

Review Article



Survival and prognostic factors in mucosal melanomas of the oral cavity: A meta-analysis

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Abstract

Background. The development of early metastases due to the high vascularization and lymphatic drainage of the oral cavity, followed by delayed diagnosis, results in a worse prognosis of oral melanomas. The present study aimed to determine the survival of oral melanoma in different periods and analyze its prognostic factors.

Methods. A search for studies on survival and prognostic factors of oral melanoma was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and Scopus. The estimation of the pooled proportion was carried out with the generic inverse variance method, using the standard error (SE) of the proportion. For dichotomous outcomes, the estimates of the effects of the intervention were expressed as odds ratios (ORs) using the Mantel-Haenszel (M-H) method, all with 95% confidence intervals.

Results. Thirty-eight studies that considered 3767 oral melanoma patients were included in this meta-analysis. Overall survival (OS) decreased from 58% at two years to 42% at three years and 29% at five years. Regarding prognostic factors, non-ulcerated oral melanomas with a high degree of pigmentation showed the best survival at 5 years. In contrast, oral tumor location and gender did not significantly affect oral melanoma survival.

Conclusion. Oral melanoma has a low survival rate, with ulcerated and poorly pigmented tumors having the worst prognosis.

Introduction

Oral melanomas account for approximately 4% of all melanomas. They are mainly diagnosed between the 4th and 7th decades of life, with a peak incidence around 60 years of age, and are slightly more prevalent in males. Unlike cutaneous melanomas, the incidence of oral melanoma has remained stable in recent years.¹ Its etiology remains unknown, although some risk factors, such as chronic inflammation induced by smoking or chronic mechanical irritation, have been suggested. Notably, a significant proportion of oral melanomas arise de novo from the apparently normal oral mucosa. However, approximately 30%-40% of cases are preceded by oral pigmentations that persist for several months or even years.² The main oral locations for melanomas are the palate and the alveolar gingival ridge. The lack of symptomatology associated with oral melanoma often results in patients delaying medical attention, which can lead to delayed diagnosis and a poor prognosis. Early and prompt diagnosis of oral melanomas is vital for the patient's prognosis, as they exhibit more aggressive behavior and worse prognosis than melanomas with other locations in the body.³ Indeed, almost one-third of patients present with lymph node metastases at the time of diagnosis of primary oral melanoma. The early

development of metastases may be attributed to the high level of vascularization and lymphatic drainage in the oral cavity.⁴ This study aimed to determine the survival of patients with oral melanoma in different periods and assess its prognostic factors.

Methods

All research steps (search, study selection, and data extraction) were achieved independently by both authors (ARA and PVM). Discrepancies in article selection were resolved by consensus.

The research question was: How do different prognostic factors influence the survival of patients with oral melanoma?

Search strategy

Table 1 shows the search strategies in each database using a combination of Medical Subject Headings (MeSH) and free-text terms. The inclusion criteria were as follows: a) all types of articles related to our purpose and b) articles written in any language and with no restrictions on publication date. The exclusion criteria were: a) articles with no full-text availability, b) articles with a relevant risk of bias (score ≤ 5 stars on the Newcastle-Ottawa

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Table 1. Search strategies for the three databases

Database	#	Search strategy	Results
PubMed	#1	"melanoma"[MeSH Terms]	112,400
	#2	"mouth"[MeSH Terms]	326,150
	#3	#1 AND #2	619
	#4	("survival"[MeSH Terms] OR "prognosis"[MeSH Terms])	1,990,947
	#5	#3 AND #4	134
Web of Science (WoS)	#6	("melanoma"[Topic] AND "mouth" [Topic])	834
	#7	("survival" [Topic] OR "prognosis" [Topic])	1,244,600
	#8	#6 AND #7	247
Scopus	#7	TITLE-ABS-KEY ("melanoma" AND "mouth")	2,718
	#8	TITLE-ABS-KEY ("survival" OR "prognosis")	2,322,214
	#9	#7 AND #8	227

methodological quality assessment scale),⁵ c) articles with no clinical data, and d) studies with non-usable data.

