



**ORIGINAL ARTICLE**

# Oral Mucosal Melanoma: clinico-pathological analysis of 30 cases in a single center

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## Abstract

**Introduction:** Oral mucosa melanoma (OMM) is a rare and aggressive disease comprising 0.26% of all head and neck malignant neoplasms. Affected individuals usually present younger than the other individuals with mucosal melanoma. Surgical treatment with extensive surgical resection was defended as the primary treatment modality, with increasing consideration for postoperative radiotherapy. **Objective:** The objective of this retrospective study with 30 subjects treated at the A.C. Camargo Cancer Center from 1954 to 2014 was to analyze the characteristics and treatments related to the tumor that could be identified as risk factors for the prognosis and consequently the overall survival.

**Materials and Methods:** The data collected were analyzed by the STATA v.12.0 program and the Kaplan-Meier curves and the log rank test were used to compare the survival curves. Of the 30 cases of oral melanoma, 56.7% (17) were men and 43.3% (13) women with a mean age of 59.7% (19 to 88 years). Regarding the symptomatology in the moment of diagnosis, 53.3% (16) of the individuals denied pain and 60% (18) bleeding.

**Results:** Considering the morphological aspects of the lesions, it was observed that 43.3% (13) had a non-ulcerated surface, 93.3% (28) were pigmented and 63.3% (19) were nodular type. From all cases, 33.3% (10) were classified as T3 tumors and 66.7% (20), as T4. Fifty-six point seven percent (17) of the lesions had slow growth and 46.6% (14) of the individuals had palpable lymph node at the time of diagnosis. Twenty three patients (76.7%) underwent radical surgery; 16.7% (5) only cryotherapy and 6.6% (2) chemotherapy. **Conclusion:** In this study we observed 23 recurrences and identified as significant factors for survival: ulceration, the T stage, the presence of N+ and the modality of therapy.

**Keywords:** melanoma; mouth neoplasms; primary treatment; mucosal melanoma; oral neoplasms; prognosis; epidemiology.

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## Introduction

Mucosal melanoma is a rare and aggressive disease that occurs most frequently in the upper aerodigestive tract, corresponds to about 1 to 3% of head and neck neoplasms, and about 0.2 to 8% of all melanomas; has an adverse prognosis with an overall survival ranging from 17.1% to 35.1% over 5 years. The oral mucosa corresponds to 0.26% of all malignancies of head and neck and has a worse prognosis when compared to nasal cavity melanomas<sup>1-4</sup>.

OMM has a peak incidence of 41-60 years and has its pathogenesis and risk factors still unknown, unlike cutaneous melanomas. It has preferential site the mucosa of the hard palate and the upper gingival border<sup>5,6</sup>.

Like the cutaneous melanomas, oral mucosa melanomas originate from melanocytic cells, which have no definite role in the oral mucosa. However, unlike cutaneous melanomas, OMM do not have well defined prognostic parameters<sup>7-9</sup>. Some studies with series of cases bring as prognostic factors isolated greater age equal to 55 years, tumors larger than 4 cm when NOMO, Presence of lymph node metastasis, vascular invasion and distant metastases<sup>5</sup>.

In our series, we observed as factors that reduce survival, the presence of ulceration, advanced staging and the presence of compromised lymph nodes. The type of treatment performed also influences the survival of these patients, being those treated with aggressive surgery the ones with the best overall survival curve as well as those found in the case series of Sun et al.<sup>5</sup> and Lund et al.<sup>10</sup> in sinus nasal melanomas. Most tumors were diagnosed in advanced stages<sup>7</sup>.

## Methods

The medical records of 30 consecutive patients with primary OMM admitted for treatment at the Department of Head and Neck Surgery and Otorhinolaryngology, A.C. Camargo Cancer Center, São Paulo, Brazil, between 1954 and 2014 were retrospectively revised. The reasons for exclusion of some cases were: four were other diagnosis after pathological review, 7 melanoma metastases from other sites and 1 case in which OMM was recently diagnosed and treated.

According the 7<sup>th</sup> TNM edition OMMs are classified only as clinical stage III and IV, different from other head and neck cancers. Stage III comprises T3 (mucosal disease) without regional or distant metastases. Stage IV is subdivided into "A", "B" and "C", in which the IVA comprises of T3 with lymph nodal disease and T4a tumors, moderately advanced local disease, with or without regional metastasis and without distant metastasis, IVB comprises of T4b tumors, very advanced local disease with any N clinical and without distant metastasis, and IVC comprises of any T and any N clinical, but with distant metastasis confirmed<sup>11</sup>.

The patients with primary OMM had a mean age of 59.7 years (range 19-88 years). There were 56.7% (17) males and 43.3% (13) females. Of these, 24 patients (80%) were Caucasian. Six (20%) patients had a history of any cancer in the family. The duration of signs and symptoms presented in the moment of diagnosis, as pain and bleeding, and comorbidities were also recorded.

