involved surgical units across Europe between January 1, 2003, and December 31, 2022. Only patients with primary oral mucosal malignant melanomas were included. The outcome of interest was the collection of uniform data regarding the epidemiology and management of odontomas.

The following data were recorded for each patient: gender, age, voluptuary habits, comorbidities, site of oral melanoma, TNM staging (according to the UICC/AJCC 8th edition), level of lymph node metastases, distant metastases, symptoms and clinical features, mucosal melanoma type according to Tanaka classification, imaging features, histopathological variants, histopathological depth of invasion, immunohistochemistry, treatment, length of hospital stay, complications, recurrence, follow up, and survival.

To categorize the site distribution, the following oral subsites were considered: vestibular and crestal maxillary gum, hard/soft palatal mucosa, tongue, buccal cheek mucosa, upper lip mucosa, lower lip mucosa, oral floor, mandibular gum. The following symptoms and clinical features were recorded: hyperpigmentation, amelanotic appearance, macular appearance, nodular appearance, hemorrhage, ulceration.

With regard to histopathological features, collected oral melanomas were phenotypically categorized as epithelioid, spindle, plasmacytoid, or mixed variants. Histopathological depth of invasion of included tumors was classified as: melanoma in situ, 1–4 mm of invasion, 5–10 mm of invasion, and >11 mm of invasion.

The following treatment options were considered and noted for each patient: surgery, chemotherapy, radiotherapy, or medical treatment. Data regarding surgical intervention, margin status, neck dissection, and surgical reconstruction were also recorded.

Statistical significance was determined using the χ^2 test or, if the sample sizes were too small, the Fisher exact test. Statistical significance was set at 0.05. Helsinki Declaration guidelines were followed, according to local laws. STROBE criteria for observational studies were followed. Ethical approval was obtained by the individual centers, if needed, according to local laws.

3. Results

In total, 29 patients (15 females, 14 males) with an oral mucosal malignant melanoma fulfilled the inclusion criteria and were included in the study.

The mean age of the study population at diagnosis was 64.4 years (median 67 years, standard deviation 14.9 years, range 26–85 years). Most patients (nine patients, 31%) were in the 60–69 years age group, followed by eight patients (27.6%) in the 70–79 years group (Table 1).

With regard to voluptuary habits, 20 patients reported neither smoking nor alcohol consumption, six patients reported smoking only, two patients both alcohol consumption and smoking, and one patient alcohol consumption only.

Overall, no comorbidities were reported in 11 patients, while the remaining 18 patients were affected by one or more comorbidities, including hypertension (11 patients), diabetes (three patients), and dyslipidemia (three patients).

The most frequent primary site for oral mucosal malignant melanoma was the vestibular and crestal maxillary gum (14 patients), followed by palatal mucosa (seven patients), and buccal cheek mucosa (three patients) (Table 2).

With regard to staging, 19 patients had been diagnosed with a T3 oral melanoma, nine patients with a T4a oral melanoma, and one with a T4b neoplasm. Staging is summarized in Table 3. At diagnosis, neck node metastases were found in eight patients, while three patients had distant metastases (two cases of lung metastasis and one case of septal mucosa metastasis).

Clinically, the most frequently observed clinical features were hyperpigmentation (17 patients), nodular appearance (17 patients), ulceration (11 patients), and hemorrhage (six patients). With regard to hyperpigmentation, most lesions had a brown appearance (eight

Table 1
Study population gender according to age group at diagnosis.

Age group	Male	Female	Total
20–29	1	0	1
30–39	1	0	1
40–49	2	0	2
50–59	3	1	4
60–69	3	6	9
70–79	3	5	8
80–89	1	3	4
TOTAL	14	15	29

Table 2
Sites of primary oral mucosal malignant melanomas.