Assessment of methodological quality

The methodological quality of the articles was screened using the Newcastle-Ottawa (NOS) methodological quality assessment scale,⁵ which is composed of eight items that evaluate three dimensions (selection, comparability, and exposure). Considering the score obtained, the studies are classified as high quality (≥ 7 stars), moderate quality (4–6 stars), and low quality (0–3 stars).

Data extraction

Overall survival (OS) of oral mucosal melanomas was established in three periods: 2, 3, and 5 years. Prognostic factors related to survival, such as the oral tumor location, the gender of the patients, the existence of ulceration of the lesion, or the degree of pigmentation of the neoplasm, were also evaluated.

Statistical analysis

For the meta-analysis, data were processed with RevMan 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark). The proportion (P) was calculated by dividing the number of positive cases (n) by the total population (N). Estimation of the proportion was carried out with the generic inverse of variance method, using the standard error (SE) of the proportion and 95% confidence intervals (95% CI). The SE was obtained using the formula $\text{SQRT}(P \times (1-P)/N)$. For dichotomous outcomes, the odds ratio (OR) with the Mantel-Haenszel chi-squared formula (M-H) was used, both with 95% confidence intervals (95% CI). Heterogeneity was determined according to the Higgins statistic (I^2). The random-effects model was applied in cases of high heterogeneity ($I^2 > 50\%$). A P-value below 0.05 was considered the minimum level of significance. The risk of publication bias was assessed using MedCalc Statistical Software version 23.1.7 (MedCalc Software Ltd., Ostend, Belgium). A funnel plot and Egger's regression test were employed, with a minimum of 10 studies required for analysis. Publication bias was considered present if

asymmetry was observed in the funnel plot and if Egger's test yielded a P value < 0.05 .

Results

Study selection

In the initial search, 608 articles were found (134 in PubMed, 247 in WoS, and 227 in Scopus) between 1955 and 2021, with 229 duplicates, leaving 379 eligible articles. A total of 341 studies were excluded due to a) articles with no full-text availability ($n=64$), b) articles with a relevant risk of bias (score ≤ 5 stars on the NOS) ($n=87$), c) articles without clinical data ($n=82$), and d) studies with non-usable data ($n=108$). After applying these criteria, 38 studies were included in this meta-analysis (Figure 1).

Table 2 summarizes the main descriptive characteristics and the methodological quality of 38 studies^{6–43} included in this meta-analysis, as assessed using the Newcastle-Ottawa Scale (NOS). A total of 3767 patients with oral mucosal melanoma were analyzed, with 50.4% males and 49.6% females. The studies were conducted in the following countries: United States of America (12 studies), China (8), Brazil (3), Japan (3), Denmark (2), France (2), Germany (2), Australia (1), Canada (1), Italy (1), South Korea (1), The Netherlands (1), and Turkey (1). According to the NOS, nine studies (23.7%) received 6 stars (moderate quality), 21 studies (55.3%) received 7 stars (high quality), and 8 studies (21.0%) received 8 stars (high quality).

Overall survival of oral melanoma at 2 years

Five studies^{9,10,23,31,42} that included 216 patients with oral melanoma (Figure 2) found a pooled 2-year OS of 58% (95% CI: 44% to 71%) with high heterogeneity between studies ($I^2: 74\%$). Study variability ranged from a maximum OS of 72% (95% CI: 62% to 82%)¹⁰ to a minimum OS of 30% (95% CI: 10% to 50%).²³

Overall survival of oral melanoma at 3 years

Seventeen studies,^{6,7,13–15,19–22,26,27,29,32–35,42} including 837 oral melanoma patients (Figure 3), found a pooled 3-year OS of 42% (95% CI: 37% to 48%) with high heterogeneity between studies ($I^2: 81\%$). Study variability ranged from a maximum OS of 68% (95% CI: 47% to 89%)²⁰ to a minimum OS of 17% (95% CI: 0% to 42%).³²

