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Difference in prognosis of oral melanoma and cutaneous melanoma: A systematic review

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LISTS OF SYMBOLS AND ACRONYMS

ABBREVIATIONS

OM	Oral melanoma
CM	Cutaneous melanoma
MM	Mucosal melanoma
PMM	Primary mucosal melanoma
OMM	Oral mucosal melanoma
OS	Overall survival
SES	Socioeconomic Status
CT	Cell Type
TIL	Tumor infiltrating lymphocyte
MR	Mitotic Rate
HPF	High power field

ABSTRACT

Background: to systematically review the literature, comparing the prognosis and of oral melanoma and cutaneous melanoma among the prognostic factors. In addition, the survival rates of the two melanoma types should be compared.

Materials and Methods: The review was organized according to the PRISMA protocol with regards to the following PICO question: patients with oral melanoma (P=Patient); the prognosis factors of oral melanoma and cutaneous melanoma (I=Intervention); between oral and cutaneous melanoma (C=Comparison); where the prognosis is expected to be worse in oral melanoma (O=Outcome). A literature search was conducted from December 2021 until February 2022 using PubMed (MEDLINE) and Scopus. Studies that performed analysis on the prognosis and survival rates of patient with oral melanoma were included. Risk of bias was assessed with the Newcastle-Ottawa quality instrument. The data synthesis was gathered with the aim of summarizing and comparing studies.

Results: After eliminating the duplicate articles and assessing which ones met the criteria for inclusion, 8 articles have been selected, which have been included in the qualitative analysis. The total number of included participants was 4453. The following parameters have been assessed to have a prognostic influence: age at diagnosis, time of diagnosis, tumor size, extent of disease, level of invasion, pigmentation, and ulceration. In terms of survival rates, the survival prognosis for cutaneous melanoma is higher, with percentages ranging between 77-85%, than the survival prognosis for OM is between 20-34%.

Discussion: Oral melanoma has a poor prognosis compared to cutaneous melanoma, as the findings of this review demonstrate that patients with cutaneous melanoma had a better long-term survival rate than those with oral melanoma. Limitations of this study indicate the importance for further research that examines the influence of the identical prognostic factors. This systematic review provides a useful summary of the most important prognostic factors for oral melanoma. Further validation studies are warranted to confirm their significance.

KEYWORDS

Oral melanoma, Cutaneous melanoma, Prognosis, Prognostic factors, Survival rate

1. INTRODUCTION

Malignant melanoma is an uncommon and aggressive tumor, such as the deadliest primary skin cancer. When these tumors occur in mucosal areas, like the oral cavity, the prognosis is significantly worse. All focally pigmented lesions and most diffusely pigmented lesions require a biopsy for diagnosis due to the possibility of oral mucosal melanoma (1). Melanomas are most seen on the skin; nonetheless, 1–8% of malignant melanomas occur in the oral mucosa, accounting for 0.5 percent of all oral malignant tumors, with an incidence of 1.2 cases per 10 million individuals per year (2,3). Unlike cutaneous melanomas (CMs), the origin, risk factors, and pathophysiology of oral melanomas (OMs) are poorly known. These tumors are commonly diagnosed when they are in more advanced stages than the usual CM due to frequent delays in diagnosis (4). The rare and deadly cancer arises from malignant transformation and clonal expansion of neural crest-derived melanocytes located in the oral epithelium's basal cell layer or the oral mucosa's lamina propria (5).

With an annual incidence of 1.2 cases per 10 million people, OMs account for less than 1% of all melanomas, 0.5 percent of all oral malignancies, and 40% of all primary malignant melanomas (PMM) of the head and neck (2,6). The distribution of the disease between men and women appears to be equal, although in several studies males are more likely than females to be impacted (2,7,8). The reported cases range in age from 20 to 80 years old. Melanoma affects people of different races in different ways. Due to the existence of melanin pigmentation in their oral mucosa, Africans are the most impacted. OMs are also common in Asia, accounting for 11-12.4 percent of all melanomas (2). While in CM white people are impacted 94-96 % and black people are affected 81-89 %, in MM white people are affected 0.7-2.1 percent of the time and black people are affected 4.7-13.4 % (9).

The most apparent difference between OM and CM is in rates, with CM being by far the most prevalent type of melanoma, whereas it rarely occurs in other parts of the body containing pigment cells. Sun exposure, which is the main risk factor for CM, is not linked to mucosal melanoma (MM), which develop in sun-protected areas. Variances in age, gender, and racial distribution, as well as survival rates and recently discovered differences in molecular alterations, are all apparent. OM has a low prognosis (5-year

survival rate), about 25%, as compared to CM, which has a five-year survival rate of 80.8% (9).

OM might be asymptomatic in its early stages. Considering symptoms such as discomfort, bleeding, and ulceration may not appear until later, most cases of OM, around 60%, are detected only when they are advanced. Lesions with a diameter more than 4 cm and distant metastases have a poor prognosis, with a survival rate of less than 17 months and only 6.6 % of patients surviving for more than five years. MMs have a significantly worse prognosis than CMs because they commonly invade the underlying tissues and metastasize. The conjunctiva, oral cavity, and sinonasal tract are the most usually affected areas of the head and neck (2).

The presence of pigmented tissue in the oral cavity might provide a diagnostic challenge for clinicians. Mucosal pigment can take several forms, ranging from focal to diffuse macular color, or a small nodular development to a large mass. The pigmented lesions' color, location, duration, distribution, and appearance may all be important for the diagnosis. To ensure an accurate diagnosis, a complete assessment of dental, medical, familial, and social histories is also required (1).

1.1. Etiology

Patients with MM appear at a significantly later age than those with CM, about one to two decades later, with most cases documented between the ages of 50 and 80, and a median age at diagnosis of 70 (10). Melanoma of the skin is associated with UV radiation, for example sun and tanning bed, and age, just like ethnicity, such as the Caucasian population, history of blistering sunburns as a child, dysplastic nevi, family history, occupational chemical exposure, fair skin and hair, such as blonde or red hair, and immunosuppression (11). Whereas sunlight is a predisposing factor for CM, no predisposing factors for MM have been discovered. There is little evidence that recurrent trauma, chronic inflammation, human papillomavirus infection, intake of alcohol or tobacco consumption have any role in the pathogenesis of OMM. However, cigarette smoking has been indicated as a risk factor since smokers have been shown to have more oral pigmented lesions (9,12). In addition, OMs are influenced by factors such as family history and pre-existing lesions (6). Due to the fact that the Japanese population has a greater frequency of OM, several researchers have proposed a link between this subtype and unidentified common genetic or environmental factors (10). However, the presence of a mucosal field of melanin hyperpigmentation is the only known risk factor. Intraoral malignant melanomas develop from the few melanocytic cells in the oral cavity that have the potential to become malignant (2). Melanoma can develop from any benign melanocytic lesion, but it can also emerge from melanocytes without any evident predisposing condition (8). They can develop spontaneously, from pre-existing pigmented regions (5-30%), or from junctional nevus (2,5).

1.2. Precursor Cells

The majority of primary OM are produced by melanocytes in the oral epithelium's basal cell layer, although some are caused by immature melanocytes in the oral mucosa's lamina propria. Oral melanocytes are produced from neural crest stem or progenitor cells, which move to their final destination in the oral epithelium's basal cell layer during embryogenesis. Several biological agents and intracellular signalling pathways are involved in the migration of precursor melanocytes and their differentiation into mature, melanin-producing, or amelanotic melanocytes, including stem cell factor and its tyrosine kinase receptor cKit signalling pathway, endothelins 1 and 3, hepatocyte growth factor, and basic fibroblast growth factor. However, some immature melanocytes remain stuck in the lamina propria during their migration towards the oral epithelium for unexplained reasons. The origin of the melanoma precursor cell is unknown, although it is most likely a tissue-specific stem or progenitor melanocyte that has undergone malignant transformation due to cytogenetic and epigenetic modifications over time. Melanoma stem or progenitor cells, like normal melanocyte progenitor cells, maintain their undifferentiated phenotypes and self-renewal potential. Otherwise, melanoma precursor cells could be derived from melanocytes that have undergone a process of dedifferentiation as a result of cytogenetic alterations and have acquired a melanoma stem or progenitor cell phenotype, either in the basal cell layer of the epithelium or in the lamina propria of the oral mucosa. These melanoma stem or progenitor cells are the reason behind the main tumor's continued growth and the formation of distant metastases. Their replication generates additional melanoma transient-amplifying cells with a high proliferative rate, which enhance tumor progression (5).

1.3. Pathogenesis

Unlike CM, the etiology and pathogenesis of OM are poorly known, and no etiological or intraoral risk factors have been discovered, other than pre-existing pigmented nevi (3,4). OM is thought to develop from pigmented nevi, pre-existing pigmented regions, or de novo (30% of the cases) from apparently normal mucosa. Mechanical trauma, such as damage from ill-fitting prostheses, infection, and tobacco use have all been suggested as probable causes in the oral cavity, although their etiological significance is doubtful. Environmental carcinogens ingested and absorbed at a high internal body temperature may have a role (4). Most melanoma precursor cells are thought to come from stem/progenitor melanocytes that have developed a malignant phenotype due to cytogenetic changes in their oncogenes, tumor-suppressor genes, and DNA repair genes (13).

Conversely, precursor melanoma cells might be adult melanocytes that have remained in the submucosa and have undergone cytogenetic changes that result in dedifferentiation (3,4). Melanoma precursor cells have a high potential for self-renewal, which allows melanoma to continue to proliferate. There is evidence that if the process of melanocyte production is not properly controlled, the potential to create oxidative stress and metabolic by-products increases. These by-products may be cytotoxic, genotoxic, and/or mutagenic, causing DNA damage in the damaged melanocytes, favoring initial cell transformation and subsequent cancer development in already converted melanocytes. The c-kit/stem cell factor pathway, the endothelin receptor type B/endothelin pathway, and the Wnt/b-catenin pathway are all defective melanocytes, as abnormal cell-adhesion molecules (4).

1.4. Clinical Features

OM normally arises from within areas of benign oral melanotic hyperpigmentation of the oral mucosa, however it has been observed that in up to one-third of cases, it arises from within areas of clinically normal-looking mucosa. The palate and maxillary gingiva are the most affected areas (approximately 80%), followed by the retromolar region and buccal mucosa (5). Early OM lesions appear flat, macular, or slightly elevated and are often painless, irregularly shaped brown to black macules or papules that may expand, develop into nodules or exophytic masses, and become more deeply pigmented over time, which commonly invades the surrounding tissues as it progresses. Advanced lesions can be painful, ulcerated, and unstable, and they can bleed considerably (5,7). The macular, plaque-like, or nodular lesion is frequently asymmetrical and manifests in brown, gray, or black tones. 10 % of patients exhibit non-pigmented lesions. The tumor may be surrounded by satellite lesions (6). Pain, bleeding, ulceration, and ill-fitting dentures are some of the symptoms. Nonspecific signs and symptoms of malignancy include tooth movement or spontaneous exfoliation, root resorption, and bone loss, just like paresthesia or anesthesia. In some cases, patients may be asymptomatic (1,6).