Lesions were evaluated clinically and reported the site, size, extension and macroscopic appearance were registered on the medical charts. The CT or MRI was used for staging and treatment planning for the last 3 decades.

Before 1990 the treatment performed did not varied much, being more conservative, most of the time the treatment decision was made by the attending surgeon oncologists and in most cases a non-radical procedure such as cryotherapy or electrosurgical resection therapy was done. After 1990, a multidisciplinary tumor team made treatment recommendations including radical resection, whenever feasible, with and without neck dissection, reconstruction and postoperative radiotherapy. For patients with non resectable tumors or those who did not accept surgical therapy, radiation alone or combined with chemotherapy was indicated. Clinical data, pathology

report, treatment information and outcomes were retrieved from the medical charts from all subjects.

STATA v.12.0 was used for statistical analysis. The survival probability was estimated by Kaplan-Meier method and the log rank test was performed to compare survival curves. The 5% level of significance was considered for all statistical tests.

### Results

The study included 30 patients with OMM treated at A.C. Camargo Cancer Center, a single center, from 1954 to 2014. Of these, 56.7% (17) were men, showing no significant difference in sex distribution. The mean age was 59.7 years (19-88 years) with predominance of the Caucasian 24 (80%). The most frequent sites of disease were gingiva 15 (50%), and hard palate 9 (30%), totaling 80% of the cases. (Table 1)

**Table 1.** Distribution of the clinical characteristics of 30 patients with OMM.

Variable	Category	Frequency (%)
Site	Gingiva	15 (50)
	Palate	09 (30)
	Other	06 (20)
Clinical stage	III	11 (36.7)
	IVa	13 (43.3)
	IVb	05 (16.7)
	IVc	01 (3.3)
Time of Treatment	1954-1980	10 (33.3)
	1981-1990	11 (36.7)
	1991-2000	03 (10)
	2001-2012	06 (20)
Treatment	Surgery (S)	15 (50.0)
	Chemotherapy (C)	02 (6.7)
	Radiotherapy (R)	00 (0.0)
	S + R	07 (23.3)
	S+ C	04 (13.3)
	S + C + R	02 (6.7)
Follow up (months)	Range	0-133
	Median	35.8
	Mean (SD)	37.9 (36.5)
Recurrence	No	07 (23.3)
	Yes	23 (76.7)
Status	Alive no disease	02 (6.7)
	Alive with disease	02 (6.7)
	Death by OMM	22 (73.3)
	Death by other disease	03 (10)
	Lost	01 (3.3)

Abbreviations: S = Surgery; C = Chemotherapy; R = Radiotherapy.

Most of the melanomas were pigmented 29 (96.6%), with irregular borders 22 (73.3%) and nodular 19 (63.3%). The surface was ulcerated in 16 (53.3%) patients and only 14 (46.6%) had palpable lymph nodes at the time of diagnosis. According with system TNM of the UICC 2010, 11 (36.7%) patients were classified as stage III; 13 (43.3%) IVa; 5 (16.7%) IVb and 1 (3.3%) IVc.

Only three (10%) patients had melanoma *in situ*, and 17 (56.6%) had deep invasion (muscular or bone). Of the 30 patients, only two (6.6%) underwent chemotherapy alone, and 25 (83.3%) underwent radical surgical treatment, and 20 (66.6%) underwent radical surgery with wide margin resection, with free margins in 17 (56.6%) patients (Figures 1-3).



**Figure 1.** Melanoma in the upper gingiva.



**Figure 2.** Appearance after resection and reconstruction.



**Figure 3.** Late post operative appearance.

Of the 14 patients with diagnosed lymph nodes, 10 performed cervical dissection and 4 patients performed only chemotherapy or cryotherapy and concomitant radiotherapy. No case of sentinel lymph node research was reported. Among the 25 patients submitted to surgery, just 10 underwent to neck dissection.

In this series of cases, 23 (76.7%) of the patients had recurrence of the disease in the minimum period of 5 years of follow-up, and 25 (83.3%) died within the same period.

## Discussion

Oral Mucosal Melanoma is a rare entity and represents 0.26% of oral malignancies, due this, the current choices for treatment is taken upon level 4 evidence, small retrospective series, with contradiction conclusions between then and poor prognosis independent of the therapeutic choice were made. This make clear that treatment choices is difficult to take<sup>4,12</sup>.

We got a slightly greater incidence in men than women, with a relation within men: women 1,2:1, the same proportion between gender or with a slightly greater men prevalence like us is reported in the literature. Concerning about age and prognosis, differently of other series, we didn't got survival differences<sup>1,13,14</sup>.