Overall survival of oral melanoma at 5 years

Thirty-three studies^{6–11,13,14,16–22,24–26,28–39,41–43} involving 2773 patients with oral melanoma (Figure 4) found a pooled 5-year OS of 29% (95% CI: 24% to 34%) with high heterogeneity between studies ($I^2: 89\%$). Study variability ranged from a maximum OS of 57% (95% CI: 35% to 80%)²⁰ to a minimum OS of 4% (95% CI: 0% to 12%).¹⁸

Overall survival of oral melanoma related to other clinical parameters

Table 3 shows the possible influence of other clinical parameters (oral location of the tumor, gender, ulceration,

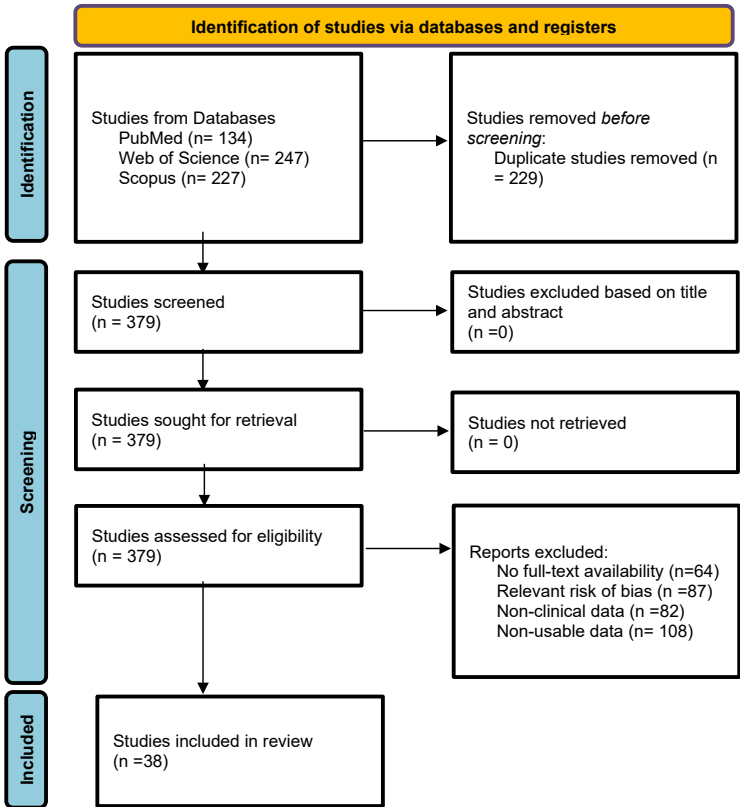


Figure 1. Study selection flowchart

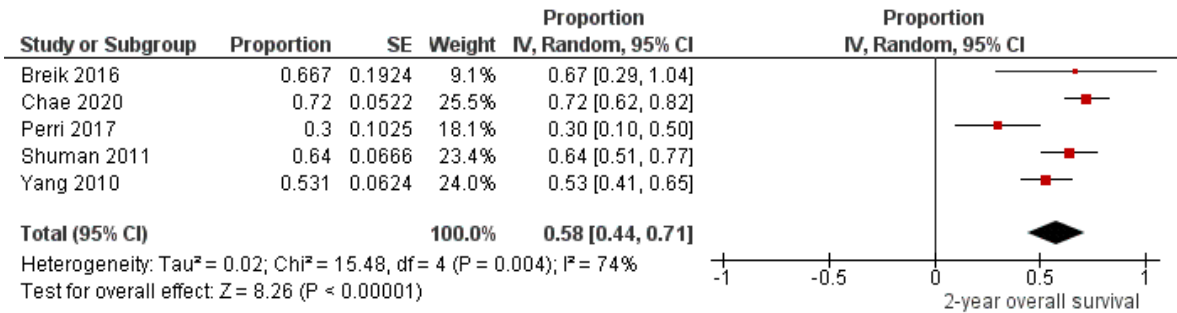


Figure 2. Study data and forest plot graph for 2-year overall survival of patients with oral melanoma. SE: standard error