Site	Number	Percentage
Vestibular and crestal maxillary gum	14	48%
Hard/soft palatal mucosa	7	24%
Buccal cheek mucosa	3	10%
Lower lip mucosa	2	7%
Mandibular gum	2	7%
Upper lip mucosa	1	4%
Total	29	100%

Table 3
Staging of oral mucosal melanoma patients.

Stage	Male patients	Female patients	Total
Stage 3	6	8	14
Stage 4a	4	5	9
Stage 4b	2	1	3
Stage 4c	2	1	3

patients), with the rest presenting grey and blue/blueish colors. The mucosal melanoma types were classified according to the Tanaka classification (Table 4).

A CT scan had been performed in all patients. In 15 patients, MRI was also performed: in the T1 sequences, hyperintensity was observed in eight cases and hypointensity in seven cases; in the T2 sequences, hyperintensity was observed in six cases and hypointensity in seven cases.

With regard to histopathological phenotypes, a mixed variant was found in 14 patients, a spindle variant in two patients, and a plasmacytoid variant in the remaining case. Table 5 summarizes the histopathological depth of invasion of included tumors. In terms of immunohistochemistry, the most frequently observed characteristics in the study population were: S-100+ (16 patients), HMB45+ (10 patients), melanA+ (nine patients), vimentin+ (eight patients), and cytokeratin− (eight patients).

The adopted treatment options are summarized in Table 6. Among the 27 surgical cases, radical/clear margins were obtained in 24 cases, non-radical/invaded margins were obtained in two cases, and in one case a non-specific result of margin positivity was found. With regard to surgical treatment of the neck, among the 27 surgical cases, no neck dissection was performed in 14 patients, while in 10 cases a neck dissection was performed. In two patients the 'sentinel lymph node biopsy' technique was applied, and in one case a nodal biopsy was performed. The surgical reconstruction options are presented in Table 7.

Among the cases who underwent radiotherapy only or radiotherapy associated with other treatment options, all patients received IMRT (see Table 8). The dosage ranged between 24 Gy and 66 Gy.

Among the seven patients who received medical treatment as the first-line management therapy, together with surgery and radiotherapy, three patients were administered immunotherapy (pembrolizumab), two patients were administered BRAF inhibitors (dabrafenib), one patient was administered high-dose interferon (IFN), and one patient was administered MEK inhibitors (tramtenib). The patient who underwent chemotherapy only was not admitted to hospital for a hospital stay.

Table 4
Oral mucosal melanomas according to the Tanaka classification.

Type	Number
Pigmented, nodular type	14
Non-pigmented, nodular type	5
Pigmented, macular type	3
Pigmented, mixed type	1
Non-pigmented, mixed type	1
Unknown	5

Table 5
Histopathological depth of invasion.

Depth	Number of patients
Melanoma in situ	1
1–4 mm	19
5–10 mm	3
≥11 mm	6

Table 6
Adopted treatment options in the study population.

Treatment option	Number	Percentage
Surgery	14	48%
Surgery + radiotherapy + medical treatment	7	24%
Surgery + chemotherapy	3	10%
Surgery + radiotherapy	3	10%
Chemotherapy	1	4%
Radiotherapy	1	4%
Total	29	100%

Table 7
Surgical reconstruction.

Type of reconstruction	Number of patients
None	13
Radial forearm flap	6
Fibula flap	2
ALT flap	1
Local flap or temporal flap	5

Table 8
Complications.

Complications	Number of patients
Oronasal communication	2
Infection	1
Hemorrhage	1
Delirium	1
Oropharyngeal incompetence	1
Osteoradionecrosis	1

Mean hospital stay for surgical patients was 10.7 days (range 2–25 days, median 10 days, SD 5.15).

Local recurrence was observed in four cases. During follow-up, regional node metastases were observed in six cases, whereas in 12 patients one or more distant metastases were observed (Table 9). The follow-up outcomes are summarized in Table 10. The overall 2-year survival was 62%. The 2-year disease-free survival was 52%.