OM is classified into five clinical types: pigmented nodular type, non-pigmented nodular type, pigmented macular type, pigmented mixed type, pigmented mixed type, and non-pigmented mixed type. A vertical development phase with or without a radial growth phase can occur in OM (2). The pigmentation is typically nonuniform, with gray, dark blue, dark brown, or black tones. Numerous independent melanomas can develop within a narrow area of oral epithelium containing atypical melanocytes that have achieved malignant transformation. Exophytic ulcerated OMs appear to have a greater probability of regional spreading than maculopapular OM (5). OM has three primary components: a nodular component in the center, a plaque component that is flat or slightly elevated and has deep brownish-black pigmentation, and a light brown non-elevated macular component (2). At the time of diagnosis, about 25% of individuals with OM reported regional lymph node metastases, and about 10% showed distant haematogenous dissemination to the lung, liver, bone, or brain (5). In contrast to sinonasal melanomas, which have a low rate of nodal metastases, OM have a 25%

incidence of lymph node metastases. When the tumor thickness exceeds 5 mm, the risk of cervical lymph node metastases rises (6). Whereas the rate of lymph node metastasis in CM is only 9% (14).

1.5. Histopathological Features

These advanced tumors appear to have the same histological appearance as their cutaneous equivalent. Indeed, the three microscopic patterns of OM are in situ, invasive, and combined. The tumor usually begins with radial proliferation of atypical melanocytes in the epithelium's basal cell layer. The lamina propria then undergoes a period of vertical development of invasive nodular aggregates of atypical melanocytes, which appears like a sheet or nested configuration (5,8). The radial in situ and vertical invasive nodular patterns of malignant growth can be recognized from the beginning in a combined lesion. If a melanoma originates from an atypical immature melanocyte or melanocytes in the lamina propria, it will first proliferate in the lamina propria or submucosa, creating nodular aggregates, before spreading and metastasizing (5). MMs are diverse, polyhedral, spherical, fusiform, epithelioid, spindle-shaped, or pleomorphic melanoma cells can be found. In MM, the spindle tumor cell type is more prevalent than in CM (5,8). Mitotic activity is a major characteristic of their nuclei, which include one or more eosinophilic nucleoli. Melanoma cells that are proliferating produce solid, loosely cohesive, pseudo alveolar, or organoid patterns. Variable quantities of melanin can be found in tumor cells, macrophages, and free extracellular particles in roughly two-thirds of cases. The volume and density of the pigment can conceal the shape of tumor cells in some situations. Melanoma cells that lack melanin are known as amelanotic cells (5). MART-1/Melan-A, HMB-45, MITF, tyrosinase, and S-100 protein are all expressed to variable degrees in OMs cells. Immunohistochemistry can be used to identify these markers. However, considering their sensitivity and specificity are not absolute, no single marker should be used to establish a diagnosis of a suspected OM. Instead, series of tests should be used to try to confirm a diagnosis of a suspected OM (5).

1.6. Suspicion of Oral Melanoma

In case an OM is suspected on a patient, a picture of the lesion should be taken to document its size and color changes. Chest radiographs should be obtained to check for lung metastases. To assess bone and soft tissue alterations, a CT scan and an MRI should be performed. Sentinel lymph node biopsy, lymphoscintigraphy, skeletal scintigraphic surveys, and PET scan can all be used to check for distant metastases. As clinical diagnosis is often challenging, histopathological confirmation is needed. All oral pigmentations that show asymmetry, border irregularity, color change, diameter of the lesion >6 m, or are evolving should be biopsied (2).

1.7. Diagnosis

Once an OMM diagnosis has been made, a comprehensive clinical and special investigation must be performed to determine if the OM is primary or metastatic. If it is primary, to determine the extent of local invasion, and whether the cancer has spread to regional lymph nodes or distant sites (5). The Breslow tumor thickness grading method and clinical staging are used to evaluate the tumor and predict prognosis. The tumor thickness grading method developed by Breslow assesses the thickness of the tumor from the epidermal surface to the invasive front. Thin melanomas with a thickness of less than 0.76 mm usually have a good prognosis. For thin melanomas, 1 mm is considered the worldwide standard beyond which the prognosis is poor (2). The metastatic potential of primary CM rises as the tumor thickness increases. Markers such as the TA90 immune complex and the MIA protein have recently been introduced to predict survival in patients with stage III illness. The expression of VEGF, VEGF receptor (VEGFR)1, TGF-1, and Bcl-2 is linked to the progression of melanoma. In addition, fluorescence in situ hybridization (FISH) has recently been utilized to investigate the genetic markers of OM (2).

Clinical Staging: (Nambiar et al. (2))

Stage I	Level 1: Pure melanoma in situ - no invasion Level 2: Invasion up to lamina propria Level 3: Invasion into muscle, bone, or cartilage
Stage II	Metastasis to regional lymph nodes (T any N1M0)
Stage III	Metastasis to distant organs (T any N any M0)

Breslow Scale for tumor thickness measuring: (Nambiar et al. (2))

Thickness (mm)	**Risk of Recurrence**
< 0.76	Low risk
0.76 - 1.50	Low to mediate risk
1.50 - 3.99	Intermediate to high risk
> 4.00	High risk

1.8. Differential Diagnosis

To reach a definite diagnosis, a complete clinical examination, histological examination, and the establishment of a differential diagnosis are required. To differentiate from other lesions, all pigmented lesions that might develop in the oral cavity should be examined, and specific stains and immunohistochemical procedures should be used. Oral pigmentation can be caused by both physiological and pathological factors. It can come from either an external or an endogenous source. A thorough clinical evaluation of the lesion's color, location, distribution, duration, and evolution is required. A complete medical history, including drug use, family history of cancer, and lifestyle changes, should be kept on file (2). Differential diagnoses to consider are oral mucosal melanin hyperpigmentation, such as melanotic maculae, melanoacanthoma, melanotic nevus or some which are tobacco-induced, drug-induced, inflammation related or associated with syndromes or systemic disease such as Peutz-Jegher syndrome, McCune-Albright syndrome, Laugier-Hunziker syndrome, Addison disease,

neurofibromatosis (4,5). Furthermore, antiproliferative disorders such as haemangioma, vascular malformations or Kaposi sarcoma must be considered. Similarly, accounting extrinsic pigment much like an amalgam tattoo or recreational tattoo. Moreover, it must be considered benign inflammatory, reactive, neoplastic growths that should be differentiated from amelanotic melanoma for example pyogenic granuloma, fibrous hyperplasia, or peripheral giant cell granuloma (5).

1.9. Treatment Approaches

Due to the disease's rarity, establishing recommendations for the clinical course of MM has been difficult. Since it is difficult to perform large, randomized, controlled studies to explore alternative treatment regimens in this subtype of melanoma, no guidelines of care have been established. Early identification, like with most cancers, offers the highest chance of survival, although it is challenging, as previously said. The anatomic location of the tumor frequently dictates surgical decisions, with adjuvant radiation a possibility for local management (10). Once malignant melanoma has been detected, the following treatment procedure should be followed: First, the primary lesion should be surgically removed with a margin of at least 1-2 cm of healthy tissue, considering the tumor's size and thickness. Second, the removal of sentinal lymph nodes and other lymph nodes affected by metastases is recommended. Third, after surgery, radiochemotherapy should be performed. Surgical removal is the most common therapy; however, it is often difficult due to anatomical limitations. Although melanoma is not very radiosensitive, radiation has shown to be effective in individuals with early melanoma or melanoma in situ. Chemotherapy, while being investigated, has not yet shown encouraging outcomes. In recent years, immunotherapy has been considered (2,8).

1.10. Prognosis

OM patients have a poor prognosis, due to the mucosa's largely hidden anatomical location, which makes regular screening difficult. As a result, OMs are typically detected in late stages, worsening the prognosis and contributing to the cancer's high mortality, with an average survival of around 18 months from the time of diagnosis (2,3,8). At the end of five years, the survival rate is less than 20-22 % (2,10). In MM, being younger at diagnosis appears to be a significant prognostic factor, whereas no significant association between sex and survival has been stated (7). Systemic illnesses, advanced clinical stage at presentation, Breslow's tumor thickness of level IV and V, vascular invasion, histological characteristics, occurrences of amelanotic melanoma, and nodal and distant metastases are all factors that influence the prognosis and survival of melanoma patients (2). To conclude, long-term survival has been demonstrated to be impaired by advanced age, numerous tumor sites, necrosis, and amelanotic tumor histology, indeed, when a MM is diagnosed, the size of the tumor appears to be the most critical factor in predicting survival (7,8). Local treatment failure is common, with recurrence rates as high as 50–90% even when the tumor is completely removed surgically. Local recurrences are thought to be a sign of simultaneous or subsequent metastatic progression. Despite extensive surgical resection and adjuvant treatment, most patients had micro metastatic disease at the time of presentation, resulting in a disease course marked by local recurrences followed by metastatic disease (10).

2. JUSTIFICATION, HYPOTHESIS AND OBJECTIVES

2.1. Justification

Oral malignant melanoma is an aggressive and enormously rare cancer with a high mortality rate. In recent years, cutaneous melanoma has been extensively examined, but due to its rarity, oral melanoma is poorly investigated. The prognosis for oral melanoma is poor since it is usually identified in advanced stages, with lymph node involvement or distant metastases, as opposed to cutaneous melanoma, which may be spotted and diagnosed in the early stages. These alarming characteristics are the consequence of an inherent biological aggressiveness, and that the diagnosis is generally confirmed at a later stage due to the relative inaccessibility of the lesions' occult anatomic locations and the rarity of early symptoms. This systematic review aims to illustrate the relevance of early OM diagnosis in the oral cavity, as well as the influence it has on prognosis and long-term outcomes.

2.2. Hypothesis

In contrast to cutaneous melanoma, oral melanoma is uncommon, and its etiology and pathogenesis are poorly understood. Due to the fact that oral melanoma is usually detected in advanced stages, making treatment difficult and survival outcome poor, the hypothesis of this systematic review is that the prognosis is worse in oral melanoma than in cutaneous.

2.3. Objectives

2.3.1: General Objective

The aim of this systematic review is to analyse the prognosis of oral melanoma in comparison to cutaneous melanoma.

2.3.2: Specific Objectives

1. Define the prognostic factors of oral melanoma.
2. Examine the survival of oral melanoma compared with cutaneous melanoma.

3. MATERIALS AND METHODS

The preparation of this systematic review has followed the guidelines established by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) declaration for the preparation of systematic reviews and meta-analysis (15).

3.1. Eligibility criteria

The PICO model (patients, intervention, comparison, and results) was used to select the study population. Including patients diagnosed with oral melanoma, it was decided to compare the prognosis factors of oral melanoma with the prognosis of cutaneous melanoma.

Table 1: *The PICO model.*

P **(Patient)**	**I** **(Intervention)**	**C** **(Comparison)**	**O** **(Outcome)**
Patients diagnosed with oral melanoma	Prognosis factors of oral melanoma and cutaneous melanoma	Cutaneous melanoma	Prognosis is worse in oral melanoma than in cutaneous

3.1.1. Inclusion Criteria

1) Studies written in English, Spanish, or German; 2) Studies published in the last 10 years; 3) Studies examined on humans; 4) Studies in vivo; 5) Cohort studies, Case-Control studies, Retrospective studies, and Randomized controlled trials.; 6) Outcomes of studies that include data related to prognostic factors; 7) Outcomes of studies that include data about survival rates.

3.1.2. Exclusion Criteria

1) Not enough information regarding the selected topic. 2) Studies focusing on gene expression or biomarkers; 3) Patients with melanoma in other sides than oral cavity or skin.

