



Oral Amelanotic Melanoma: A Systematic Review of Case Reports and Case Series

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Abstract

Oral amelanotic melanoma (OAM) is a rare, non-pigmented mucosal neoplasm representing less than 2% of all melanoma. The present study analyses the available data on OAM and describes its clinicopathological features, identifying potential prognostic factors. Online electronic databases such as PubMed-Medline, Embase, and Scopus were searched using appropriate keywords from the earliest available date till 31st March 2021 without restriction on language. Additional sources like Google Scholar, major journals, unpublished studies, conference proceedings, and cross-references were explored. 37 publications were included for quantitative synthesis, comprising 55 cases. The mean age of the patients was 59.56 years, and the lesions were more prevalent in males than in females. OAM's were most prevalent in the maxilla (67.2%) with ulceration, pinkish-red color, nodular mass, and pain. 2 patients (3.36%) were alive at their last follow-up, and 25 were dead (45.4%). Univariate survival analysis of clinical variables revealed that age older than 68 years ($p=0.003$), mandibular gingiva ($p=0.007$), round cells ($p=0.004$), and surgical excision along with chemotherapy & radiation therapy ($p=0.001$) were significantly associated with a lower survival rate. Oral Amelanotic Melanoma is a neoplasm with a poor prognosis, presenting a 6.25% possibility of survival after 5 years. Patients older than 68 years, lesions in the mandibular gingiva, round cells, and surgical excision along with chemotherapy and radiotherapy, presented the worst prognosis. However, they did not represent independent prognostic determinants for these patients.

Keywords Melanoma · Oral cavity · Amelanotic · Mucosal melanoma · Oral amelanotic melanoma · Immunohistochemistry · Prognosis

Introduction

Mucosal melanoma (MM) is a malignant neoplasm of melanocytes derived from mucosal sites. The rarest melanoma subtype contrasts with cutaneous melanomas, which are a hundred times more common and biologically distinct. They are caused by unknown factors and exhibit different cytogenetic alterations and clinical course [1]. MM occurs most frequently in the head and neck region (55%), followed by the anogenital site. In the head and neck region, MM represents < 1% of all melanomas and predominantly arises in two primary sites, the sinonasal region (66%) and the oral cavity (25%). Oral mucosal melanoma (OMM) accounts for about 0.5% of melanomas. They frequently occur on the hard palate and gingiva, show a slight male predominance with a median age range of 55–66 years [2].

Amelanotic melanoma (AM) lack pigmentation clinically, with melanin formation in less than 5% of tumor cells on histological examination [3]. Less than 2% of all

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melanomas lack pigmentation; however, up to 75% of cases are amelanotic in the oral mucosa [4, 5]. Oral amelanotic melanoma (OAM) constitutes 40% of oral MM, and maxillary gingiva is the most commonly involved site followed by the palate; it rarely affects the mandibular gingiva [6]. The neoplasm is often asymptomatic and appears irregular, erythematous, flat, or nodular lesion with ulceration seen in one-third cases [2]. A higher incidence of regional lymph node and distant metastasis, mainly to the lung or the liver, has been reported for OAM [6]. Histologically, OAM displays diverse cell types, which include undifferentiated epithelioid, spindle, and plasmacytoid morphology. Thereby building immunohistochemistry as an essential tool for confirming the tumor phenotype and conclude the diagnosis. An extensive immunohistochemical panel with the marker of neural, neuroendocrine, lymphoid, or epithelioid differentiation is used to rule out other neoplasms [7]. A combination of surgery and surgery with adjuvant therapy is the treatment of choice, while radiotherapy or chemotherapy alone has also been used [6].

Consequently, the absence of melanin pigmentation in OAM, both clinically and microscopically, poses a diagnostic challenge that varies widely, from reactive or nonneoplastic proliferative lesions to infectious diseases and other oral malignancies. This leads to delayed diagnosis, intrinsic aggressiveness with a poor prognosis. Because of the rarity of the neoplasm, few case reports and scarcely any series have been published to date. As a result, it has been difficult to establish valuable data related to OAM. All relevant case series and case reports were systematically reviewed to clarify the natural history and reinforce knowledge about OAMs and epidemiological predilections. The present study conjoins the available data on OAM into an updated extensive review of their clinicopathological, immune profile, therapeutic and prognostic features. This will help further to perceive the possible biologic profile of the tumor and enhance knowledge about this unusual tumor for its timely diagnosis, treatment planning, and outcome.

Methods

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [8].