There were no statistically significant differences in survival according to age, sex, primary site, node or distant metastases, depth of invasion, or treatment.

4. Discussion

The objective of this European multicenter study was to present clinical and histological characteristics of oral malignant melanoma, as well as details of treatment and prognosis. Due the rarity of oral

Table 9
Localizations of distant metastases at follow-up.

Site of distant metastasis	Number
Lung	8
Bone	5
Liver	3
Brain	2
Abdomen	1

Table 10
Follow-up outcomes.

Outcome	Number of patients	Months of follow-up (mean)
DOD, died of disease	12	24.3 months
AWD, alive with disease	2	43 months
NED, no evidence of disease	11	44.5 months
Dead of unknown/other cause	3	16.7 months
Lost to follow-up	1	12 months

malignant melanoma, it is difficult to perform extensive population studies. For this study, the data from 11 different European departments of maxillofacial and oral surgery were combined to improve the quality of the data and to decrease the bias of patient selection.

Melanocytes are ectomesenchymally derived dendritic cells that represent the cells of origin of primary melanocytic lesions, being present in the germinative layer of the epidermis and mucosal epithelium (Ascierto et al., 2017; Chae et al., 2020; Kuk et al., 2016).

Oral mucosal melanomas typically arise later than cutaneous melanomas, with a possible explanation being the late detection of mucosal melanomas.

According to the literature, the mean age for oral melanoma diagnosis has been most often reported to be in the fifth decade, although it has been recorded in patients aged between 20 and 80 years (Meleti et al., 2007; Patrick et al., 2007; Rapidis et al., 2003). Our multicenter study revealed a mean age of 64.4 years, with the sixth decade being the most frequently involved.

The etiology of oral melanomas remains unclear, and the proposed roles of denture irritation, tobacco smoking, and chewing as etiological factors have not been demonstrated. Similarly, the reason for predilection of oral melanoma for the vestibular and crestal maxillary gum remains unknown (Sortino-Rachou et al., 2009; Tamura et al., 2024; Tsushima et al., 2024). Our study population confirmed that the most frequent primary location of oral mucosal melanoma was the vestibular and crestal maxillary gum, followed by the palatal mucosa and buccal cheek mucosa.

Mucosal melanomas cannot be classified into the same categories as their skin counterparts (nodular, superficially spreading, lentigo maligna, acral lentiginous) due to different clinical and histological characteristics. Clinically, oral melanomas do not present a uniform pattern and clinical presentation may vary, involving hyperpigmentation, nodular appearance, ulceration, and hemorrhage, as illustrated in this study. With regard to hyperpigmentation, a brown color was the most frequently observed, followed by grey/greyish and blue/blueish colors (Fig. 1) (Tsushima et al., 2024; Tyrrell and Payne, 2018; Umeda et al., 2002). Unfortunately, such symptoms often present relatively late in the course of the disease, so that a significant vertical invasion of the tumor cells into the underlying tissues has already occurred at the moment of the diagnosis.

It seems that two entities of oral mucosal melanoma can be considered: melanomas that have developed on a preexisting melanosis area (this may represent a radial growth phase before the lesion evolves into a vertically infiltrating lesion), and melanomas with only a vertical growth phase (which have a faster clinical course) (Meleti et al., 2007; Patrick et al., 2007; Rapidis et al., 2003).

According to the AJCC Staging Manual, the T stage does not consider the size of the tumor, but instead depends on the invaded underlying tissue. The typically late diagnosis of oral melanomas was confirmed by the staging in our study population — 19 patients diagnosed with a T3 oral melanoma, nine patients with a T4a oral melanoma, and one patient with a T4b neoplasm — with neck node metastases found in eight patients and distant metastases in three patients.

Imaging features are not clear for oral melanomas. While a CT scan is usually performed to search for bone invasion, MRI does not allow a uniform interpretation of T1 and T2 sequences. Indeed, in our study population, in both T1 and T2 sequences around half of the melanomas showed hyperintensity and the others showed hypointensity (Fig. 2).