3.2. Information sources and search strategy

A search of articles was carried out in the PubMed (MEDLINE) and Scopus databases between December 2021 and February 2022, using the following search terms: ("MELANOMA"[Title]) AND ("Cutaneous"[Title] OR "Dermal"[Title] OR "Skin"[Title]) AND ("Outcome"[Title] OR "Prognosis"[Title] OR "Prognostic*"[Title]) or ("Melanoma"[Title]) AND ("Mouth"[Title] OR "Oral"[Title] OR "Mouth Mucosa"[Title] OR "Buccal"[Title] OR "oral cavity"[Title] OR "Lips"[Title] OR "Tongue"[Title] OR "Mucosa"[Title] OR "Mucosal"[Title]) AND ("Outcome"[Title] OR "Prognosis"[Title] OR "Prognostic*"[Title]).

The search in the databases has been organized from a PICO question, with each one of the search concepts completely specified and delimited. The P (Patient) refers to the terms that include the type of patients studied; patients diagnosed with oral melanoma. The I (Intervention) bring together all the terms referring to prognosis and prognostic factors. And the C (Comparison) incorporates the terms related to compare oral melanoma with cutaneous melanoma. Once the PICO question has been formulated and the terms have been organized within each of the sections, these terms were linked together using Boolean operators. The Boolean operator OR (union) has been used to confront the terms of the same section, and the Boolean operator AND (intersection) was employed to cross the different groups (Diagram 1).

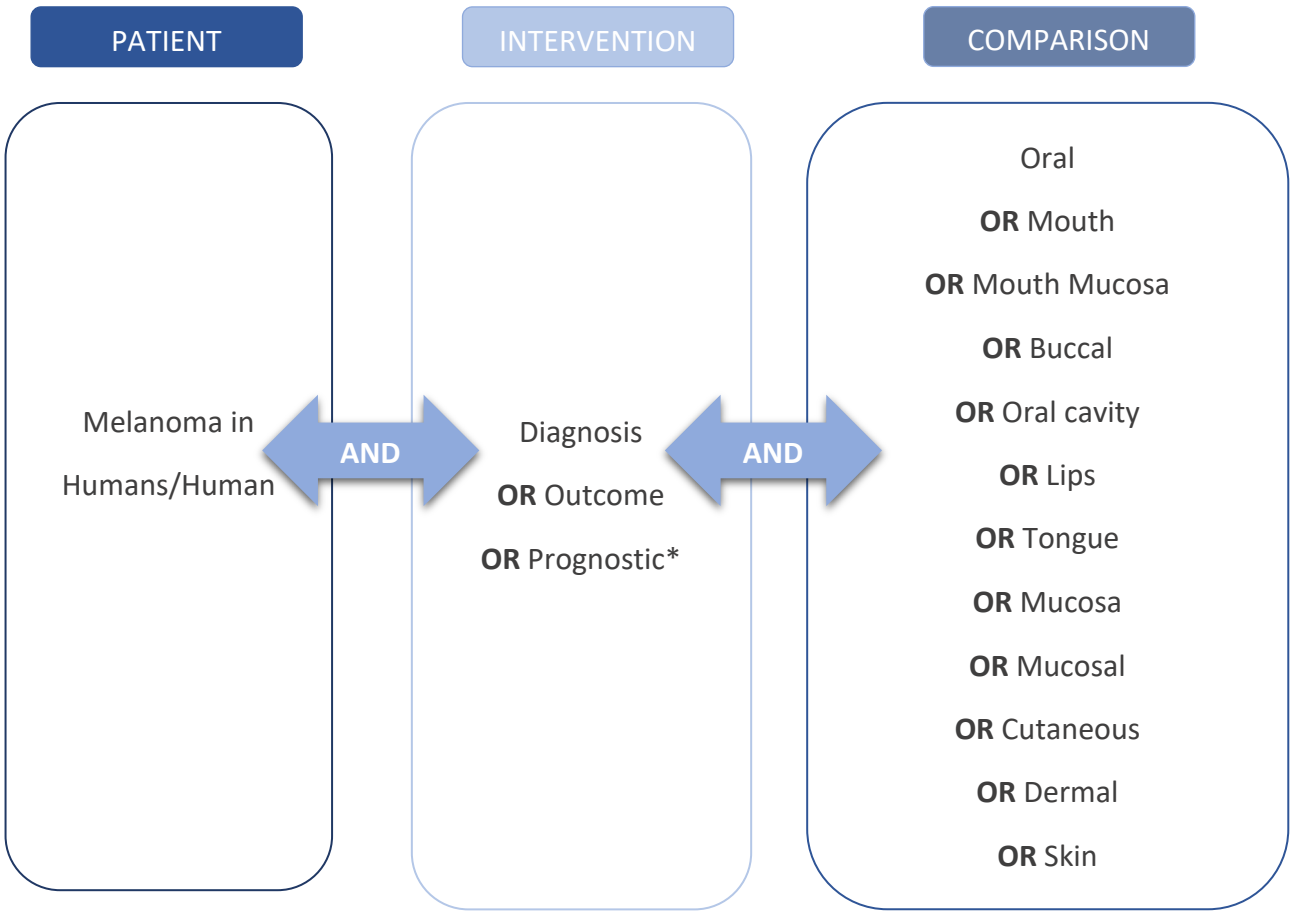

Diagram 1. *The search terms grouped by the concept of the PICO question and interrelated with the Boolean operators, which were used in the search strategy.*

The titles of the articles resulting from the electronic search were screened for relevance and afterwards the articles fulfilling with the topic of the literature review were selected. Additionally, the abstracts of the selected articles were screened for relevance. All articles not meeting the stated exclusion criteria or not containing relevant information were excluded. For the electronic search in the cited databases, a type of restriction has been applied regarding the date of publication, which was in the last 10 years. The language has been a criterion for the exclusion of articles, if they were not in English, Spanish, or German.

Table 2: *Consulted Databases.*

Database	Search	Filters	Date	Number of Articles
Medline	Cutaneous Melanoma: ("MELANOMA"[Title]) AND ("Cutaneous"[Title] OR "Dermal"[Title] OR "Skin"[Title]) AND ("Outcome"[Title] OR "Prognosis"[Title] OR "Prognostic*"[Title])	Results by year: 2011-2021 Article Type: All * Publication date: Last 10 years Species: Humans Language: English, Spanish, German	21.12.2021 - 15.03.2022	374
Medline	Oral Melanoma: ("Melanoma"[Title]) AND ("Mouth"[Title] OR "Oral"[Title] OR "Mouth Mucosa"[Title] OR "Buccal"[Title] OR "oral cavity"[Title] OR "Lips"[Title] OR "Tongue"[Title] OR "Mucosa"[Title] OR "Mucosal"[Title]) AND ("Outcome"[Title] OR "Prognosis"[Title] OR "Prognostic*"[Title])	Results by year: 2011-2021 Article Type: All * Publication date: Last 10 years Species: Humans Language: English, Spanish, German	21.12.2021 - 15.03.2022	63
Scopus	Cutaneous Melanoma: (TITLE (melanoma) AND TITLE ("Cutaneous" OR "Dermal" OR "Skin") AND TITLE ("Outcome" OR	Year: 2011-2021 Document Type: Article Language: English, Spanish, German	21.12.2021 - 15.03.2022	361

	"Prognosis" OR "Prognostic*"))			
Scopus	Oral Melanoma: (TITLE (melanoma) AND TITLE ("Mouth" OR "Oral" OR "Mouth Mucosa" OR "Buccal" OR "oral cavity" OR "Lips" OR "Tongue" OR "Mucosa" OR "Mucosal") AND TITLE ("Outcome" OR "Prognosis" OR "Prognostic*"))	Year: 2011-2021 Document Type: Article Language: English, Spanish, German	21.12.2021 - 15.03.2022	91

***** During the Medline research there was no specific article type selected (Article type: All), because all articles shown were screened subsequently for meeting the criteria as a cohort study, case-control study, or randomized controlled trial.

The search in the previous databases has been complemented with a manual literature search, as the bibliographical references cited in the selected articles have been manually reviewed, with the aim of identifying studies not detected by the primary search. The search has been updated in March 2022, in order to detect the most recent studies published about the field of interest of the review, to correspondingly be able to include them.

3.3. Study selection

Duplicate records were removed, then study titles were independently reviewed by two objective reviewers (LSS, ARA) for the inclusion of the studies as per the eligibility criteria. The literature was first screened for the title, afterwards for the abstract. Subsequently, studies that satisfied the eligibility criteria were included through full-text assessment.

3.4. Data extraction

After a detailed reading of the studies included in the review, a series of variables present in all of them have been selected that provide information and assist in better understanding the prognosis of melanoma in OM or CM. The variables evaluated in each of the studies are: first author´s surname, year of publication, country of origin, type of study, sample size, demographic variables of the patients (sex and age), cancer stage, anatomic site, tumor thickness, metastasis, overall survival, and the follow-up period. The data extraction process was carried out by a single researcher (LSS), who has worked independently, any doubt regarding the data extraction process has been resolved through the intervention of a second investigator (ARA) and reaching an agreement between both.

3.5. Quality assessment

Risk of bias for included studies was assessed using the Newcastle- Ottawa Scale (NOW) for assessing the quality of cohort studies (16). A quality rating of high risk, low risk and unclear risk of bias was assigned independently by one reviewer (LSS) based on a set of criteria, and discrepancies were discussed with a second reviewer (ARA) until full consensus was reached.

4. RESULTS

4.1. Study Identification.

A search of the two databases identified 889 studies that fit the search terms. After removal of duplicates, 543 articles remained to be potential studies. Of these, 407 were screened by title and subsequently excluded because they did not meet the inclusion criteria. After screening the abstracts, 98 articles were excluded. Once fully reading the 38 articles, 30 articles were eliminated due to several exclusion criterias, which can be seen in ***Anexo 1***. It was determined that 8 studies met all the inclusion criteria, and these were incorporated in this systematic review. ***Diagram 2*** shows a flow diagram of the literature research.