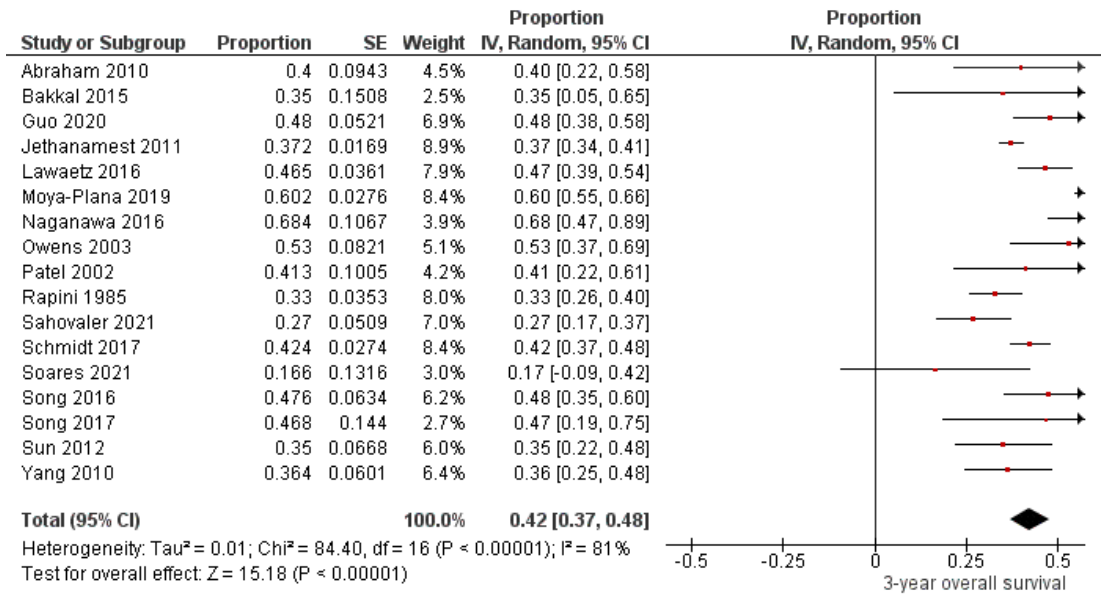


Figure 3. Study data and forest plot graph for 3-year overall survival of patients with oral melanoma. SE: standard error

Table 2. Descriptive characteristics and methodological quality evaluation of the 38 studies included in this meta-analysis