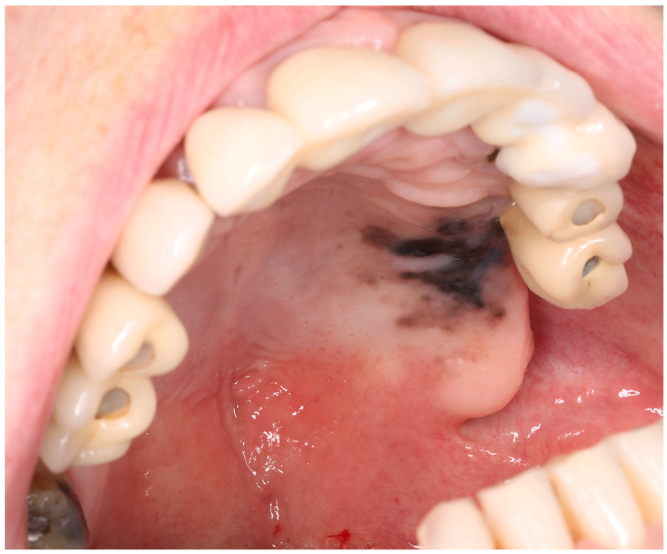

Fig. 1. Patient from the Oviedo center. Intraoral image of a patient affected by oral mucosal malignant melanoma: a brownish hyperpigmented irregular area in the palatal mucosa region can be observed.

Several diagnostic procedures have been proposed, but histopathological examination of an incisional or excisional biopsy remains the most accurate diagnostic tool. In the head and neck region, an excisional biopsy with a 1–2 mm margin for small lesions or an incisional biopsy may be considered (Meleti et al., 2007; Patrick et al., 2007; Rapidis et al., 2003).

Histologically, oral mucosal melanomas are characterized by the proliferation of neoplastic melanocytes (Fig. 3) with variable phenotypes (epithelioid, spindle, and plasmacytoid tumor cells). These cells may be arranged in a sheet-like, organoid, alveolar, solid, or desmoplastic architecture.

According to the literature, tumors with mixed cell phenotypes seem to be more aggressive and to be associated with a higher prevalence of vascular invasion and metastasis (Sortino-Rachou et al., 2009; Tamura et al., 2024; Tsushima et al., 2024).

In our study population, a mixed variant was found in 14 patients, a spindle variant in two patients, and a plasmacytoid variant in the remaining case. Most oral melanomas (19 patients) showed a depth of invasion ranging between 1 mm and 4 mm, whereas three patients presented a 5–10 mm depth of invasion and six patients an invasion of at least 11 mm.

Some immunohistochemical stains may help distinguish mucosal melanomas from other malignancies and, for this reason, they are recommended on a type C basis (general consensus) (Arnett et al., 1999; Gjørup and Athanasiou, 1991; Blanchette et al., 1996; Phillips and Smuts, 1996; Gladilin and Ivanov, 2009; Zhong et al., 2024). Our study population confirmed this finding, with positive stains for S-100 (16 patients), HMB-45 (10 patients), melan-A (nine patients), and vimentin (eight patients), and a negative stain for cytokeratin (eight patients).

Treatment options for oral mucosal melanoma include surgery, immunochemotherapy, and radiation therapy. Surgical resection of primary lesions remains the gold standard for the management of oral mucosal melanoma, although it may be debilitating. However, as for neck dissection, opinions remain controversial. Some authors advocate prophylactic lymph node dissection, especially for clinically apparent, large, and symptomatic disease, while other studies have shown that neck dissection does not seem to improve the patient's overall survival due to the rapid progression and metastatic nature of the tumor (Sortino-Rachou et al., 2009; Tamura et al., 2024; Tsushima et al., 2024).