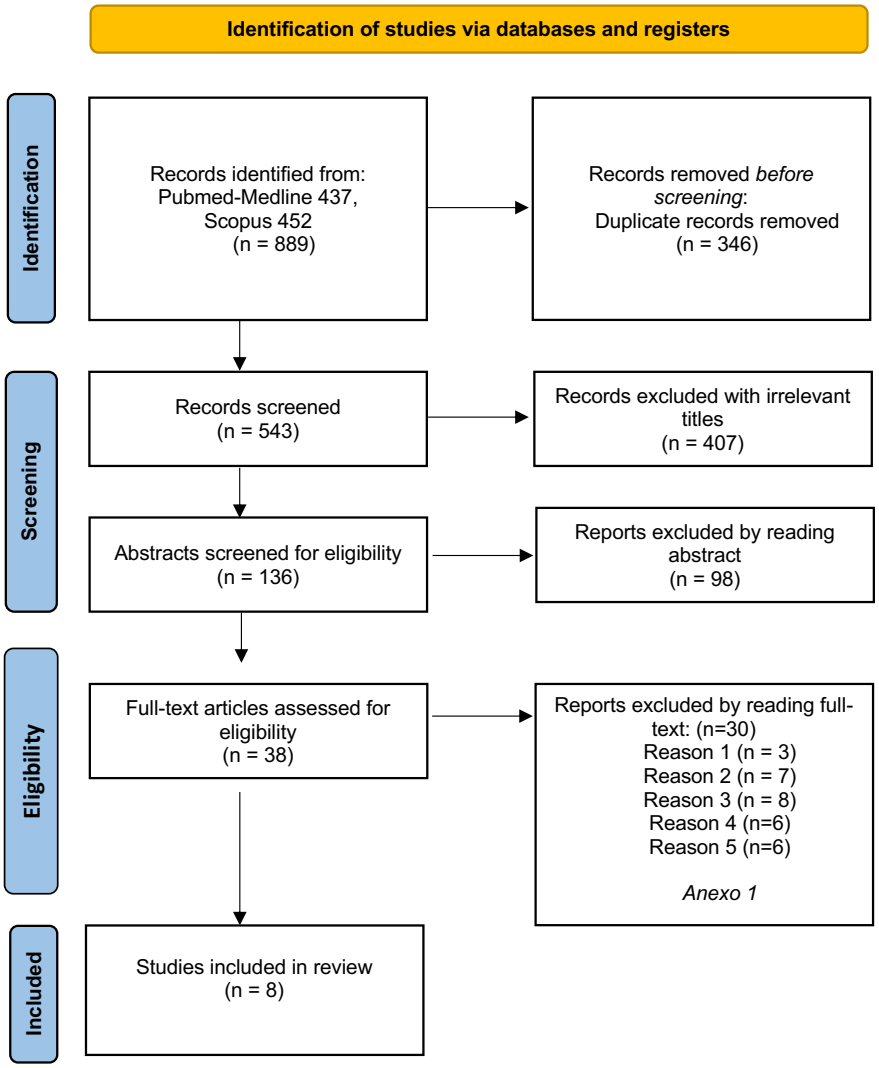

Diagram 2. *PRISMA Flow Diagram.*

Reason	Motive of exclusion
1	Review, not a cohort study.
2	Not relevant to the research question and outcomes.
3	Insufficient results about oral melanoma, focussing more on general mucosal melanomas.
4	Do not evaluate the survival rate.
5	Patient population.

Anexo 1. *Reasons why the reports were excluded by reading full text.*

4.2. Study characteristics.

Table 3. *Characteristics of included studies.*

Study	Study design	Type of melanoma	Sample size	Male	Female	Median Age (In years)	Years of patient inclusion
Buja et al. *(19)* Italy 2021	Cohort, Retrospective	Cutaneous	1279	678	601	58	5
Perez-Aldrete et al. *(21)* Mexico 2019	Cohort, Retrospective	Cutaneous	323	152	171	59	10
Lee et al. *(22)* USA 2017	Cohort, Retrospective	Oral	232	111	121	-	39
Song et al. *(18)* China 2015	Cohort, Retrospective	Oral	82	45	37	55,2	10
Maurichi et al. *(20)* Italy 2014	Cohort, Retrospective	Cutaneous	2243	1023	1220	43	8
Tas et al. *(23)* Turkey 2013	Cohort, Retrospective	Oral, Cutaneous	OM: 21 CM: 94	OM: 11 CM: 51	OM: 10 CM: 43	63	OM: 11 CM: 12
Sun et al. *(17)* China 2012	Cohort, Retrospective	Oral	51	36	15	55	29
Berzina et al. *(24)* Latvia 2011	Cohort, Retrospective	Mucosal, Cutaneous	124	43	81	67,36	9

The remaining eight studies included were retrospective cohort studies. In total information was available from 4453 patients and the average age between them was 56,57 years. Two studies were conducted in China (17,18), and two in Italy (19,20). One study was performed in Mexico (21), one in the USA (22), one in Turkey (23), and one in Latvia (24). All included studies examined the prognosis of melanoma. However, three

studies focused on cutaneous melanoma (19–21), while three focused on oral melanoma (17,18,22), and two included both (23,24). The characteristics of the eight studies are presented in ***Table 3***. Additionally, the objectives and conclusions of each study are stated in ***Table 4***.

Table 4. *Objectives and Conclusions of the included studies.*

Study	Objective of the study	Conclusion of the study
Buja et al. *(19)* Italy 2021	To investigate the five-year melanoma-specific survival, taking demographic and clinical-pathological variables into consideration.	Older age, tumor site, histotype, mitotic count, and tumor stage were independently associated with a higher risk of death.
Perez-Aldrete et al*. (21)* Mexico 2019	To investigate the clinicopathological characteristics for CM and the relationship these characteristics had to prognosis.	The results transmit the characteristics and prognosis of patients with the diagnosis of cutaneous melanoma.
Lee et al. *(22)* USA 2017	To determine the epidemiologic, outcome, and prognostic factors in patients with OM.	Age at diagnosis, decade of diagnosis, extent of disease, tumor size, and socioeconomic status are prognostic factors related to OMM survival. Surgical resection and radiation therapy both improve OMM survival.
Song et al. *(18)* China 2015	To investigate the histopathologic predictors of overall survival and metastatic failure of OMM.	The cell type was an independent prognostic factor of overall survival. Patients with epithelioid cell type OMM had a poor prognosis. Patients without tumor infiltrating lymphocyte had a higher risk of distant metastasis.
Maurichi et al. *(20)* Italy 2014	To investigate new prognostic factors and construct a nomogram for predicting survival in individual patients.	The findings suggest including lymph vascular invasion and regression as new prognostic factors in the melanoma staging system. The nomogram appears useful for risk stratification in clinical management and for recruiting patients to clinical trials.
Tas et al. *(23)* Turkey 2013	To define clinical characteristics and outcomes of patients and emphasize MM differences from CM.	MM did not share same clinicopathologic characteristics with CM. However, the survival rates seem identical. There are not widely accepted prognostic and predictive factors.
Sun et al. *(17)* China 2012	To evaluate the treatment and prognosis of OMM and provide basic data for clinical treatment.	Patients older than 55 years and large tumor of size had a worse prognosis. Combined treatment with surgery and biotherapy can significantly improve the prognosis.
Berzina et al. *(24)* Latvia 2011	To describe the prognostic factors and epidemiological characteristics of cutaneous and mucosal melanoma and to identify the variables associated with mortality from this disease.	Female sex, advanced age, facial skin, tumor thickness, nodular subtype and ulceration carried a relevant risk of poor prognosis.

4.3. Quality assessment and risk of bias of the selected studies.

Table 5. *Newcastle-Ottawa scale for cohort studies.*

Quality Assessment criteria									
	SELECTION				COMPARABILITY		OUTCOME		
Author	Represent-ativeness of exposed cohort?	Selection of the non-exposed cohort?	Ascertainment of exposure?	Outcome of interest was not present at start of study?	Study control for age/gender and additional factor?	Assessment of outcome?	Was follow-up long enough for outcome to occur?	Adequacy of follow-up of cohort?	Overall Quality Score (max=9)
Buja et al. *(19)*	*	*	*	*	**	*	*	*	9
Perez-Aldrete et al. *(21)*	*	-	*	*	**	*	*	*	8
Lee et al. *(22)*	*	*	*	*	*	*	-	*	7
Song et al. *(18)*	*	-	*	*	*	*	*	*	7
Maurichi et al. *(20)*	*	*	*	*	*	*	*	*	8
Tas et al. *(23)*	*	*	*	*	*	*	*	*	8
Sun et al. *(17)*	-	-	*	-	*	-	*	*	4
Berzina et al. *(24)*	*	*	*	*	*	*	-	-	6

The Newcastle-Ottawa Scale quality instrument is scored by awarding a point for each answer that is marked with a star. Possible total points are 4 points for Selection, 2 points for Comparability, and 3 points for Outcomes. The mean value for the 9 studies assessed was 7.12. Low risk of bias is defined by 3 or 4 stars in selection domain, 1 or 2 stars in comparability domain and 2 or 3 stars in outcome domain. Intermediate risk of bias is defined by 2 stars in selection domain, 1 or 2 stars in comparability domain and 2 or 3 stars in outcome domain. High risk of bias is described as 0 or 1 star in selection domain or 0 stars in comparability domain or 0 or 1 stars in outcome domain (16). The ***Table 5*** presents the scores of the included studies. Seven out of eight studies showed a low risk for the overall judgement, while two showed an unclear risk. Supplementary Diagrams show the QUADAS-2 Proportion of studies in % and a summary about each domain for each included study (See *Diagram 3 and 4*).

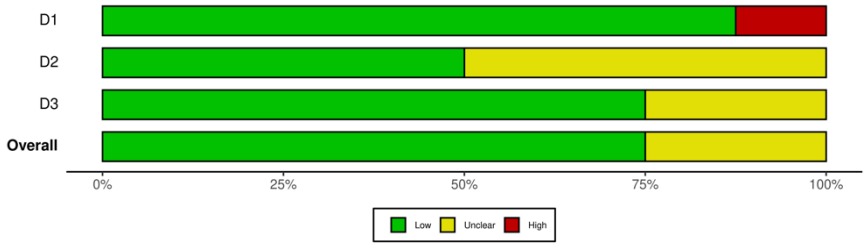

Diagram 3. *Risk of bias: Weighted bar plots of the distribution of risk of bias judgements within each bias domain.*

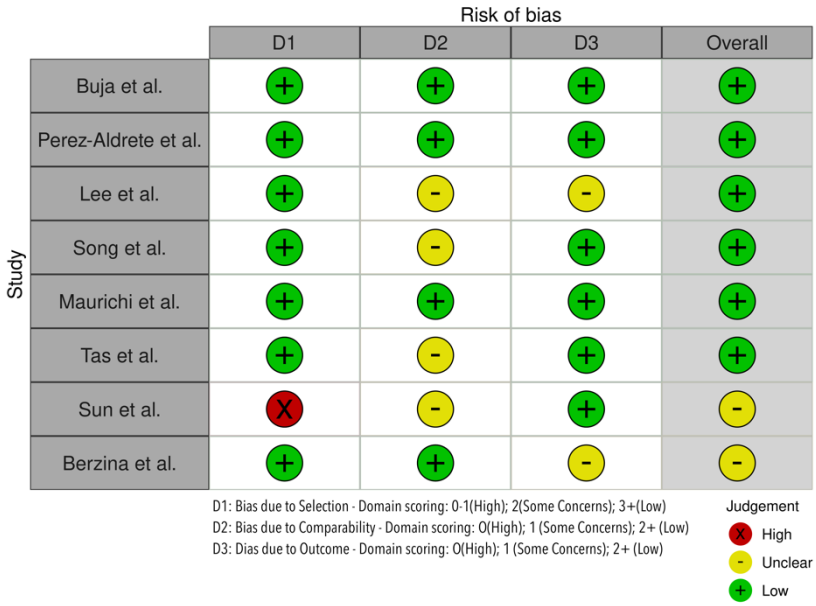

Diagram 4. *Risk of bias: Traffic light-plots of the domain-level judgements for each individual study.*

4.4. Outcomes.

Due to its rarity, OM remains to be poorly understood. Indeed, the histology of OM differs from that of CM, and the prognosis of OM is worse, requiring more aggressive therapy and investigation into its prognostic factors (18).

4.4.1. Prognostic factors of oral melanoma.

After reviewing the current literature, summary of the variables which have a prognostic significance were summarized in ***Table 6*** (17,18,22–24). The method most commonly used by the studies was univariate and multivariate Cox proportional hazards models to determine the influences of the pathologic parameters. Among the five studies reporting prognostic factors of OM the following factors were assessed by multiple studies and were found to have a prognostic influence: age at diagnosis, time of diagnosis, tumor size, extent of disease, level of invasion, pigmentation, and ulceration. Factors commonly studied that did not have significant prognostic influence were sex and the decade of diagnosis.