Study, year	Country	Study populations (gender distribution, mean age)	Other parameters assessed	NOS
Abraham, 2010 ⁶	USA	27 pat. (15M, 12F; 68y)	Race, treatment, stage, follow-up, OS	6
Bakkal, 2015 ⁷	Turkey	10 pat. (6M, 4F; 66y)	Treatment, stage, follow-up, local recurrence, regional recurrence, OS	6
Berthelsen, 1984 ⁸	Denmark	38 pat. (31M, 7F; 64y)	Treatment, stage, follow-up, OS	7
Breik, 2016 ⁹	Australia	14 pat. (8M, 6F; 65y)	Treatment, pathology, stage, follow-up, OS	6
Chae, 2020 ¹⁰	South Korea	74 pat. (41M, 33F; 59y)	Treatment, bone invasion, resection margin status, stage, follow-up, OS	8
Conley, 1974 ¹¹	USA	52 pat. (36M, 16F; 60y)	Treatment, stage, follow-up, OS	8
Francisco, 2016 ¹²	Brazil	51 pat. (31M, 20F; 59y)	Race, treatment, stage, recurrence, follow-up, OS	8
Guo, 2020 ¹³	China	92 pat. (40M, 52F; na)	Treatment, pigmentation, stage, recurrence, follow-up, OS	6
Jethanamest, 2011 ¹⁴	USA	815 pat. (382M, 433F; na)	Race, treatment, stage, follow-up, OS	7
Lawaetz, 2016 ¹⁵	Denmark	98 pat. (41M, 57F; na)	Treatment, stage, pigmentation, ulceration, follow-up, OS	7
Lian, 2017 ¹⁶	China	706 pat. (233M, 473F; 55y)	Treatment, stage, BRAF mutation, cKIT mutation, follow-up, OS	7
Meleti, 2008 ¹⁷	The Netherlands	14 pat. (5M, 9F; 57.9y)	Treatment, stage, follow-up, OS	6
Moore, 1955 ¹⁸	USA	26 pat. (na, na; na)	Race, treatment, stage, follow-up, OS	6
Moya-Plana, 2019 ¹⁹	France	45 pat. (31M, 14F; 64y)	Treatment, stage, margins, follow-up, OS	7
Naganawa, 2016 ²⁰	Japan	19 pat. (9M, 10F; na)	Treatment, stage, follow-up, OS	6
Owens, 2003 ²¹	USA	48 pat. (39M, 9F; 55.5y)	Treatment, stage, follow-up, OS	7
Patel, 2002 ²²	USA	59 pat. (34M, 25F; 63y)	Treatment, stage, vascular invasion, follow-up, OS	8
Perri, 2017 ²³	Italy	20 pat. (14M, 6F; 54y)	Treatment, stage, pigmentation, ulceration, follow-up, OS	6
Prasad, 2002 ²⁴	USA	40 pat. (30M, 10F; 59.5y)	Treatment, stage, pigmentation, ulceration, follow-up, OS	8
Prinzen, 2019 ²⁵	Germany	50 pat. (25M, 25F; 65y)	Treatment, stage, sentinel node biopsy, follow-up, OS	7
Rapini, 1985 ²⁶	USA	124 pat. (78M, 46F; na)	Treatment, stage, follow-up, OS	7
Sahovaler, 2021 ²⁷	Canada	76 pat. (33M, 43F; 66.3y)	Treatment, stage, margins, follow-up, OS	7
Schaefer, 2017 ²⁸	Germany	32 pat. (22M, 10F; 64.5y)	Treatment, stage, follow-up, OS	7
Schmidt, 2017 ²⁹	USA	326 pat. (180M, 146F; 66y)	Treatment, stage, neck dissection, follow-up, OS	7
Shah, 1977 ³⁰	USA	74 pat. (47M, 27F; na)	Race, treatment, stage, follow-up, OS	7
Shuman, 2011 ³¹	USA	52 pat. (21M, 31F; 66y)	Treatment, stage, margins, follow-up, OS	7
Soares, 2021 ³²	Brazil	8 pat. (6M, 2F; 53.6y)	Treatment, stage, pigmentation, biomarkers, follow-up, OS	6
Song, 2016 ³³	China	62 pat. (34M, 28F; 55.4y)	Treatment, stage, follow-up, OS	8
Song, 2017 ³⁴	China	62 pat. (34M, 28F; 55.4y)	Treatment, stage, BAP1 expression, follow-up, OS	7
Sun, 2012 ³⁵	China	51 pat. (36M, 15F; na)	Treatment, stage, pigmentation, neck dissection, follow-up, OS	7
Tanaka, 2004 ³⁶	Japan	35 pat. (14M, 21F; 65.2y)	Treatment, stage, follow-up, OS	8
Temam, 2005 ³⁷	France	69 pat. (36M, 33F; na)	Treatment, stage, follow-up, OS	7
Trodahl, 1970 ³⁸	USA	42 pat. (36M, 6F; 49.5y)	Treatment, stage, follow-up, OS	7
Wang, 2013 ³⁹	China	81 pat. (50M, 31F; na)	Treatment, stage, heparanase expression, follow-up, OS	7
Wu, 2018 ⁴⁰	China	170 pat. (91M, 79F; na)	Treatment, stage, ulceration, follow-up, OS	8
Yamada, 2017 ⁴¹	Japan	38 pat. (24M, 14F; 65.2y)	Treatment, stage, follow-up, OS	7
Yang, 2010 ⁴²	China	78 pat. (50M, 28F; 53.8y)	Treatment, stage, recurrence, follow-up, OS	7
Yii, 2003 ⁴³	UK	89 pat. (43M, 46F; 64y)	Race, treatment, stage, follow-up, OS	7

NOS: Newcastle-Ottawa methodological quality scale; pat.: patients with oral mucosal melanoma; M: male; F: female; y: mean age in years; na: data not available; OS: overall survival.