Search Strategy

An exhaustive literature search was conducted for the clinical features, immunohistochemistry, histopathological features of Oral Amelanotic Melanoma (OAM), and the rate of metastasis and the prognosis of the disease. Online electronic databases such as PubMed-Medline, Embase, and

Scopus were searched from the earliest available date till 31st March 2021 without restriction on language. Additional sources like google scholar, unpublished studies, conference proceedings, and cross-references were explored. Non-English language publications were translated into the English language using Google Translate [9]. We also searched for relevant articles in journals allied to oral pathology, oral medicine, and oral surgery. A detailed search strategy for PubMed is given in Fig. 1 and tailored to other databases when necessary (Supplementary Table 1).

Eligibility Criteria

1. Case reports and case series of oral amelanotic melanoma.
2. Histopathologically confirmed patients and clinically diagnosed as oral amelanotic melanoma.
3. Patients with primary and secondary oral amelanotic melanoma.
4. Patients with no other associated malignant tumors orally or extra orally.
5. Amelanotic Melanoma other than oral cavity and past hospital records were excluded.

Screening and Selection

The papers were independently scanned by two reviewers (SD and VM), first by the title and abstract. Reviews, commentary, or clinical trials were not included in the search. If the search keywords were present in the title and or the abstract, the papers were selected for full-text reading. Papers without abstracts but with titles suggesting that they were related to the objectives of this review were also selected to screen the full text for eligibility. After selection, full-text papers were read in detail by two reviewers. (SD and VM) Those papers that fulfilled all of the selection criteria were processed for data extraction. Two reviewers (SD and VM) searched the reference lists of all selected studies for additional relevant articles. Disagreements between the two reviewers were resolved by discussion. If a disagreement persisted, the judgment of a third reviewer (SB) was considered decisive.

Risk of Bias

The selection criteria included available information about immunohistochemistry analysis to confirm the diagnosis of OAM, which reduced the risk of bias and the publications with sufficient clinical and histological data. A higher risk of bias is comprised of insufficient clinical, histological and immunohistochemical information to confirm the diagnosis of OAM.

Sr. No.	Domains	Keywords
1	Amelanotic melanoma	(Melanoma, Amelanotic) OR (Amelanotic mucosal melanoma) OR (oral metastatic melanoma, amelanotic) OR (amelanotic) OR (melanoma, non-pigmented) OR (melanoma, hypopigmented) OR (melanoma, desmoplastic)
2	Location	(Oral cavity) OR (Oral mucosa) OR (oronasal) OR (Tongue) OR (gingiva)
3	Immunohistostaining	(Immunohistochemistry) OR (histopathological) OR (microscop*)
4	Local recurrence rate	(Neoplasm Recurrence, Local) OR (Recurren*) OR (relapse)
5	Distant metastasis	(Lymphatic Metastasis) OR (Metastasis) OR (Neoplasm Invasiv*) OR (distant metastases) OR (Lymph node metastases) OR (regional metastases)
6	Clinicopathology	(early diagnosis) OR (early stage) OR (Clinical features) OR (Prognosis) OR (early detection) OR (clinicopatholog*) OR (Diagnosis)

* Indicates wild card in PubMed

Fig. 1 Search strategy in PubMed

Data Extraction

Two authors (SD and VM) independently extracted data using specially designed data extraction forms, utilizing Microsoft Excel software. Any disagreement was resolved by discussion between the authors. For each selected study, the following data were then extracted from a standard form (when available): author and year of publication, the number of patients, country, location, patient sex (male or female), age, the time elapsed before reporting the case, clinical presentation, radiographic features, histologic features, treatment, prognosis, recurrence, distant metastasis, and outcome of the disease. For those articles that had inadequate data

to be included in quantitative synthesis, the corresponding authors were contacted to procure additional data.

Analysis

The data were analyzed using R, version 3.3.1. (R Foundation for Statistical Computing) Confidence intervals were set at 95%, and a p-value ≤ of 0.05 was considered statistically significant. The mean and percentages are presented as descriptive data. Overall survival rates were estimated by Kaplan–Meier analysis and compared using a log-rank test to identify potential prognostic features.

The systematic review was registered with the International Prospective Register of Systematic Reviews on March 31, 2021, which was in accordance with the guidelines and was last revised on January 1, 2021. (Registration Number CRD42020216187).

Results

Search Selection and Results

The PubMed-Medline, Embase, Scopus, and additional sources identified 786 search results, out of which 581 were duplicates. The remaining 205 unique studies were screened for the titles and abstracts, and 33 articles were selected for full-text screening (Fig. 2). A total of 44 articles [4, 6, 7, 10–50] that matched the eligibility criteria were processed

for data extraction (Supplementary Table 2). Analysis of the remaining 37 articles [4, 6, 7, 13, 14, 16–41, 44, 46–50] resulted in the exclusion of 7 papers [10–12, 15, 42, 43, 45] (Supplementary Table 3) which did not meet the inclusion criteria or provide sufficient clinical, histological and immunohistochemical information to confirm the diagnosis of OAM. Finally, a total of 55 cases were included in the descriptive and statistical analyses.