The most frequent sites of oral melanoma were gingiva in 15 patients (50%), hard palate in 9 patients (30%) and hard palate and gingiva in 2 patients (6.4%), which is consistent with data from the literature, in which the gingiva is the most frequent site, followed by the hard palate, both responsible for up to 80% of cases of oral mucosa melanoma<sup>4,5,13</sup>.

Palpable lymph nodes were seen in 14 (46.6%) at the time of diagnosis. The incidence of clinical lymph nodes at diagnosis varies greatly in the literature; in oral mucosa, the majority is around 25% (10 to 76%). Only 1

(2.7%) patient presented distant metastasis at diagnosis, not corroborating with the literature, in which the incidence of distant metastasis is higher up to 13.5%<sup>2,5,15-17</sup>.

In our study, most patients progressed with local or systemic recurrence during follow-up, 23 (74.1%) patients presented recurrence of the disease, corroborating with other studies that also show a high recurrence rate, in which local recurrences range from 17-82%, regional 19-36% and distance 25-71%, reinforcing the aggressiveness of this type of tumor<sup>1,14</sup>.

Overall survival in our study at 2 and 5 years was 50% and 28%, respectively. Most retrospective studies show survival at 5 years <30%, Lopez et al.<sup>15</sup> in a recent review with 18 studies shows overall survival at five years ranging from 14% to 47%. This low survival compared to cutaneous melanomas is due not only to different tumor biology, but also to the advanced stage at the time of diagnosis and to the vital structures involved<sup>2,16,18</sup>.

Overall 2-year and 5-year survival were compared to the clinical-pathological characteristics and type of treatment performed, in which patients with ulcerated lesions showed a 2 and 5-year survival of 48% and 9%; Non-ulcerated lesion 59% and 52%, respectively, which shows that the absence of ulceration is a relevant prognostic factor ( $p=0.015$ ). Ulceration is a well know poor prognostic factor in cutaneous melanoma and two previous studies described similar conclusions about ulceration in mucosal melanomas corroborating our results<sup>5,6,13,19</sup>.

Surgery was the therapeutic approach that presented better survival rates; in 2 and 5 years, the overall survival of patients treated with radical surgery was 62% and 31% and those who did not submitted surgical treatment were 20% and 19%, respectively. ( $P = 0.004$ ). Similar results in previous studies with overall survival at 2 years and at 5 years 70.1 and 58.4% respectively for operated patients and 25 and 12.5% for non-operated patients. The T3 tumors presented better survival compared to patients with T4 tumors, with survival at 2 and 5 years corresponding to 85% and 55%, 27% and 13%, respectively ( $p = 0.015$ ). Independent of the classification used for staging, advanced stages in most studies present worse prognostic rates, but in the Sun et al.<sup>5</sup> series, exclusive of oral mucosa melanomas, no difference in prognosis was found between the different stages and it is considered that this is due to the different therapeutic modalities adopted and only one stage IVc case at diagnosis<sup>17,20</sup>.

Of the 25 (83.3%) patients submitted to surgery 17 (68%) presented free margins. Free margins (5mm) are in most series an important prognostic factor, with a 21-fold increase in the risk of dying from the disease when margin compromised, but in our study we did not observe a significant difference in survival between patients who obtained free margins. Perhaps this difference is due to the high rate of systemic recurrence of the disease independent of the better local control obtained with resection with free margins associated or not with adjuvant radiotherapy<sup>2,5,14,17,21,22</sup>.

Wide margins (1.5-2.0 cm) are the standard treatment, but it is often difficult to obtain free margins due to the advanced stage of the disease at diagnosis, proximity to vital structures, tumor multicentricity and microscopic infiltration

beyond the clinically diagnosed. To improve the rate of free margins in the last 2 cases, we used freezing and obtained 100% free margin in the surgery, a result that was confirmed in paraffin. Traditionally, intraoperative assessment of melanoma margins is difficult, but Tajudeen et al.<sup>23</sup> have shown a good correlation between freezing and HE in head and neck mucosal melanomas<sup>5,24</sup>.

Of the 25 patients submitted to surgery 4 (16%) had complications, without postoperative mortalities within 30 days. The published articles did not report postoperative complications or mortality rates.

As in previous studies, positive lymph nodes have been shown to be a poor prognostic factor. Patients with positive lymph nodes at the time of diagnosis had an overall survival of 20% and 13% at 2 and 5 years; and patients with negative lymph nodes 75% and 44% of overall survival, respectively, the patients with positive lymph nodes had lower overall survival ( $p = 0.002$ )<sup>12,17,18,20</sup>.

In our service, lymphadenectomy was performed only when clinically positive lymph nodes. Elective lymphadenectomy at levels I-III or I-V has been proposed by some studies for oral mucosal melanomas because of the high lymph node metastasis rate of up to 85%. Sun et al.<sup>5</sup> showed lower lymph node recurrence in Tany N1M0 after lymphadenectomy (28.8%) than in TanyN0M0 without lymphadenectomy (36.4%), but with no overall survival gain. Currently, most guidelines maintain the procedure of indicating lymphadenectomy only in cases of clinically positive lymph nodes. (Table 2)<sup>16,25</sup>.