Table 6. *Prognostic factors of OM associated with good or poor survival.*

Prognostic factors	**Measure Good survival**	**Measure Poor survival**	**Studies measuring factor (Study reference)**
Age	< 50	>70	Lee et al. (22)
	<55	>55	Sun et al. (17)
Sex	F/M	F/M	Lee et al., Tas et al. (22,23)
	M	F	Sun et al. (17)
Time of diagnosis	Early	Late	Sun et al., Song et al., Lee et al., Tas et al., Berzina et al. (17,18,22–24)
Decade of diagnosis	2000	1970	Lee et al. (22)
Extension	Confined	Metastatic	Lee et al. (22)

Tumor size	<2cm	>4cm	Lee et al., Berzina et al. (22,24)
Surgery	Surgery performed	No Surgery	Lee et al. (22)
SES	Higher	Lower	Lee et al. (22)
Preoperative biopsy	Yes	No	Sun et al. (17)
Cell type:	Non-epithelioid	Epithelioid Nodular	Song et al. (18) Berzina et al.(24)
cTNM Stage	III	IV, V	Sun et al., Berzina et al.(17,24)
	II or III		Tas et al. (23)
Level of invasion	Non-deep	Deep	Song et al., Berzina et al. (18,24)
Pigmentation	Strong	Weak or absent	Sun et al., Song et al. (17,18)
TIL	Absence	Presence	Song et al. (18)
Ulceration	Absent	Present	Song et al., Berzina et al. (18,24)
Mitotic rate	<1 per HPF	>1 per HPF	Song et al. (18)
Necrosis	Absent	Present	Song et al. (18)

(F = Female, M= Male, SES = Socioeconomic status, TIL = Tumor infiltrating lymphocyte, HPF= High power field)

Socioeconomic status (SES) is a parameter that takes into account median family income, unemployment rate, percentage of adults 25 years or older who had less than 12 years of education, and percentage of people below the federal poverty threshold (22). One of five studies measured this parameter, and this criterion is defined in Table 4. The study found that patients having a higher SES had a significantly better survival prognosis.

The cell type (CT) was found to be associated to survival in patients with OM. CTs were divided into two categories: non-epithelioid cell type (less than 50% epithelioid cells) and epithelioid cell type (more than 50% epithelioid cells). OMM cells displayed a wide range of shapes. Spindle cells and epithelioid cells made up the majority of them. Polyhedral cells with abundant cytoplasm and wide round-to-oval nuclei with pronounced nucleoli were known as epithelioid cells. In the tumor architecture, they can occasionally spread far apart. Patients with epithelioid cell types were also more likely to develop distant metastases (18).

One study analysed the effect of pigmentation on survival. Pigmentation was categorized as absent (no pigmentation), weak (present in less than half of the melanoma cells with noticeable cytological characteristics), and strong (present in more than half of the melanoma cells with noticeable cytological details). When compared to non-pigmented (absent and weak) melanoma, strong pigmentation was linked to a better prognosis (18).

The Tumor infiltrating lymphocyte (TIL) was assessed by the study of *Song et al.* The presence of TIL in patients has been well established as a positive prognostic marker, implying efficient host resistance to the tumor. TIL deficiency was discovered to be a reliable predictor of distant metastases. Patients with TIL were shown to have a decreased probability of distant metastatic failure. (18)

In OMM, the mitotic rate (MR) was found to be a predictive factor of metastasis. The higher the mitotic count, the more probable the tumor has metastasized and the more likely a sentinel lymph node biopsy would be positive. The mitotic rate is calculated by measuring the number of cells that undergo mitosis, also known as dividing cells (18,25). To define MR, high power field (HPF) were used. HPF is a technique that is frequently used in the reporting of certain pathology diagnosis (26). Mitoses were counted in 10 ×400 high power fields (18). High survival was defined as less than 1 HPF, whereas poor survival was defined as more than 1 HPF.

4.4.2. The survival of oral melanoma compared with cutaneous melanoma.

Survival varies significantly between different melanoma types, especially between oral and cutaneous ones. Four studies evaluated the survival rates of oral melanoma using the Kaplan-Meier curve method. Three studies found that patients in the 5-year overall survival (OS) had a considerably poor survival prognosis with percentages ranging between 20-34%, and the study *Tas et al*. had a higher survival percentage with 53%. (See *Table 7* for survival rates) In general, the median overall survival for OM was 2,5 years (17,18,22,23).

Table 7. *Survival rates of oral melanoma.*

Study	**Method**	**Sample Size**	**1-year OS**	**2-year OS**	**3-year OS**	**5-year OS**	**OS**
Lee et al. (22)	Kaplan-Meier curve	232	-	-	-	25%	-
Song et al. (18)	Kaplan-Meier curve	82	-	63,4%	49,4%	33,8%	-
Tas et al. (23)	Kaplan-Meier curve	21	79%	-	-	53%	-
Sun et al. (17)	Kaplan-Meier curve	51	-	-	35%	20,7%	-

(OS = Overall Survival)

Four studies evaluated the survival rates of CM using the Kaplan-Meier curve method. Three studies found that patients in the 5-year OS and the OS had a significantly high survival prognosis with percentages ranging between 77-85%, and the study *Tas et al*. had a noticeable lower survival percentage with 43%. (See *Table 8* for survival rates)

Table 8. *Survival rates of cutaneous melanoma.*

Study	**Method**	**Sample Size**	**1-year OS**	**2-year OS**	**3-year OS**	**5-year OS**	**OS**
Buja et al. (19)	Kaplan-Meier curve	1279	-	-	-	83,8%	-
Perez-Aldrete et al. (21)	Kaplan-Meier curve	323	-	-	-	-	77%
Maurichi et al. (20)	Kaplan-Meier curve	2243	-	-	-	-	85,3%
Tas et al. (23)	Kaplan-Meier curve	94	86%	-	-	43%	-

(OS = Overall Survival)

There was a significant difference between the survival rates of OM and CM. All OMs appear to have a much worse overall prognosis and outcome with survival percentages ranging between 20-34% compared to the cutaneous percentages of 77-85%.

5. DISCUSSION

OM is a very rare malignancy. It's a highly aggressive cancer that can spread and infiltrate neighbouring tissues. OMM commonly manifests asymptomatically within the early stages, which may contribute to its late identification, poor prognosis, and low survival rates (22). It is important to consider prognostic factors related to survival outcomes. Based on the qualitative analysis of the included studies, it has been possible to reach a consensus that prognostic factors identified in this review can be categorized into age at diagnosis, time of diagnosis, tumor size, extent of disease, level of invasion, pigmentation, and ulceration.

The most significant factor influencing survival is early diagnosis. Early diagnosis is crucial because a prompt discovery can greatly improve the chances of survival. Therefore, Lee et al. states that clinicians must integrate early OMM screenings into their patient examinations, to contribute to an earlier detection (22). Similarly, Tas et al. mentions that OMs appear to be detected in a later stage, behave more aggressively, and have a considerably poorer prognosis and outcome (23). Song et al. comments that given the rarity of OMM, an early diagnosis, particularly for lesions with poor pigmentation, seems to be challenging and therefore the poor prognosis of OM may be due to a delayed diagnosis (18). These results are supported by another study from Santana et al., declaring that any suspected pigmented lesion should be histopathologically evaluated, since early detection and surgical excision are critical for a favorable prognosis (27). Another study by Aloua et al. agrees with the importance of early diagnosis, because according to them, most melanomas are painless in their early stages, the detection is generally delayed until signs such as ulceration, growth, or bleeding appear before diagnosing them. Educating patients on frequent oral self-examination and assisting them in identifying early suspicious lesions are two preventive approaches for oral malignant melanoma (28).

The age at which a person is diagnosed has also been found to be a prognostic factor. In this study, being under 55 years old was found to be a positive predictor for prognosis, however being beyond 70 years old had a negative impact (22). Although Sun et al. pronounces patients over the age of 55 had a greater risk of dying than those under the age of 55 (17). Indeed, another study from Zhu et al. revealed that patients under the

age of 70 survive longer than those over 70, with a statistically significant difference (29). Bishop et al., Shuman et al., Sarac et al. and Kerr et al. also indicated that advanced age, had a considerable impact on survival (30–33).

Tumor factors such as size have a consistently prognostic influence on survival. Tumors greater than 4 cm had a 1.6-year survival rate, whereas tumors less than 2 cm had a 3.3-year survival rate (Lee et al.)(22). This pattern is consistent with what has been discovered in the literature. Patients with tumors smaller than 2 cm had a considerably longer survival time than those with tumors greater than 2 cm, according to Zhu et al. (29). These results can be confirmed with the results of a study of Gru et al., mentioning that tumors with a maximum size of more than 3 cm had an average survival of 12.75 months, whereas those with a maximum dimension of less than 3 cm had an average survival of 38.3 months (34). Additionally other studies correspondingly found that the size of the tumor is a significant predictive factor (Frakes et al., Sarac et al.) (32,35).

The extent of disease has been found to be a significative prognostic factor. In terms of prognosis, the extent of the disease at the time the patient seeks treatment may be the most important determinant of survival. Extent of disease was determined to be an independent predictive risk factor for OS in our research. The degree of disease extent was linked to a lower chance of survival, with a prognosis that was worsened by a distant extent, showing that the OS reaches about 0.8 years (Lee et al.) (22). This conclusion is consistent with Singh et al. which found that three patients with OMM who sought treatment at an advanced stage all died within one year of diagnosis (36). Kumar et al. discovered that the disease's severity is linked to its prognosis in another study (37).

Another significant prognostic factor has been discovered: Level of invasion. Song et al. classified levels of invasion as follows: micro invasion (in situ or invasive individual or clusters of 10 abnormal melanocytes near the epithelial-subepithelial junction); moderate invasion (invasion restricted to the lamina propria); deep invasion (invasion beyond the lamina propria) (deep tissue invasion into submucosa, bone, skeletal muscle). They discovered a link between invasion levels and patient outcomes in patients with primary MM of the head and neck. In patients with localized OMM, the amount of invasion was also shown to be a predictive factor, according to the results of

their study (18). Other studies also significantly associated decreased survival with deep invasion levels (Keller et al., Breik et al.) (38,39).

Strong pigmentation was shown to be a positive prognosis factor by Song et al. Their research found no significant difference in OS between individuals with pigmented (weak or strong) melanoma and those with amelanotic melanoma, however strong pigmentation was linked to a better prognosis when compared to non-strong pigmented (absence and weak) melanoma (18). Whereas, another study by Kerr et al. discovered that the presence or lack of melanin pigmentation had no effect on the outcome (33). Contrary, Aloua et al. confirms the hypothesis that pigmentation is a prognostic factor, saying that the majority of primary OMs present as new lesions on apparently normal mucosa, although around 30% to 50% of them are preceded by oral pigmentations that can last months or even years. Mucosal melanosis and a variety of melanocytic nevi are examples of pre-melanoma lesions. In 30 to 73 percent of individuals, oral melanosis has been identified as a predisposing factor for the development of OM (28). Given the rarity of OMM, an early diagnosis, particularly for lesions with little pigmentation, looks to be problematic. The poor prognosis of OMM may be due to a delayed diagnosis (18). Certainly, Breik et al. is confirming that poor pigmentation has a poor prognosis. In the oral cavity, amelanotic MMs have also been documented. Because they generally occur at an advanced stage and attaining adequate margins during resection is challenging, they have been reported to have a relatively low survival rate (39).