Description of the Studies and Analyses

Forty-four publications reporting 63 cases were included for qualitative synthesis (Supplementary Table 3). The epidemiological results are described in Fig. 3, which reveals Japan (23 cases), Brazil (11 cases), India (8 cases), New Zealand, and Iran (3 cases) to be the countries with the highest numbers of cases described. Table 1 presents the

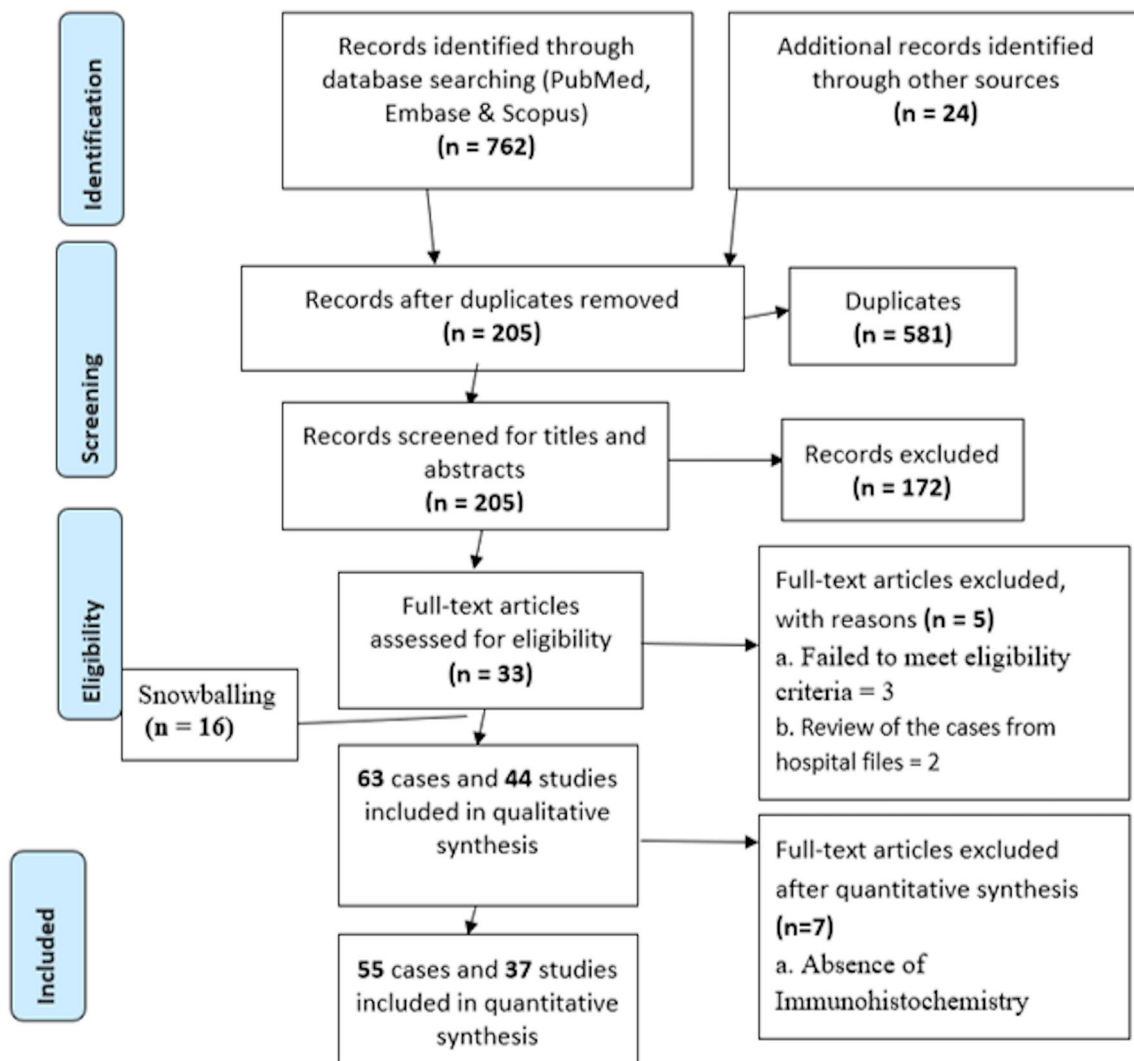
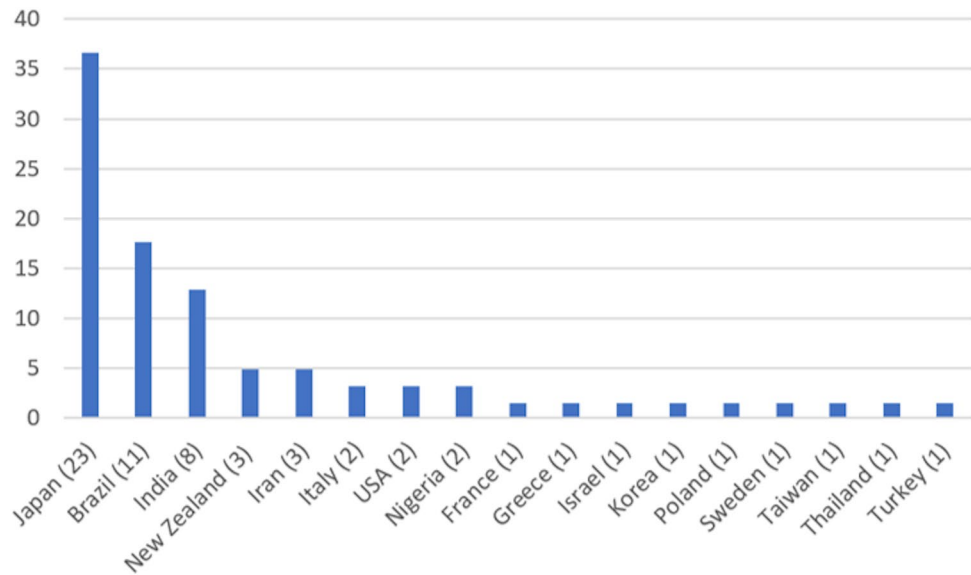