Table 3. Analysis of different clinical parameters related to 5-year survival of oral melanomas

Parameter	References	Value	OR	[95% CI]	I ² (%)	P
Oral location of melanoma	17,39,42	Palate	1.49	[0.58 to 3.81]	0%	0.41
Gender	17,26,33,39,42	Female	1.41	[0.91 to 2.18]	0%	0.13
Ulceration	24,25,42,43	No	3.78	[2.24 to 6.39]	0%	<0.001*
Degree of pigmentation	13,24-26,39	Highly pigmented	2.47	[1.46 to 4.19]	0%	<0.001*

OR: odds ratio; CI: confidence interval; I² (%): Higgins statistic for heterogeneity (percentage); *Statistically significant.

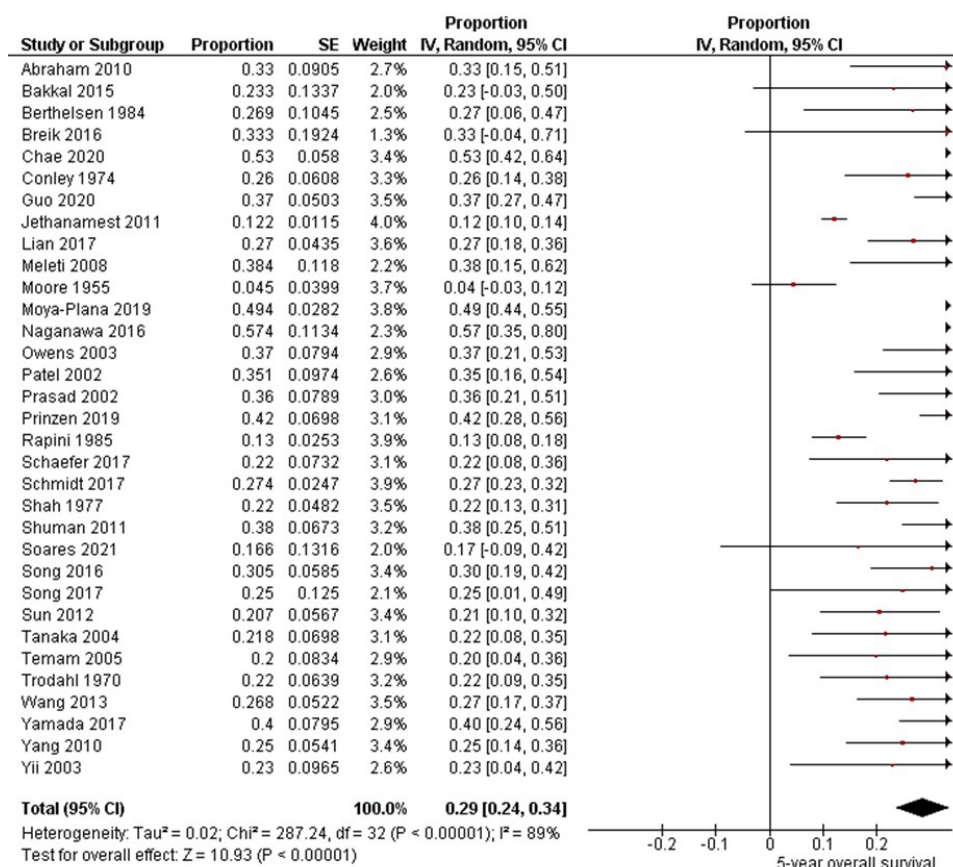


Figure 4. Study data and forest plot graphs for 5-year overall survival of patients with oral melanoma. SE: standard error

and the degree of pigmentation) on the OS of oral mucosal melanomas.

Three studies^{20,39,40} evaluated the oral location of the melanoma, observing a higher probability of 5-year survival in tumors located in the palate, although without reaching statistical significance (OR=1.49, 95% CI: 0.58 to 3.81, $P=0.41$). Five studies^{20,25,35,39,40} focused on the patient's gender. Although females exhibited a longer 5-year survival compared to males, the results were also not statistically significant (OR=1.41, 95% CI: 0.91 to 2.18, $P=0.13$).