Radiotherapy adjuvant to surgery or palliative with chemotherapy was performed in 9 patients (30%) in our series. Melanoma has been traditionally known as a radioresistant tumor but good results in local control was obtained with radiotherapy recently. For definitive treatment newly radiation techniques, such intensity-modulated radiation therapy (IMRT), carbon-ion therapy, neutrons, and proton therapy permit the achievement of dose upper of 50 Gy with local control comparable to surgery with a 5 years survival 25%, although it is not the standard treatment option and still as clinical trials mainly for patients that refuse surgery or with unresectable disease that is more frequent in sinonasal melanomas<sup>26-29</sup>.

Adjuvant radiotherapy doesn't show improvement in overall survival but most part of centers indicates it when positive or close margins and for recurrent or inoperable cases. The absence of improvement in overall survival can be for selection bias or due the systemic pattern of recurrence<sup>30-32</sup>.

Post-operative neck radiotherapy is suitable for patients with a single metastatic node of 3 cm or larger, two or more positive neck or parotid glandnodes, extra-capsular spread, and in cases with lympho-vascular or peri-neural invasion. Li et al.<sup>33</sup> in a metanalises with 1593 patients recommend adjuvant radiotherapy for better local control. But Konuthula et al.<sup>16</sup> in a epidemiologic study with 695 patients as Li et al.<sup>33</sup> didn't see benefits in overall survival with RT, even in almost homogeneous groups and because of the collateral effects of radiotherapy advises against RT suggesting radical surgery with close follow up or palliative resection.

In the presence of recurrence, 6 patients (20%) used chemotherapy. Traditional chemotherapy such as dacarbazine has low response rate, ranging from 10-20% and are not long-lasting responses. In the last 5 years many systemic treatment options have arisen, but the responses in

**Table 2.** Overall survival (5 years) and patients characteristics.

Clinical Parameters	Number (%)	Death Number	p value
Gender			
Male	17 (56.7%)	16	0.0396
Female	13 (43.3%)	9	
Age			
< 59	15 (50%)	11	0.1409
> 59	15 (50%)	14	
cTNM Stage			
III Stage	10 (33.3%)	8	0.0146
IV Stage	20 (66.7%)	17	
Pigmentaion			
Yes	28 (93.3%)	24	0.0545
No	2 (6.7%)	1	
Ulceration			
Yes	17 (56.7%)	15	0.0151
No	13 (43.3%)	10	
Lymph Nodes			
Positive	14 (46.7%)	14	0.0020
Negative	16 (53.3%)	11	
Neck Dissection			
Yes	10 (33.3%)	8	0.0146
No	20 (66.7%)	17	
Therapy			
No Surgery	7 (23.3%)	7	0.0037
Surgery	23 (76.7%)	18	

P value obtained by logrank test.

mucosal melanoma are worse than in cutaneous melanomas due to different patho-genetic mechanism origin<sup>1,34</sup>.

Imatinib, a tyrosine kinase inhibitor, showed regression in up to 42% of patients with 51% of them alive at the end of 1 year<sup>35</sup>. Hodi et al.<sup>36</sup> related Ipilimumab, a monoclonal antibody against T lymphocyte-associated antigen-4 (CTLA4), showed a improved overall survival, 10.1 months against 6.4 months, for unresectable or stage IV cutaneous melanomas. Although Del Vecchio didn't get the same results with a response rate of 12% with and overall survival of 6.4 months in mucosal melanomas<sup>37</sup>. Anti PD1 had been tested in mucosal melanoma with one case report of almost complete and durable response. Long time response didn't was seen with other drugs<sup>38</sup>.

We see that despite changes in the pattern of treatment over the decades the overall survival has not changed which demonstrates the need of new systemic treatments<sup>17</sup>. There are new drugs in testing phase for cutaneous melanoma that bring hope for survival improvement also in the treatment of mucosal melanomas<sup>34</sup>.

## Conclusion

There is a lack of prospective studies and a greater number of cases to better establish oral mucosa melanoma treatments patterns, so most guidelines are based on retrospective studies. In this scenario our study is one of the largest that deals specifically with oral mucosal melanoma without including paranasal melanomas.

In this study, the factors influencing the survival were the ulceration, the T stage, lymph node involvement and type of treatment performed. Patients without ulcerated melanomas, T3 stage, negative lymph nodes and treated with radical surgery are those with better survival.

Unlike studies involving all head and neck mucosal melanomas, in this study with only oral mucosal melanomas, there was no difference in survival over surgical margins which should be taken into consideration when surgery for complete resection includes noble structures.

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