Fig. 2 Flowchart summarizing the article selection process (*n*—number of studies)

Fig. 3 Countries with cases of oral amelanotic melanoma described in qualitative synthesis and the number of cases in each country. Japan has reported the most cases, followed by Brazil, India, New Zealand, and Iran



demographic, clinical, radiographical, and histological features and the results of the survival analysis. The mean age of the patients was 59.56 years (range 15–97 years); females were older (mean age 62.04 years, range 16–85 years) than males (mean age 57.6 years, range 19–97 years). The lesions were more prevalent in males than in females, with a male to female ratio of 1.29:1. OAM's were most prevalent in the maxilla ($n=37$, 67.2%), mandible ($n=13$, 23.6%) and others ($n=5$, 9.2%). The mean lesion size was $29.4 \times 28.97 \times 11.42$.

The OAM mainly showed ulceration, pinkish-red color, nodular mass, sessile, pain, bleeding, and erythema. Malignancy was described as the first clinical impression of this tumor in 13 (23.6%) patients, followed by melanoma and epulis in 5 (9.09%) patients, benign tumor in 3 (5.45%) patients, pyogenic granuloma in 2 (3.6%) patients, and metastatic tumor and peripheral giant-cell granuloma in 1 (1.8%) patient. Bone destruction was observed in 24 (43.6%) patients. The patients presented a mean duration of lesion evolution of 6.23 months (range 0.5–36 months). Histological analysis revealed different cell types and the presence of melanin in 5 cases (9.09%) and the absence of melanin in 9 cases (16.3%). Lymph nodes were involved in 23 (41.8%) patients, regional lymph nodes were seen in 14 (25.45%), and distant lymph nodes were seen in 6 (10.9%). Metastasis was mainly seen in the lungs, cervical lymph nodes, and liver. Treatment was described for all 55 patients and included surgical excision and chemotherapy (CT) in 12 (21.8%), surgical excision alone in 11 (20%), surgical excision along with radiation therapy (RT) in 8 (14.5%), RT alone in 7 (12.7%), and CT associated with RT and CT along with surgical excision and immunotherapy in 2 (3.6%). A small number of cases (1.8%) underwent CT, surgical excision associated with CT and RT and RT along with CT and immunotherapy. Recurrence was observed in

5 (9.09%) patients. Two patients (3.36%) were alive at their last follow-up, 25 were dead (45.4%), and this information was not available for 28 cases (50.9%).

The overall survival probability at 3-years and 5-years is 18.75% and 6.25% respectively (Fig. 4). Univariate survival analysis of clinical variables revealed that age older than 68 years ($p=0.003$), mandibular gingiva ($p=0.007$), round cells ($p=0.004$), and surgical excision along with CT and RT ($p=0.001$) were significantly associated with a lower survival rate (Table 1, Fig. 5). The immunohistochemistry panel for OAM is shown in Table 2.

Discussion

Amelanotic melanoma (AM) is a unique subset of melanoma with little or no clinically visible pigmentation and lack of melanin in the cytoplasm of tumor cells, wherein some authors have quantified the presence of melanin in less than 5% of tumor cells [3, 51]. Though AM cells demonstrate melanin-forming ability amelanosis may result from the insufficient activity of specific melanin formation enzymes, such as tyrosinase and germline mutations in genes for MC1R, MITF, and p14ARF. Alcohol, smoking, and exposure to formaldehyde are weakly associated with the pathogenesis of OMM [51–53]. However, the mechanism underlying amelanosis is still unclear. Also there is scarce information on OAM in the literature regarding its clinical course and prognosis, with only a few reports and series currently available. Therefore, we attempted this study to systematically review the available data on OAM to determine the clinicopathological features of this tumor and the affected patients.