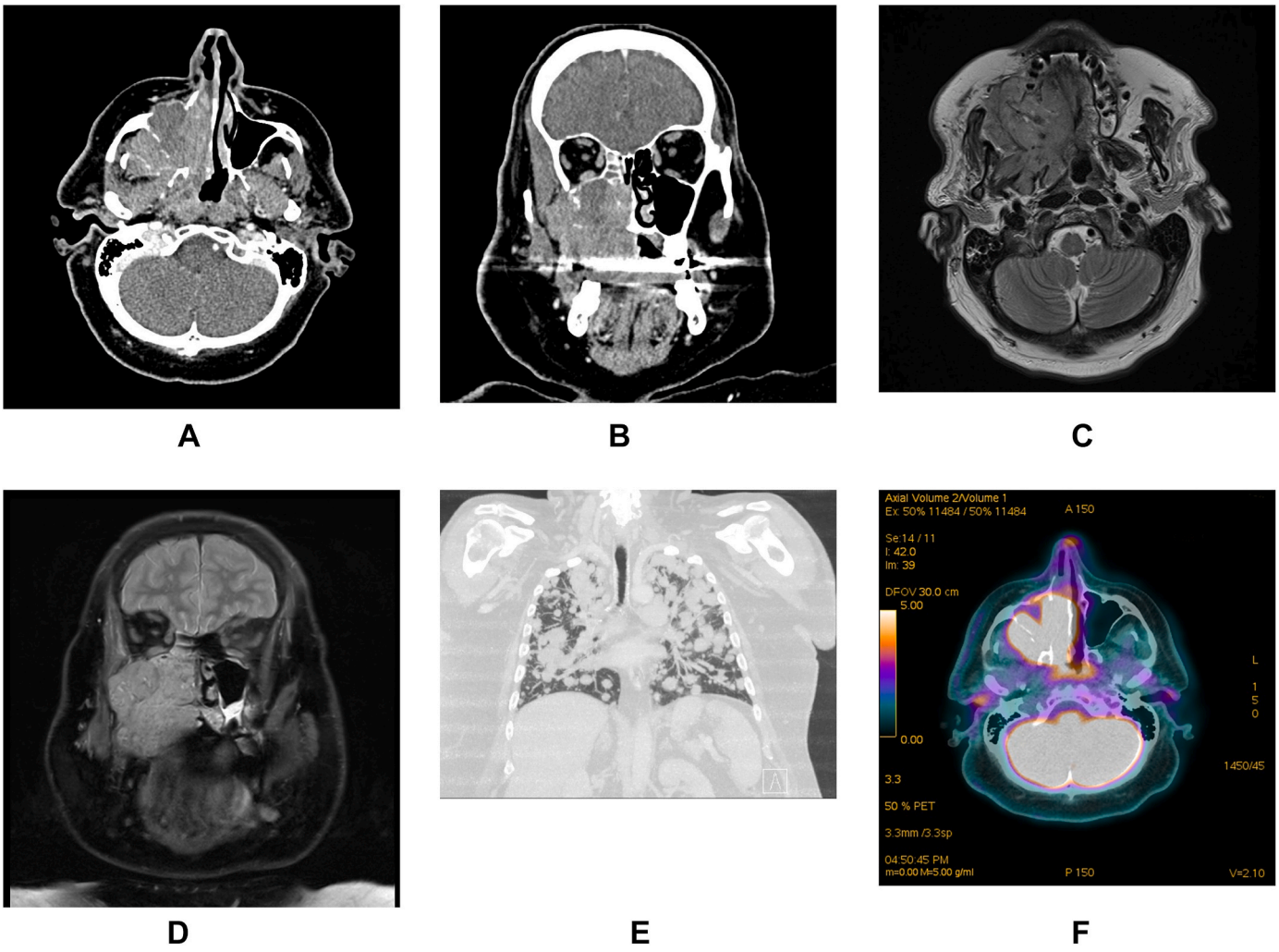

Fig. 2. Patient from the Besancon center, with a T4c oral mucosal melanoma of the maxilla, with lung metastases at diagnosis. Axial (A) and coronal (B) head and neck CT scans, and axial (C) and coronal (D) T1 MRI images show the extent of the neoplasm. (E) Thoracic CT scan showing multiple lung metastases. (F) PET/CT scan of the lesion.