Four studies^{12,33,34,40} compared oral ulcerated and non-ulcerated melanomas concerning 5-year survival. Patients with non-ulcerated melanomas were 3.78 times more likely to be alive at 5 years with a highly significant association (OR=3.78, 95% CI: 2.24 to 6.39, $P<0.001$).

Five studies^{13,33-35,39} examined the degree of pigmentation of melanomas. Patients with highly pigmented tumors were 2.47 times more likely to be alive at 5-year follow-up. After statistical analysis, highly significant differences were found (OR=2.47, 95% CI: 1.46 to 4.19, $P<0.001$).

Publication bias

Table 4 presents the assessment of publication bias based on Egger's regression test. Publication bias was confirmed by the presence of asymmetry in the funnel plot with $P<0.05$ in Egger's test for 5-year OS ($P=0.0029$) but not for 3-year OS ($P=0.8653$).

Table 4. Analysis of publication bias according to Egger's regression test

Parameter	n*	t	[95% CI]	P value
OS oral melanoma at 2 years	5	NA	NA	NA
OS oral melanoma at 3 years	17	0.1760	[-1.9971 to 2.3490]	0.8653
OS oral melanoma at 5 years	33	2.3638	[0.8710 to 3.8566]	0.0029
Oral location of melanoma	3	NA	NA	NA
Gender	5	NA	NA	NA
Ulceration	4	NA	NA	NA
Degree of pigmentation	5	NA	NA	NA

* Minimum of 10 studies to perform the analysis; OS: overall survival; n: number of studies; t: intercept; CI: confidence interval; NA: not assessable.

Discussion

The present meta-analysis on survival and prognostic factors related to oral melanoma included data from 38 studies.

In this study, the 2-year survival of oral melanomas was 58%. Of the five studies that analyzed this parameter, four^{9,10,31,42} reported percentages similar to the current paper, whereas one study²³ found a considerably lower survival (30%). In the present study, the 3-year survival of oral melanomas reached 42%. Of the seventeen studies that evaluated this variable, thirteen^{6,7,13-15,21,22,26,29,33-35,42} found similar percentages, two^{19,20} found significantly higher percentages (>60%), and two other studies^{27,32} found much lower survival percentages (<30%). In this study, the 5-year survival rate for oral melanoma was 29%. Of the 35 studies examining this parameter,

18 studies^{6-9,11,16,22,24,28-30,32,33,36,38,39,42,43} reported a 5-year survival percentage similar to that of this study (range: 22–36%); seven studies^{13,17,19-21,25,41} obtained a relatively higher survival (>37%), and six others^{14,18,26,32,35,37} reported significantly lower 5-year survival percentages (<21%).

Oral melanomas carry a worse prognosis than cutaneous melanomas due to their propensity for local invasion and distant metastasis. This is primarily attributed to delayed diagnosis, atypical clinical presentation, and continuous trauma related to their anatomical location, often resulting in ulcerated lesions as the disease progresses.⁴⁴ Resection of primary oral melanoma lesions is the gold standard of treatment for these lesions. The main problem stems from the early metastatic nature of oral melanomas. Lymph node metastases are common, and neck dissection does not affect the development of future distant metastases or OS. Survival of patients with oral melanoma varies according to the tumor site and decreases when brain or liver metastases are present. The primary site of oral melanoma location, bone invasion, resection margins, depth of tumor invasion, and distant metastases are critical factors in predicting prognosis. They should be considered when selecting the most appropriate therapeutic option for treating oral mucosal melanoma.¹⁰ Other factors with a relevant influence on oral melanoma survival are the type of melanoma, with amelanotic melanomas having the worst prognosis probably due to diagnostic delay³² or the overexpression of certain genes such as the BAP1 gene that regulates cell differentiation, division, and death.³⁴ The BAP1 gene encodes a tumor suppressor protein that plays a pivotal role in the pathogenesis of uveal melanoma. However, its relevance in oral melanomas remains poorly understood. In uveal melanoma, high BAP1 expression has been significantly associated with a favorable clinical prognosis. Conversely, in oral melanomas, BAP1 overexpression appears to be linked to an adverse prognosis and decreased OS. Evidence suggests that BAP1 inactivation in oral mucosal melanomas may play a role in tumor progression by promoting a more aggressive biological phenotype and reduced patient survival.⁴⁵ Similarly, overexpression of heparanase, an enzyme released in the metabolism of tumor cells, also leads to poorer survival in oral melanomas, as they have a worse biological behavior.³⁹ In oral mucosal melanomas, the transition from the radial growth phase to the invasive phase represents a critical step in tumor progression, as malignant cells migrate and infiltrate the underlying connective tissue. This process involves the synthesis and release of enzymes required for extracellular matrix degradation, such as heparanase.⁴⁶