Table 1 Demographic characteristics, clinical features, and survival analysis of cases of oral amelanotic melanoma described in the literature (N=55)

Variables	N = 55	Log-rank univariate survival analysis, p-values	
Age, n (%) (mean age – 59.56)			
< 68 years	36 (65.5%)	0.003*	
> 68 years	19 (35.5%)		
Sex, n (%) (male:female ratio—1.29:1)			
Male	31 (56.4%)	0.57	
Female	24 (43.6%)		
Location: maxilla, 37 (67.2%)			
Hard palate	17 (30.9%)	0.10	
Gingiva	15 (27.3%)		
Soft palate	3 (5.5%)		
Alveolar ridge	2 (3.6%)		
Location: mandible, 13 (23.6%)			
Mandibular gingiva	7 (12.7%)	0.007*	
Alveolar ridge	4 (7.3%)		
Retro molar	2 (3.6%)		
Location: other, 5 (9.2%)			
Lateral margin of tongue	2 (3.6%)	0.76	
Anterior 2/3rd tongue	1 (1.8%)		
Buccal mucosa	1 (1.8%)		
Lip	1 (1.8%)		
Clinical features, n (%)			
Ulcerated	26 (47.2%)	0.56	
Pinkish red color	19 (34.5%)		
Nodular mass	15 (27.2%)		
Sessile	7 (12.7%)		
Pedunculated	4 (7.27%)		
Erythema	5 (9.09%)		
Greyish white color	2 (3.63%)		
Pigmentation in other sites	3 (5.45%)		
Well circumscribed	3 (5.45%)		
Ill-defined	8 (14.5%)		
Mobility in associated tooth	2 (3.63%)		
Asymptomatic	24 (43.6%)		
Pain	13 (23.6%)		
Bleeding	4 (7.27%)		
NA	14 (25.4%)		
First clinical impression, n (%)			
Malignancy	13 (23.6%)		0.67
Melanoma	5 (9.09%)		
Epulis	5 (9.09%)		
Benign tumor	3 (5.45%)		
Pyogenic granuloma	2 (3.6%)		
Peripheral giant-cell granuloma (PGCG)	1 (1.8%)		
Metastatic tumor	1 (1.8%)		
NA	25 (45.4%)		
Radiographic features, n (%)			
Bone destruction	24 (43.6%)	0.58	
No abnormality detected	5 (9.09%)		
NA	26 (47.2%)		

Table 1 (continued)

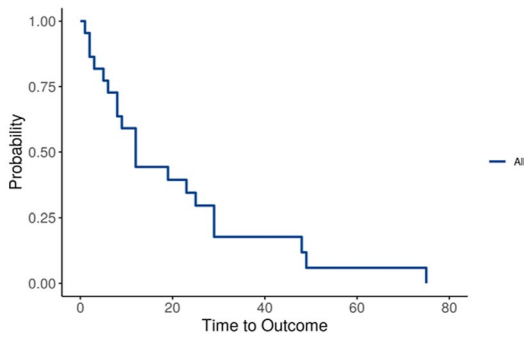
Variables	N = 55	Log-rank univariate survival analysis, p-values	
Histological features (cell types) n (%)			
Spindle cells	24 (43.6%)	0.004*	
Epithelioid	12 (21.8%)		
Round to spindle cells	8 (14.5%)		
Round cells	7 (12.72%)		
Undifferentiated	4 (7.27%)		
Melanin on histopathology, n (%)			
Present	5 (9.09%)	0.65	
Absent	9 (16.3%)		
NA	41 (74.5%)		
Lymph node, n (%)			
Present	27(49.1%)	0.23	
Absent	23 (41.8%)		
NA	5(9.1%)		
Distant metastasis, n (%)			
Present	14 (25.4%)	0.48	
Absent	6 (10.9%)		
NA	35 (63.6%)		
Treatment, n (%)			
SX + CX	12 (21.8%)	0.001*	
SX	11 (20%)		
SX + RX	8 (14.5%)		
RX	7 (12.7%)		
NA	6 (10.9%)		
No T/t	4 (7.27%)		
CX + RX	2 (3.6%)		
CX + SX + IX	2 (3.6%)		
CX	1 (1.8%)		
SX + CX + RX	1 (1.8%)		
RX + CX + IX	1 (1.8%)		
Recurrence, n (%)			
Absent	7 (12.7%)		0.91
Present	5 (9.09%)		
NA	43 (78.18%)		
Status, n (%)			
Dead	25 (45.4%)	0.58	
Alive	2 (3.36%)		
NA	28 (50.9%)		