In our study population, 27 patients out of 29 underwent surgery (alone or combined with other treatment), with radical/clear margins obtained in 24 cases. With regard to surgical treatment of the neck, among the 27 surgical cases, no neck dissection was performed in 14 patients, while in 10 cases a neck dissection was performed; in two patients the 'sentinel lymph node biopsy' technique was applied, and in one case a nodal biopsy was performed. Nevertheless, no difference in survival was found when considering radical/clear margins or the performance of neck dissection.

Immunotherapy, BRAF inhibitors, high-dose interferon, and MEK inhibitors were used in seven patients as an adjuvant to surgical resection and radiation therapy. Radiation therapy was applied mainly in patients unable to undergo surgery or as an adjuvant to surgical treatment, with a dosage range of 24–66 Gy. Malignant melanoma is generally considered to have poor radiosensitivity, but postoperative radiotherapy may be useful when prognostic pathological features are poor, such as histopathological evidence of non-radical excision or regional lymph node involvement.

In line with other studies (Chae et al., 2020; Kuk et al., 2016; Meleti et al., 2007), postoperative radiotherapy and chemotherapy were performed in our study population when the lesions were large and invaded the adjacent anatomical structures or extracapsular regions of lymph nodes.

The results of our study were in accordance with previous studies in reporting poor prognosis of oral melanomas. The literature suggests a 5-year survival of 13–20%. In our study, the overall 2-year survival was 62%, although only 11 patients out of 29 showed no evidence of disease with a mean follow-up of 44.5 months.

The aggressiveness of this pathology was confirmed by the fact that four patients developed local recurrence, six developed regional node metastases, and 12 presented one or more distant metastases during follow-up.

Several hypotheses may be proposed for such a poor prognosis — for example, the involved anatomical structures adjacent to oral melanomas can make radical surgery extremely challenging. Furthermore, mucosal melanomas might invade the deeper structures much more easily and rapidly than skin melanomas. However, it seems that late diagnosis may play a crucial role in the poor prognosis of oral melanomas, since they are often asymptomatic for a long time prior to diagnosis.

Our study had some shortcomings and limitations, which should be kept in consideration. The retrospective nature of the study, although probably necessary due to the extreme rarity of this neoplasm, represented a limitation to drawing conclusions. Nevertheless, this retrospective observational study allowed us to obtain a population of 29 patients, thus providing extensive information about this peculiar pathology. Further limitations associated with this study were the long recruitment time, the changes in technology during the study time frame, missing data, and the relatively short follow-up. With regards to