The presence of ulcers has been revealed to be a significant prognostic factor. According to Berzina et al., ulceration is independently linked with greater rates of distant metastasis and lower overall survival in melanoma (24). Kerr et al. claims that ulceration is separately associated with higher rates of distant metastasis and poorer overall survival in melanoma (33). Shuman et al. share this viewpoint, indicating that the lack of ulceration predicts better outcomes, and that the presence of ulceration has a higher than 3-fold influence on OS (31). According to Keller et al., the presence of sentinel nodes was linked to thicker and ulcerated tumors and was a significant predictor of disease-free survival (38). Finally, MMs that show as ulcerated lesions, according to Breik et al., may have a poorer prognosis (39). Comoglu et al., on the other hand, characterize ulceration as not being linked with OS (40). Indeed, the appearance of ulceration in

microscopic sections of CMs is a significant detrimental factor of survival, according to Cui et al. The presence of ulceration, on the other hand, had a substantial prognostic effect on melanoma patients in their large cohort of MMs. In their patient series, 60–70% of the tumors displayed pathological ulcers of the original MMs, which may have hampered the capacity of tumor ulceration to distinguish survival differences. For CMs, ulceration of original melanomas may have prognostic importance, however we were unable to detect this as an independent prognostic marker for MM (41).

In contrast, comparing the prognostic factors with CM, Cherobin et al. declares that their univariate analysis detected four significant prognostic factors: male gender, nodular clinical and histologic subtype, Breslow thickness > 4mm, and histologic ulceration (42). In this study, Berzina et al. proclaims that both share the fact that if the tumor is thin at the time of diagnosis, the prognosis for melanoma is good. 5-year survival for CM in this situation is 95-97 percent. When melanoma is detected at a late stage (tumor Breslow thickness >4mm), the chance of metastasis increases dramatically. As a result, early melanoma detection is critical since it improves the disease's prognosis (24). The most powerful prognostic value is tumor Breslow thickness, although rising Clark invasion level is also linked to more frequent mortality, according to Berzina et al. Indeed, they discovered that ulcerated tumors, thick melanomas (Breslow thickness 4 mm), and Clark level of invasion V all had a significantly poorer prognosis. Tas et al. implies that the implications of prognostic variables on survival are still debated in the literature. In the majority of the current research, prognostic variables linked with a poor prognosis include advanced stage, male sex, and older age. Others, on the other hand, discovered that the patients' age, gender, primary tumor location, and presence of regional nodal disease had no effect on survival rates. The existence of distant metastases, on the other hand, was found to have an impact on overall prognosis. Patients with metastatic disease had a much worse chance of survival. While they discovered that patient age and gender had no influence on survival in this investigation, severe illness (stages II and III) at presentation was a significant predictive factor for patient prognosis. Only individuals with oral cavity localization, were found to have this result (23). Wisco et al. share this viewpoint, as tumor thickness is the most

important prognostic parameter, the mitotic rate and ulceration are used to further subcategorize the Breslow thickness and improve prognosis accuracy. Tumor thickness is the most significant prognostic indication for localized CM, and as thickness rises, 5- and 10-year survival rates decrease significantly. Patients with 0.01 to 0.5 mm thick localized CMs have a 10-year survival rate of 96 percent, whereas those with localized melanomas more than 6.00 mm thick had a 10-year survival rate of 42 percent (43).

Focusing on the discrepancies in survival rates between OM and CM. To begin with OM, the studies from Lee et al., Song et al. and Sun et al. had a significantly poor survival prognosis, with percentages ranging from 20 to 34 percent whereas Tas et al. research had a better survival percentage of 53 percent (17,18,22,23). Most of the other studies evaluated survival by the Kaplan-Meier method and plotted in a Kaplan- Meier curve representing overall survival. MMs from the head and neck are thought to be particularly aggressive and rapidly fatal, and long-term survival is dismal, with only around half of patients living three years after diagnosis. In the literature, a broad range of survival rates have been documented. The overall 3-year and 5-year survival rates in a Chinese study of exclusively OMs were 35 and 20.7 percent, respectively (17). The total 5-year survival rate of 31.7 percent of the study from Breik et al. was comparable to previous studies. Aggressive local disease and hematogenous dissemination have been blamed for the low survival rate (39). Despite the fact that none of the patients in Breik et al. sample exhibited indications of distant metastases at the time of presentation, six of the nine have died as a result of distant metastases. The lung was the most prevalent location of metastasis. In individuals with MM of the head and neck, locoregional failure is a significant prognostic factor. Patients who had locoregional recurrence after first treatment failure had a higher chance of distant recurrence than those who did not have locoregional recurrence. Similarly, individuals who had regional failure had a considerably worse 4-year overall survival rate in a multicenter trial in Japan (44). All of these findings emphasize the need of rigorous locoregional management in improving survival. The findings in the literature are highly comparable to our findings. The prognosis for MM is extremely poor, according to Zhang et al., with a median survival period of 10–13 months and a 5-year overall survival rate of fewer than 5% (14). While

Shuman et al. observed comparable outcomes to ours, with overall survival rates of 64 percent and 38 percent after two and five years, respectively (31). The 52-month median overall survival and 38% 5-year overall survival are comparable with larger studies published in the literature. According to Keller et al., the head and neck MM subtype has a poor prognosis. The overall 5-year survival rate for all subtypes of MM has been reported to be 25%. They showed for a median 64.5 month follow-up, the median OS were 24.4 months for all patients, and 34.6 months for curatively resected MM patients, which is in accordance with previous studies. They found that during a median follow-up of 64.5 months, the median OS was 24.4 months for all patients and 34.6 months for patients with curatively resected MM, which is consistent with prior research (38).

Overall survival rates for MM patients were low, ranging from 20% to 40%, according to Frakes et al. (35). Indeed, Beaudaux et al. agrees that, in comparison to CM, the prognosis for MM is exceedingly dismal, with a five-year disease-specific survival rate of around 25%. The five-year disease-specific survival rate was 31.8 percent, with a median disease-specific survival duration of 23.9 months. Their findings support PMM's dismal overall prognosis, with a median specific survival rate of 23.9 months and a five-year disease-specific survival rate of 31.8 percent, which is close to the relative survival rate of 34 percent seen in Bishop et al. American's population-based analysis (30,45). Furthermore, Breik et al. declared that MM is a dangerous cancer with a dismal prognosis, with less than half of patients surviving three years after diagnosis. According to reports, the total 5-year survival rate is as low as 24% (39).

When OM patients are compared to CM patients, patients with CM had in the 5-year OS and overall survival a very good survival prognosis with percentages ranging from 77-85 percent in three trials from Buja et al., Perez et al. and Maurichi et al., but Tas et al. had a significantly lower survival percentage with 43 percent. Another study from Bishop et al. found that OM had a considerably worse five-year relative survival rate (34 percent on average, ranging from 3 to 69 percent) than CM (89 percent). The data show poor survival in early-stage extracutaneous melanomas despite high rates of radical resections and radiation, as well as no increase in total extracutaneous melanoma survival rates from 1990 to 2010(30). According to Mehra et al., "our data

indicate the poorer survival rates of MM in agreement with the literature." Indeed, individuals with CM have a 5-year and 10-year survival rate of about 80% and 70%–80%, respectively (46). Patients with CM, as per Beaudaux et al., have a much higher survival rate than those with other mucosal locations (45). Crocetti et al. shares this viewpoint, stating that in Europe, the five-year survival rate for individuals with CM at any stage at diagnosis was recently evaluated at 83 percent (47).

In Contrast to CM, according to Comoglu et al., MMs of the head and neck have worse survival rates than CM of the head and neck; the 5-year OS range for localized CM is 79 percent–97 percent, whereas this range drops to 16 percent–47 percent for MM. In most series, the OS for MM is less than 30%, with an average of around 24%. They discovered 65 percent for 1-year, 35 percent for 2-year, 29 percent for 3-year, and 17 percent for 5-year OS, and the mean overall-survival time was 41 months, which was consistent with previously reported institutional series (40). Beaudaux et al. supposes that the improved prognosis for CM is largely explained by the frequent earlier identification of CM in comparison to internal and less visible locations. Interestingly, among patients without symptoms, 50% of CM was detected only on a simple visual examination, and the median tumor size for CM (3 mm) was substantially less than for other locations (23 mm) (45). Sarac et al. further add that, unlike CM, MMs epidemiological data and prognostic variables have not been adequately established. Because the cutaneous tumor is frequently visible or accessible, most MM cases are detected at an advanced stage. Regardless of stage, it is known that MMs have a poorer prognosis than CM (32).

Certain limitations should be recognized when interpreting the findings of this systematic study. Despite the fact that individuals with OM are uncommon and the incidence is low, the inclusion criteria intended to focus on a clearly defined sample of patients in the studies included in the qualitative analysis. Moreover, in order to avoid publication bias, the recommended search method for finding relevant literature was entered into two databases. In addition, the study only discovered publications in English, German, and Spanish.

The level of evidence of the research studied, which determines the link between the different prognostic factors and survival rates, is based on the quality of the studies

included in the present qualitative analysis. The moderate (7.2) level of evidence for this research was determined from the quality of the included research, which was rated between moderate or low in the majority of the assessed studies, based on the Newcastle-Ottawa Scale. Another aspect of studies that should be regarded as a constraint in some situations is the loss of patients throughout the trial. Patient follow-up during therapy implies losses for a variety of causes. Even yet, small patient losses are to be expected in studies with such extended follow-up durations. Another limitation is the fact that some of the comparative studies in the discussion on overall survival were not specific to the oral cavity. Therefore, despite a large proportion of oral population was included in most studies, some just involved MM and the information was only regarding to general head and neck MMs, not specifying the oral cavity. Subsequently, the information just for OM could not be extracted as they were not divided based on their anatomical location.

In light of the limitations of the research included in the analysis, the systematic review's strengths must also be considered. Despite the inclusion criteria in the included studies having limitations, it should be noted that the instrument or tool used to record the overall survival of the patients throughout the follow-up period in the various studies analyzed was the Kaplan-Meier graph and log-rank tests. The fact that the same index was used in all of them, could be considered a strength. Considering this, it should be emphasized that the application of the inclusion criteria has allowed the sample of included studies to be limited to those that employ registered and validated methodologies for overall survival evaluation. While there was sometimes a lack of information in the survival rate, some just stated the overall survival rate, while others concentrated on the 2-year and 5-year survival rates. We suggest guidelines for reporting a survival percentage each year based on the difficulties in extracting data.

All of this indicates to the importance for further research that examines the influence of prognostic factors, based on studies of high methodological quality. Studies that focus on a broader population, and that regulate follow-up of patients to the greatest extent possible. And by using the same index in all the investigations, which has been recorded and validated, biases may be avoided.

6. CONCLUSION

- Oral melanoma is an uncommon and aggressive tumor with a poor prognosis, compared to cutaneous melanoma.
- The prognostic factors for oral melanoma that were most consistently reported were age at diagnosis, time of diagnosis, tumor size, extent of disease, level of invasion, pigmentation, and ulceration. Where patients with a higher age, late diagnosis, metastasis, deep levels of invasion, weak or absent pigmentation and ulceration presented the worst prognosis.
- The findings of this review demonstrate that individuals with cutaneous melanoma had a better long-term survival rate than those with oral melanoma. While the survival rate for cutaneous melanoma is significantly higher, with percentages ranging between 77-85%, the survival rate for oral melanoma is between 20-34%.
- As some prognostic factors are poorly studied in the literature, more research is needed to determine their significance in the prognosis of oral melanoma.