NA not available, T/t treatment, SX surgical excision, CX chemotherapy, RX radiation therapy, IX immunotherapy

*p-value < 0.05, significant result

The incidence of melanomas differs among different ethnic groups and races. Based on the qualitative synthesis of 63 cases in the present review, the occurrence of OAM was most frequently seen in Japan, followed by Brazil, India, New Zealand, and Iran. Our findings are in accordance with the high incidence of OAMs reported among Japanese than Caucasians by Takagi et al. [54] and Steidler

et al. [55]. Also, in Asian/Pacific islanders, more MMs have been reported than non-Hispanic Whites [56, 57]. As there is limited data on intra-oral amelanotic melanoma, most cases are unreported and the literature is disparate, it is possible that Japanese clinicians publish case report more often than in other countries.



Kaplan–Meier curve for overall survival indicating the reduced probability of survival over time. The overall survival probability is 44% at 1 year, 18.75% at 3 years and 6.25% for 5 years.

Fig. 4 Kaplan–Meier curve for overall survival indicating the reduced probability of survival over time

The quantitative analysis of 55 cases reflected that OAMs occur mostly in the older age group with high prevalence in the fifth to seventh decades of life and a mean age of 59.6 years. The literature review illustrated a similar pattern [5, 7, 52, 58, 59]. This review revealed a mean duration of 6.2 months until diagnosis, which could be attributed to this tumor’s asymptomatic growth and benign appearance. In

the present study, male predominance was observed (M:F, 1.29:1), which is concurrent with several studies [3, 4, 13, 21, 42, 60] while some studies showed female predominance [61–63] or no sex predilection [64]. Regarding location, the maxilla was more commonly involved than the mandible (ratio, 2.8:1) which is in agreement with the literature. We observed the palate as the most frequently affected site followed by maxillary gingiva and mandibular gingiva. It is worth mentioning that the development and anatomically close association of the palate with the nasal cavity, which marks the common site for head and neck melanomas, may partly explain this finding [4]. The extensive literature review revealed maxillary gingiva as the most common site of occurrence followed by palate and mandibular gingiva [4, 13, 21, 25, 65]. Cases have also been reported on the tongue, lip, and buccal mucosa. Clinically, OAMs presented as an asymptomatic, ill-defined, ulcerated or pinkish-red color, sessile, or pedunculated nodular mass. Bleeding, bone erosion, and tooth mobility were observed, with pain typically present in advanced cases. A small amount or few flecks of melanin may be detected on close inspection in few cases. These findings are in accordance with previous studies [7, 24, 66–68]. The absence of clinically significant melanin pigmentation makes OAM’s difficult to diagnose, and the