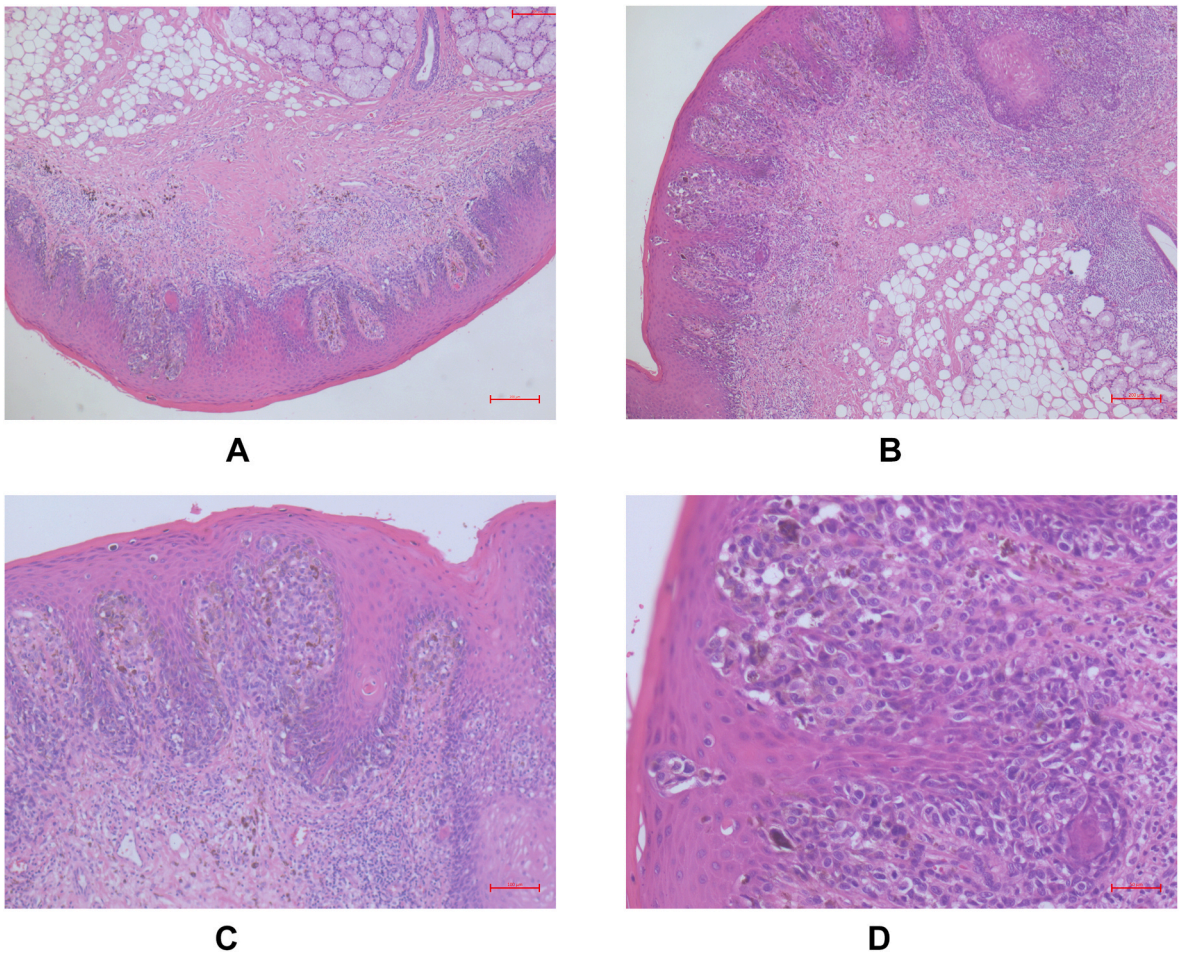

Fig. 3. Patient from the Novi Sad center. (A–D) Histological hematoxylin- and eosin-stained images with different magnifications, showing the proliferation of neoplastic melanocytes.

the long recruitment time (20 years, between 2003 and 2022), this was considered to be necessary for collecting a reasonable number of patients, in spite of the inevitable changes in technology and treatment options during this extended study time frame. Nevertheless, in spite of the missing data associated with the retrospective nature of the study, and the possible changes in treatment options due to emerging technologies, the consistently aggressive behaviour of oral mucosal melanomas was evident over the study time frame. The aggressive nature of this neoplasm, unfortunately, influenced the chosen length of follow-up.

5. Conclusion

Oral mucosal melanoma is an aggressive malignancy. The overall survival for patients with oral mucosal melanoma is poor, with high rate of distant metastasis, independently from the performed treatment. For a proper diagnosis, a biopsy is needed. Regular oral examinations are recommended for everyone, with early biopsy of suspicious lesions suggested to improve the diagnosis of oral mucosal melanoma.

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Declaration of competing interests

All authors declare that they have no conflicts of interest.

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