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8. ANNEXES

Table 9. *PRISMA 2020 for Abstract Checklist (15).*

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	YES
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	YES
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	YES
Interpretation	10	Provide a general interpretation of the results and important implications.	YES
OTHER			
Funding	11	Specify the primary source of funding for the review.	NO
Registration	12	Provide the register name and registration number.	NO

Table 10. *PRISMA 2020 for Systematic Review Checklist (15).*

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	48
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	17
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	18
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	19
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	18-19
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	22
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	23
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	23
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	23
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	24
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	25
Study characteristics	17	Cite each included study and present its characteristics.	25
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	27
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	29-33
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	34
	23b	Discuss any limitations of the evidence included in the review.	34-40
	23c	Discuss any limitations of the review processes used.	40
	23d	Discuss implications of the results for practice, policy, and future research.	41
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

Journal Section: Oral Medicine
Publication Type: Review

Difference in prognosis of oral melanoma and cutaneous melanoma: A systematic review

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Abstract

Background: to systematically review the literature, comparing the prognosis of oral melanoma and cutaneous melanoma among the prognostic factors.

Materials and methods: Following the recommended methods for systematic review (PRISMA) an electronic literature search was conducted from December 2021 until February 2022 using PubMed (MEDLINE) and Scopus. Studies that performed analysis on the prognostic factors and survival rates of patients with oral melanoma were included in this systematic review.

Results: The following parameters have been assessed to have a prognostic influence: age at diagnosis, time of diagnosis, tumor size, extent of disease, level of invasion, pigmentation, and ulceration. In terms of survival rates, the survival prognosis for cutaneous melanoma is higher, with percentages ranging between 77-85%, than the survival prognosis for oral melanoma is between 20-34%.

Conclusions: Oral melanoma has a poor prognosis compared to cutaneous melanoma, as the findings of this review demonstrate that patients with cutaneous melanoma had a better long-term survival rate than those with oral melanoma.

Key words: *Oral melanoma, Cutaneous melanoma, Prognosis, Prognostic factors, Survival rate*

Introduction

Malignant melanoma is an uncommon and aggressive tumor, such as the deadliest primary skin cancer. When these tumors occur in mucosal areas, like the oral cavity, the prognosis is significantly worse. All focally pigmented lesions and most diffusely pigmented lesions require a biopsy for diagnosis due to the possibility of oral mucosal melanoma (1). Melanomas are most seen on the skin; nonetheless, 1–8% of malignant melanomas occur in the oral mucosa, accounting for 0.5 percent of all oral malignant tumors, with an incidence of 1.2 cases per 10 million individuals per year (2,3). Unlike cutaneous melanomas (CMs), the origin, risk factors, and pathophysiology of oral melanomas (OMs) are poorly known. These tumors are commonly diagnosed when they are in more advanced stages than the usual CM due to frequent delays in diagnosis (4). The rare and deadly cancer arises from malignant transformation and clonal expansion of neural crest-derived melanocytes located in the oral epithelium's basal cell layer or the oral mucosa's lamina propria (5). OM might be asymptomatic in its early stages. Considering symptoms such as discomfort, bleeding, and ulceration may not appear until later, most cases of OM, around 60%, are detected only when they are advanced. Lesions with a diameter more than 4 cm and distant metastases have a poor prognosis, with a survival rate of less than 17 months and only 6.6 % of patients surviving for more than five years. MMs have a significantly worse prognosis than CMs because they commonly invade the underlying tissues and metastasize (2). Patients with mucosal melanoma (MM) appear at a significantly later age than those with CM, about one to two decades later, with most cases documented between the ages of 50 and 80, and a median age at diagnosis of 70 (6). Melanoma of the skin is associated with UV radiation, for example sun and tanning bed, and age, just like ethnicity, such as the Caucasian population, history of blistering sunburns as a child, dysplastic nevi, family history, occupational chemical exposure, fair skin and hair, such as

blonde or red hair, and immunosuppression (7). Whereas sunlight is a predisposing factor for CM, no predisposing factors for MM have been discovered. There is little evidence that recurrent trauma, chronic inflammation, human papillomavirus infection, intake of alcohol or tobacco consumption have any role in the pathogenesis of OM. However, cigarette smoking has been indicated as a risk factor since smokers have been shown to have more oral pigmented lesions and they are influenced by factors such as family history and pre-existing lesions (8–10). The aim of this review was to analyse the prognosis of OM in comparison to CM. Specially to define the prognostic factors of OM and to examine the survival of OM compared with CM.

Materials and Methods

This systematic review complies with the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (11).

- Focus question

The review was organized with regards to the following PICO question: patients with oral melanoma (P=Patient); the prognosis factors of oral melanoma and cutaneous melanoma (I=Intervention); between oral and cutaneous melanoma (C=Comparison); where the prognosis is expected to be worse in oral melanoma (O=Outcome).

- Information sources and data search

An electronic literature search was conducted in two electronic databases: PubMed (MEDLINE) and Scopus with the following key words ("MELANOMA"[Title]) AND ("Cutaneous"[Title] OR "Dermal"[Title] OR "Skin"[Title]) AND ("Outcome"[Title] OR "Prognosis"[Title] OR "Prognostic*"[Title]) or ("Melanoma"[Title]) AND ("Mouth"[Title] OR "Oral"[Title] OR "Mouth Mucosa"[Title] OR "Buccal"[Title] OR "oral cavity"[Title] OR "Lips"[Title] OR "Tongue"[Title] OR "Mucosa"[Title] OR "Mucosal"[Title]) AND ("Outcome"[Title] OR "Prognosis"[Title] OR "Prognostic*"[Title]). The search

contemplated papers published in english, german or spanish from 2011 up to 2022.

- Eligibility criteria

Articles were included in this systematic review if they met the following inclusion criteria: 1) Studies written in English, Spanish, or German; 2) Studies published from 2011-2022; 3) Studies examined on humans; 4) Studies in vivo; 5) Cohort studies, Case-Control studies, Retrospective studies, and Randomized controlled trials.; 6) Outcomes of studies that include data related to prognostic factors; 7) Outcomes of studies that include data about survival rates.

- Search strategy

The search strategy was carried out by two independent reviewers (LSS, ARA). Publications that did not meet the inclusion criteria were excluded. In the first phase, titles were screened in order to eliminate irrelevant publications. In the second phase, abstracts were filtered and the studies without enough information were deemed for full-text assessment. The third phase consisted of a full reading of each text to confirm study eligibility upon the predetermined inclusion and exclusion criteria (Fig. 1).

- Extraction data

Evidence tables were created with the study data. The following data were collected from the publications: first author´s surname, year of publication, country of origin, type of study, sample size, demographic variables of the patients (sex and age), prognostic factors, cancer stage, anatomic site, tumor thickness, metastasis, survival rates, and the follow-up period.

The data extraction process was carried out by a single researcher (LSS), who has worked independently, any doubt regarding the data extraction process has been resolved through the intervention of a second investigator (ARA) and reaching an agreement between both.

- Qualitative analysis

The quality of the included cohort studies was assessed with the Newcastle-Ottawa Scale (12). A quality rating of high risk, low risk and unclear risk of bias was

assigned independently by one reviewer (LSS) based on a set of criteria, and discrepancies were discussed with a second reviewer (ARA) until full consensus was reached.

- Data synthesis

With the aim of summarizing and comparing studies, mean data on main variables were gathered.

Results

- Study selection

A total of 889 articles were obtained that fit the search terms. (PubMed=437, Scopus=452). Of these, 407 were screened by title and subsequently excluded because they did not meet the inclusion criteria. After screening the abstracts, 98 articles were excluded. The fulltext articles were subsequently obtained and thoroughly evaluated. It was determined that 8 studies met all the inclusion criteria, and these were incorporated in this systematic review (Figure 1).

- Study characteristics

The remaining eight studies included were retrospective cohort studies. In total information was available from 4453 patients and the average age between them was 56,57 years. All included studies examined the prognosis of melanoma. However, three studies focused on cutaneous melanoma, while three focused on oral melanoma, and two included both (Table 1).

- Risk of bias

The Newcastle-Ottawa Scale quality instrument is scored by awarding a point for each answer that is marked with a star. Possible total points are 4 points for Selection, 2 points for Comparability, and 3 points for Outcomes. Seven out of eight studies showed a low risk for the overall judgement, while two showed an unclear risk. Supplementary Diagrams show the QUADAS-2 Proportion of studies in % and a summary about each domain for each included study (Figure 2 and 3).

- Synthesis of results

Due to its rarity, OM remains to be poorly understood. Indeed, the histology of OM differs from that of CM, and the prognosis of OM is worse, requiring more aggressive therapy and investigation into its prognostic factors (13). Among the five studies reporting prognostic factors of OM the following factors were assessed by multiple studies and were found to have a prognostic influence: age at diagnosis, time of diagnosis, tumor size, extent of disease, level of invasion, pigmentation, and ulceration. Factors commonly studied that did not have significant prognostic influence were sex and the decade of diagnosis (13–17) (Table 2). Survival varies significantly between different melanoma types, especially between oral and cutaneous ones. Four studies evaluated the survival rates of OM using the Kaplan-Meier curve method. Three studies found that patients in the 5-year OS had a considerably poor survival prognosis with percentages ranging between 20-34%, and the study *Tas et al*. had a higher survival percentage with 53%. In general, the median overall survival (OS) for OM was 2,5 years (Table 3). Four studies evaluated the survival rates of CM using the Kaplan-Meier curve method. Three studies found that patients in the 5-year OS and the OS had a significantly high survival prognosis with percentages ranging between 77-85%, and the study *Tas et al*. had a noticeable lower survival percentage with 43% (Table 4) (16,18–20). There was a significant difference between the survival rates of OM and CM. All OMs appear to have a much worse overall prognosis and outcome with survival percentages ranging between 20-34% compared to the cutaneous percentages of 77-85% (13–16,18–20).

Discussion

OM is a very rare malignancy. It's a highly aggressive cancer that can spread and infiltrate neighbouring tissues. OM commonly manifests asymptomatically within the early stages, which may contribute to its late identification, poor prognosis, and low survival rates (15). It is important to consider prognostic factors related to survival outcomes. Based on the qualitative analysis of the included studies, it has been possible to reach a consensus that prognostic factors identified in this review

can be categorized into age at diagnosis, time of diagnosis, tumor size, extent of disease, level of invasion, pigmentation, and ulceration. The most significant factor influencing survival is early diagnosis. Early diagnosis is crucial because a prompt discovery can greatly improve the chances of survival. Therefore, Lee et al. states that clinicians must integrate early OM screenings into their patient examinations, to contribute to an earlier detection (15). Similarly, Song et al. comments that an early diagnosis, particularly for lesions with poor pigmentation, seems to be challenging and therefore the poor prognosis of OM may be due to a delayed diagnosis (13). These results are supported by another study from Santana et al., declaring that any suspected pigmented lesion should be histopathologically evaluated, since early detection and surgical excision are critical for a favorable prognosis (21). Another study by Aloua et al. agrees with the importance of early diagnosis, because most melanomas are painless in their early stages, the detection is generally delayed until signs such as ulceration, growth, or bleeding appear before diagnosing them (22).

The age at which a person is diagnosed has also been found to be a prognostic factor. In this study, being under 55 years old was found to be a positive predictor for prognosis, however being beyond 70 years old had a negative impact (14). Indeed, another study from Zhu et al. revealed that patients under the age of 70 survive longer than those over 70, with a significant difference (23). Bishop et al., Shuman et al., Sarac et al. and Kerr et al. also indicated that advanced age, had a considerable impact on survival (24–27).