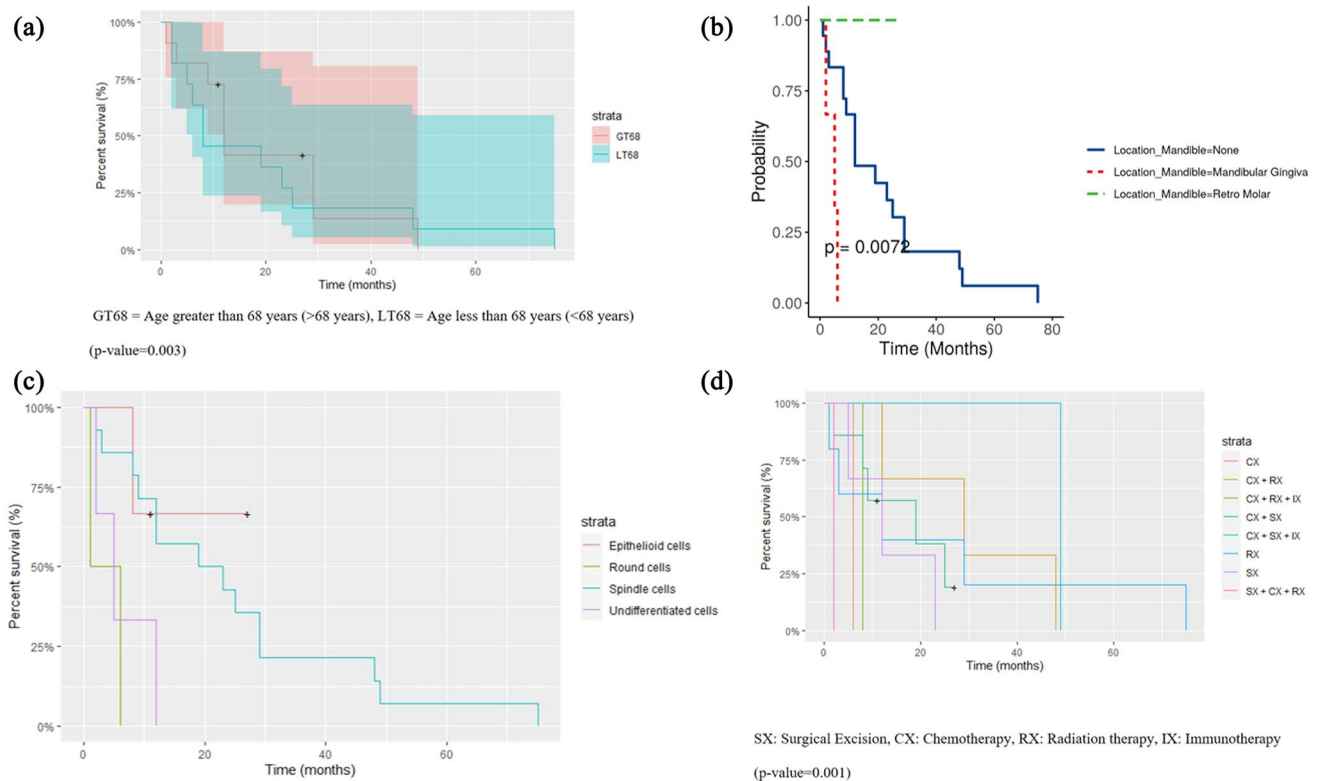


Fig. 5 Kaplan–Meier curves. **A** Kaplan–Meier curves for survival associated with age. **B** Kaplan–Meier curves for survival associated with Mandible location. **C** Kaplan–Meier curves for survival associ-

ated with histological features (cell types). **D** Kaplan–Meier curves for survival associated with treatment

Table 2 Markers used in the diagnosis of the cases analyzed (N=55)

Markers	Immunohistochemistry analysis	
	Positive	Negative
HMB-45	96.8%	3.12%
S-100	95.8%	4.1%
Melan A	66.6%	33.3%
AE1/AE3	11.7%	88.2%
Vimentin	84.2%	15.7%
Ki-67	100%	0%
SOX10	100%	0%
Desmin	12.5%	87.5%
LCA	0%	22.7%
α -SMA	0%	100%
EMA	0%	100%

differential diagnosis ranged from reactive, inflammatory, non-neoplastic to neoplastic lesions. The present review noted that malignancy was described as the first clinical impression of this tumor. This could be due to the lower evolution time until diagnosis and associated bone destruction seen on the radiograph in most of the cases.

Microscopically, OAM's show a diverse cell morphology which includes epithelioid, spindle, round, round to spindle, fusiform, plasmacytoid, or undifferentiated small blue round cells. The size of the cell ranges from small to large with a high nuclear-cytoplasmic ratio, with or without prominent nucleoli. Loss of epithelial stratification (due to ulceration and necrosis), mitoses, lymphovascular and perineural invasion are the other features [2]. OAM exhibits a vertical growth pattern which rapidly forms invasive phenotype involving adjoining structures, while association of radial growth with melanization has also been suggested [51]. These features may explain the biological aggressiveness of the tumor [4, 5, 24]. The present study paralleled the literature review in which the spindle and epithelioid cell morphology were the most common and undifferentiated morphology was the least common cell type in OAM, however, few studies have shown undifferentiated and epithelioid cell morphology more prominent [7, 24]. We also, observed that out of 55 cases of OAM's, only 14 cases reported the presence/absence of melanin in the tumor cells. Hence reporting of pigmentation presence/absence is vital.

OAMs should be differentiated through immunohistochemistry from other histologically overlapping lesions like poorly differentiated squamous cell carcinoma, small blue cell tumors (rhabdomyosarcoma and olfactory neuroblastoma), high-grade carcinomas, neuroendocrine carcinomas, diffuse large B-cell lymphoma, and Ewing sarcoma/primitive neuroectodermal tumor because of varied cell morphology and absence of melanin pigment histologically. Immunohistochemistry with HMB-45 and S-100 is more sensitive in differentiating this tumor from the other neoplasms [69, 70].

It is worthwhile to mention that 8 cases of OAMs showed 100% sensitivity to SOX10 markers, which requires further speculation [7]. In this review, quantitative synthesis was carried out with only cases diagnosed with immunohistochemistry to decrease the risk of misdiagnosis; however, the high variability in the immunohistochemical panels among the reports is still considered a potential limitation.