In the present study, melanomas located on the palate had a higher probability of 5-year survival, although statistical significance was not reached ($P=0.41$). Two^{39,40} of the three studies that considered tumor location coincided in indicating the palatal location, while the other one²⁰ did not. This longer survival in tumors located in the palate could be conditioned by the achievement of

negative resection margins at the time of surgery. This is much more difficult in other melanoma sites, such as the pharynx or paranasal sinus.²⁰

Although women had a longer 5-year survival than men in this work, the results were also not statistically significant ($P=0.13$). Of the five studies that focused on the patient's gender, four^{12,20,25,35} confirmed this longer survival in females, while for one,³⁹ it was longer in males. The reason for the shorter survival of males with oral melanoma may lie in the higher incidence of this malignant tumor in males. The actual influence of gender on the biological behavior of oral mucosal melanomas remains to be elucidated.³⁹ Women's greater awareness of health problems may lead to an earlier diagnosis of oral melanoma and a longer survival time.²⁵

In the present work, non-ulcerated melanomas increased the probability of 5-year survival by 3.78 times, with highly significant statistical differences ($P<0.001$). All studies^{12,33,34,40} that further examined this parameter corroborated this increased survival in non-ulcerated lesions. Ulceration is a clinical sign of long-term lesions found in the more advanced stages (III or IV) of the disease. These melanomas have a higher degree of invasion and deep infiltration that drastically decreases survival.⁴⁰

In this study, patients with more pigmented melanomas were 2.47 times more likely to be alive at 5-year follow-up, with a highly significant statistical association ($P<0.001$). All studies^{13,33-35,39} that looked at the degree of pigmentation agreed that the more pigmented the melanoma, the higher the probability of 5-year survival. Due to their clinical presentation as red-like lesions, poorly pigmented melanomas (amelanotic melanomas) present delays in diagnosis. There is often diagnostic confusion with lesions of inflammatory-infectious origin. The diagnosis is made later, as they are metastatic lesions with a worse prognosis.¹³

Limitations

This study had some limitations. It was not possible to properly analyze certain parameters that significantly influence survival in oral melanomas, such as the evolution time of the tumor lesion or the presence of lymph nodes and distant metastases. Nor was it possible to evaluate the impact on survival of the different treatment alternatives of oral melanomas. Finally, the significant variability between studies may have conditioned the results, requiring a cautious interpretation.

Conclusion

In this meta-analysis, the OS of oral mucosal melanoma patients decreased from 58% at two years to 42% at three years and 29% at five years. Considering the prognostic factors, non-ulcerated oral melanomas with a high degree of pigmentation showed the highest 5-year survival. In contrast, oral tumor location and gender did not significantly affect oral melanoma survival.

Authors' Contribution

Conceptualization: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Data curation: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Formal analysis: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Investigation: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Methodology: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Project administration: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Resources: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Supervision: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Validation: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Writing—original draft: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Writing—review & editing: Alberto Rodriguez-Archilla, Pablo Valverde-Martinez.

Competing Interests

None.

Ethical Approval

Granada University Stomatology Department Scientific Committee (code EST/UGR/19-2024).

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