Tumor factors such as size have a consistently prognostic influence on survival. Tumors greater than 4 cm had a 1.6-year survival rate, whereas tumors less than 2 cm had a 3.3-year survival rate, according to Lee et al. (15). This pattern is consistent with what has been discovered in the literature and that the size of the tumor is a significant predictive factor (Frakes et al., Sarac et al, Gru et al.,Zhu et al.) (23,26,28,29). The extent of disease has been found to be a significative prognostic factor. The degree of disease extent was linked to a lower chance of survival, with a prognosis that was worsened by a distant extent, showing that the

OS reaches about 0.8 years, according to Lee et al. (15). Another significant prognostic factor has been discovered: Level of invasion. Song et al. discovered a link between invasion levels and patient outcomes in patients with localized OM, the amount of invasion was also shown to be a predictive factor, according to the results of their study (13). Other studies also significantly associated decreased survival with deep invasion levels (Keller et al., Breik et al.) (30,31).
Strong pigmentation was shown to be a positive prognosis factor by Song et al. (13). Whereas, one study by Kerr et al. discovered that the presence or lack of melanin pigmentation had no effect on the outcome, another study by Aloua et al. confirms the hypothesis that pigmentation is a prognostic factor, saying that the majority of primary OMs present as new lesions on apparently normal mucosa, although around 30% to 50% of them are preceded by oral pigmentations that can last months or even years and the mucosal melanosis and a variety of melanocytic nevi are examples of pre-melanoma lesions (22,27). In 30 to 73 percent of individuals, oral melanosis has been identified as a predisposing factor for the development of OM (22,27). The presence of ulcers has been revealed to be a significant prognostic factor. According to Berzina et al., ulceration is independently linked with greater rates of distant metastasis and lower OS in melanoma (17). Shuman et al. share this viewpoint, indicating that the lack of ulceration predicts better outcomes, and that the presence of ulceration has a higher than 3-fold influence on OS (25).

In contrast, comparing the prognostic factors with CM, Cherobin et al. declares that their univariate analysis detected four significant prognostic factors: male gender, nodular clinical and histologic subtype, Breslow thickness > 4mm, and histologic ulceration (32). In this study, Berzina et al. proclaims that both share the fact that if the tumor is thin at the time of diagnosis, the prognosis for melanoma is good (17). Tumor thickness is the most significant prognostic indication for localized CM, and as thickness rises, 5- and 10-year survival rates decrease significantly. Patients with 0.01 to 0.5 mm thick localized CMs have a 10-year

survival rate of 96 percent, whereas those with localized melanomas more than 6.00 mm thick had a 10-year survival rate of 42 percent (33).

Focusing on the discrepancies in survival rates between OM and CM. MMs from the head and neck are thought to be particularly aggressive and rapidly fatal, and long-term survival is dismal, with only around half of patients living three years after diagnosis. In the literature, a broad range of survival rates have been documented. The overall 3-year and 5-year survival rates in a Chinese study of exclusively OMs were 35 and 20.7 percent, respectively (14). The findings in the literature are highly comparable to our findings (Shuman et al.,Keller et al.) (25,30). Indeed, Beaudaux et al. agrees that, in comparison to CM, the prognosis for MM is exceedingly dismal, with a five-year disease-specific survival rate of around 25% (34). When OM patients are compared to CM patients, patients with CM had in the 5-year OS and overall survival a very good survival prognosis with percentages ranging from 77-85 percent in three trials from Buja et al., Perez et al. and Maurichi et al. (18–20). Beaudaux et al. supposes that the improved prognosis for CM is largely explained by the frequent earlier identification of CM in comparison to internal and less visible locations (34). Certain limitations should be recognized when interpreting the findings of this systematic review. Despite the fact that individuals with OM are uncommon and the incidence is low, the inclusion criteria intended to focus on a clearly defined sample of patients in the studies included in the qualitative analysis. Moreover, in order to avoid publication bias, the recommended search method for finding relevant literature was entered into two databases. In addition, the study only discovered publications in English, German, and Spanish. The level of evidence of the research studied, which determines the link between the different prognostic factors and survival rates, is based on the quality of the studies included in the present qualitative analysis. The moderate (7.2) level of evidence for this research was determined from the quality of the included research, which was rated between moderate or low in the majority of the assessed studies, based on the Newcastle-Ottawa Scale.

Conclusion

OM is an uncommon and aggressive tumor with a poor prognosis, compared to CM. The prognostic factors for OM that were most consistently reported were age at diagnosis, time of diagnosis, tumor size, extent of disease, level of invasion, pigmentation, and ulceration. Where patients with a higher age, late diagnosis, metastasis, deep levels of invasion, weak or absent pigmentation and ulceration presented the worst prognosis. The findings of this review demonstrate that individuals with CM had a better long-term survival rate than those with OM. While the survival rate for CM is significantly higher, with percentages ranging between 77-85%, the survival rate for OM is between 20-34%. As some prognostic factors are poorly studied in the literature, more research is needed to determine their significance in the prognosis of OM.

Table 1. *Characteristics of included studies.*

Study	Study design	Type of melanoma	Sample size	Male	Female	Median Age (In years)	Years of patient inclusion
Buja et al. *(18)* Italy 2021	Cohort, Retrospective	Cutaneous	1279	678	601	58	5
Perez-Aldrete et al. *(19)* Mexico 2019	Cohort, Retrospective	Cutaneous	323	152	171	59	10
Lee et al. *(15)* USA 2017	Cohort, Retrospective	Oral	232	111	121	-	39
Song et al. *(13)* China 2015	Cohort, Retrospective	Oral	82	45	37	55,2	10
Maurichi et al. *(20)* Italy 2014	Cohort, Retrospective	Cutaneous	2243	1023	1220	43	8
Tas et al. *(16)* Turkey 2013	Cohort, Retrospective	Oral, Cutaneous	OM: 21 CM: 94	OM: 11 CM: 51	OM: 10 CM: 43	63	OM: 11 CM: 12
Sun et al. *(14)* China 2012	Cohort, Retrospective	Oral	51	36	15	55	29
Berzina et al. *(17)* Latvia 2011	Cohort, Retrospective	Mucosal, Cutaneous	124	43	81	67,36	9

Table 2. *Prognostic factors of OM associated with good or poor survival.*

Prognostic factors	Measure Good survival	Measure Poor survival	Studies measuring factor (Study reference)
Age	< 50	>70	Lee et al. (15)
	<55	>55	Sun et al. (14)
Sex	F/M	F/M	Lee et al. (15), Tas et al. (16)
	M	F	Sun et al. (14)
Time of diagnosis	Early	Late	Sun et al., Song et al., Lee et al., Tas et al., Berzina et al. (13-17)
Decade of diagnosis	2000	1970	Lee et al. (15)
Extension	Confined	Metastatic	Lee et al. (15)
Tumor size	<2cm	>4cm	Lee et al. (15), Berzina et al. (17)
Surgery	Surgery performed	No Surgery	Lee et al. (15)
SES	Higher	Lower	Lee et al. (15)
Preoperative biopsy	Yes	No	Sun et al. (14)
Cell type:	Non-epithelioid	Epithelioid Nodular	Song et al. (13), Berzina et al. (17)
cTNM Stage	III	IV, V	Sun et al. (14), Berzina et al. (17)
	II or III		Tas et al. (16)
Level of invasion	Non-deep	Deep	Song et al. (13), Berzina et al. (17)
Pigmentation	Strong	Weak or absent	Sun et al. (14), Song et al. (13)
TIL	Absence	Presence	Song et al. (13)
Ulceration	Absent	Present	Song et al. (13), Berzina et al. (17)
Mitotic rate	<1 per HPF	>1 per HPF	Song et al. (13)
Necrosis	Absent	Present	Song et al. (13)

(F=Female, M= Male, SES = Socioeconomic status, TIL = Tumor infiltrating lymphocyte, HPF= High power field)

Table 3. *Survival rates of OM.*

Study	Method	Sample Size	1-year OS	2-year OS	3-year OS	5-year OS	OS
Lee et al. *(15)*	Kaplan-Meier curve	232	-	-	-	25%	-
Song et al. *(13)*	Kaplan-Meier curve	82	-	63,4%	49,4%	33,8%	-
Tas et al. *(16)*	Kaplan-Meier curve	21	79%	-	-	53%	-
Sun et al. *(14)*	Kaplan-Meier curve	51	-	-	35%	20,7%	-

(OS = Overall Survival)

Table 4. *Survival rates of CM.*

Study	Method	Sample Size	1-year OS	2-year OS	3-year OS	5-year OS	OS
Buja et al. *(18)*	Kaplan-Meier curve	1279	-	-	-	83,8%	-
Perez-Aldrete et al. *(19)*	Kaplan-Meier curve	323	-	-	-	-	77%
Maurichi et al. *(20)*	Kaplan-Meier curve	2243	-	-	-	-	85,3%
Tas et al. *(16)*	Kaplan-Meier curve	94	86%	-	-	43%	-

(OS = Overall Survival)

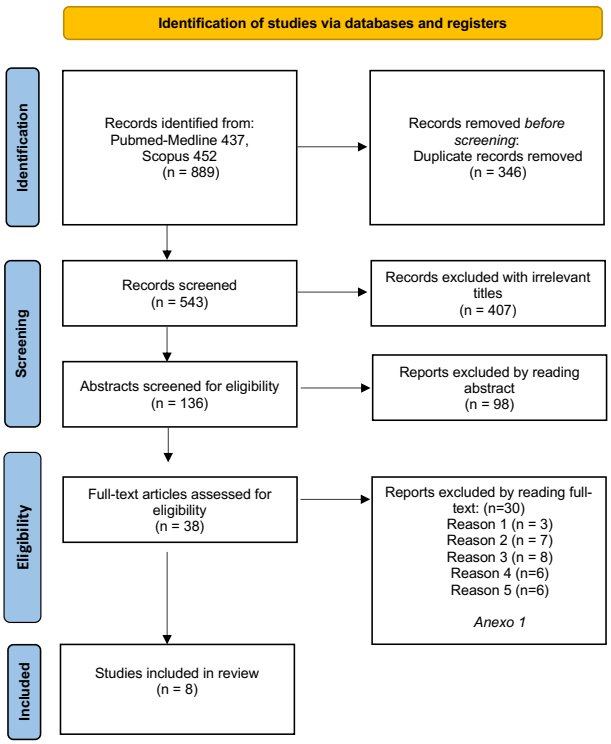

Figure 1. *PRISMA flowchart of searching and selection process of articles.*

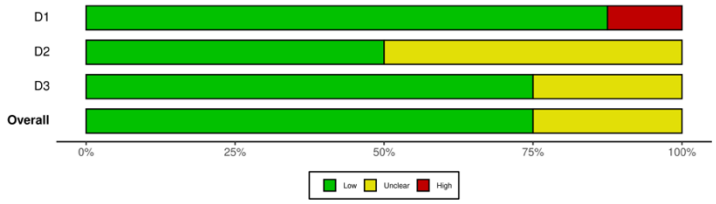

Figure 2. *Risk of bias: Weighted bar plots of the distribution of risk of bias judgements within each bias domain.*

Figure 3. *Risk of bias: Traffic light-plots of the domain-level judgements for each individual study.*

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Conflict of interest

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