In the present review, 41.8% of patients exhibited lymph node involvement on clinical examination and 29.1% presented distant metastasis, while Soares et al. [7] has reported a higher incidence of 55% in both. The distant metastasis is seen mainly in the lungs, followed by liver, heart, bone, other systemic and visceral sites. The early identification of cervical lymph node metastasis could help patients with a high risk of distant metastasis to avail of early treatment, resulting in a better prognosis and outcome. The 8th edition of the American Joint Committee on Cancer (AJCC) has proposed the TNM staging of mucosal melanomas based on tumor thickness, presence of ulceration, involvement of lymph nodes, and distant metastasis. Stage I and stage II include tumor thickness and presence of ulceration, stage III and stage IV are based on the involvement of lymph node and distant metastasis respectively (A, B). In the present review, with reference to available data, 4 cases were classified as stage I and stage II while stage III and stage IV showed 2 cases and 14 cases respectively. For the remaining 35 cases, the data was incomplete for TNM staging [2, 71]. Earlier studies were based on the 7th edition of AJCC TNM staging for assessment of OAM [4, 6, 7].

The current data showed surgery as the main therapeutic approach, alone or in combination with chemotherapy and radiotherapy, in agreement with the literature. Local tumor excision with surrounding healthy tissue and radical bone resection in cases where tumor-free margins are difficult to obtain is performed [6, 30, 72]. Radiotherapy and chemotherapy is not effective when used in isolation. MMs are radio-resistant [73, 74] and irradiation is occasionally used in the elderly or medically compromised patients and post-surgically, when surgical margins cannot be obtained, to increase local control and reduce metastasis but not necessarily enhance survival [2, 72]. However, Tanaka et al. [24] reported a higher success rate with radiotherapy than surgery for OMMs. Chemotherapy is reserved for preoperative use to reduce the size of the tumor and for metastatic patients. Systemic immunotherapy has also been used, as adjuvant therapy, in cases involving widespread metastasis. In the future, detection of genetic alteration and developing molecular targeted therapy may be more effective and improve survival rates [6].

In the current review, 27 patients with reported follow-up, 25 died due to the tumor within 1–49 months after initial diagnosis. We observed, overall 3-years survival rate of patients was 18.75% and the 5-years survival rate was

6.25%; whereas Soraes et al. [7] noted a 1-year survival rate in 20% cases, and Nandapalan et al. [75] reported 20% survival at 3 years in OAM. Literature review shows a high mortality rate in OAM, 5-year survival in 5% cases, compared to pigmented oral mucosal and cutaneous melanomas, 58% survival at 3 years [30, 34, 35, 76]. We also observed recurrence in 9.1% cases of OAM, while the data was unavailable in 78.2% cases, at a mean interval of 3–16 months.

To identify the significant prognostic markers affecting patient survival, the clinicopathological variables in the present review were subjected to statistical analysis. de Paulo et al. [6] in his study could not find any significant prognostic factor for OAM. We observed patients older than 68 years demonstrated a lower survival rate. The higher death rate in elderly patients could be attributed to the tumor specifically or due to treatment complications, underlying systemic diseases or other causes. In addition, cases involving the mandibular gingiva showed lower survival rates, indicating that the tumor location also plays a vital role in the survival analysis. Histopathologically, we observed that OAMs having round cells had a lower survival rate, while Soares et al. [7] in their study on OMM suggested poor prognosis in tumors with epithelioid cell morphology. The treatment modality which consisted of an amalgamation of surgery, CT, and RT, seen in a single case of our study, showed a significantly lower survival rate. Late diagnosis, surgically challenging site (soft palate), high proliferative index (> 70%), lymph node involvement, or delayed treatment could partly explain the poor prognosis in this case. The lack of significance of survival rate with respect to other clinical features is due to the small number of cases investigated in this review. We could not identify independent prognostic factors by including the statistically significant parameters in the univariate analysis due to the low sample size. The nonresponse of several authors made it difficult to assess the reasons for incomplete information or missing data. This insufficient source of information from the retrieved data is a reason for methodological limitation to our study. Given the limitations of this systematic review that retrieved clinicopathological data, it is important to highlight that the results obtained in our study need to be further validated.

To conclude, the OAM is a rare neoplasm with a poor prognosis, presenting a 6.25% possibility of survival after 5 years. Patients older than 68 years, lesions in the mandibular gingiva, round cells, and surgical excision along with chemotherapy and radiotherapy, presented the worst prognosis. However, they did not represent independent prognostic determinants for these patients. Further, published reports with complete data are required to uncover the prognostic factors and describe the distinct biological behavior of OAMs.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12105-021-01366-w>.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr. SB, Dr. SSD, Dr. VM, Dr. AA and Dr. RSD. The first draft of the manuscript was written by Dr. SB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability Search strategy for Embase, Scopus, Pubmed.

Code Availability R version 3.3.1 (R foundation for Statistical Computing).

Declarations

Conflict of interest There are no conflicts of interest/The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval This is an observational study. The Ethics Committee of Nair Hospital Dental College (IEC-NHDC) has confirmed that no ethical approval is required.

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