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Cutaneous Melanoma of the Lip: A SEER Analysis of Epidemiology and Survival Outcomes With Focus on Surgery and Other Treatment Options

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Abstract. *Background/Aim: Cutaneous melanoma of the lip (LM) is a rare malignancy with a low overall survival (OS). Few studies exist in the literature to aid its diagnosis and treatment. The purpose of this study was to assess the different treatment modalities by collecting cases from a single database and to provide current information on the epidemiologic characteristics of cutaneous lip melanoma. Patients and Methods: The SEER database was searched for demographic, clinical-pathological, and therapeutic characteristics. The Kaplan-Meier model was used to analyze the overall survival (OS) of the study population, and survival curves were modelled. Univariable analysis between subgroups was carried out using the log-rank test. Surgery was further assessed with a multivariable cox regression, where the surgical procedure was adjusted for Breslow thickness. Results: Patients aged 62.4 years on average, and 62.7% of them were males. A total of 386 melanomas of the cutaneous lip were identified. Mean OS was 155.1 months, median OS was 187 months, and 67.4% had localized disease. Conclusion: LM has a poor prognosis with a 5-year OS of 75.2%. Surgery remains the mainstay of treatment, with less invasive surgical approaches yielding a comparable overall survival to surgery with greater margins.*

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Cutaneous melanoma (CM) is a malignancy that accounts for about one in five new cases of diagnosed skin cancer, with about 320,000 reported cases diagnosed in 2020 and associated with about 57,000 deaths worldwide. Its incidence has been steadily increasing over the last 50 years, especially in fair-skinned people with European ancestry and is predicted to reach 510,000 new cases and 96,000 deaths by 2040 (1).

With its incidence and death rising at a similar rate and being one of the most common cancers in young adults, CM remains a major global public health concern (1-6). CM develops from melanocytes, pigmented dendritic-like cells found in the basal layer of epithelium of the skin. These cells can also be found in other anatomical locations such as mucosa, lymph nodes, eyes, *etc*. Several studies have indicated that cutaneous lip melanoma (LM) is commonly found in people with fair skin and people who had prolonged exposure to ultraviolet (UV) radiation (7-9). However, the International Agency for Research on Cancer cautions that the diagnosis of LM is frequently a combination of cutaneous and oral mucosal cancer, which may behave differently (10). Representing only 0.05% to 0.31% of all melanomas, less than 0.3% of lip malignancies, and 0.3% to 2.2% of head and neck melanoma, LM continues to be a rare disease that primarily affects the elderly. As a result, there is a paucity of evidence available about LM in the literature (11-15).

Despite its low incidence, previous studies have shown that LM is associated with an elevated risk for melanoma-specific death compared with other localizations (16-18). Lips are a complex anatomical region with serious aesthetic concerns that similarly to other areas of the head and neck region, require complex surgical treatment. In order to

minimize surgical excision, maintain safety, optimize reconstruction and limit aesthetic sequelae, proper surgical planning and a multidisciplinary team approach involving dermatologists, oncologists, and plastic surgeons is required. Surgical strategies for melanoma necessitate total tumor removal, with safety margins differing based on AJCC staging (19). The recommended margin of safety of surgical excision ranges from 0.5 cm to 2 cm, based on *in situ* tumors and the Breslow Index (20).

The purpose of this study was to assess the various treatment modalities by collecting cases from a single database and to provide current information on the epidemiologic characteristics of LM. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program was selected because it provides extensive statistical monitoring and is considered to be representative of the American population (21). It has the advantage that all patients within the cohort are categorized and assessed according to the same standards. Our goal is to provide information that will help investigations and guide on treatment options for this relatively uncommon malignant tumor.

Patients and Methods

Patient selection. Using the ICD-O3 codes 8720/03 to 8772/3 and primary site localization code C44.0 [skin of lip, not otherwise specified (NOS)], all cases of LM between 2000 and 2019 were searched in seventeen SEER registries. *In situ* melanomas were not reported.

Variable selection. The SEER database was searched for demographic, clinical-pathological, and therapeutic characteristics. The surgery variable was divided into subgroups that included no surgery, tumor resection/destruction without margin, Mohs surgery (regardless of margins), surgery with margins of less than 1 cm, surgery with margins of 1 to 2 cm, and surgery with margins of more than 2 cm. In other cases, margins were merely listed as greater than 1 cm, which placed them in the 1 to 2 cm category. In order to conduct an age-related survival analysis, patients were arbitrarily divided into three age groups: equal to or less than 49, 50 to 69, and 70 or more. The goal of this section was to determine whether younger, middle-aged, and elderly patients had different rates of survival.

Four subcategories of Breslow thickness were established: 0.1 to 1 mm, 1.1 to 2 mm, 2.1 to 4 mm, and greater than 4 mm. This subdivision follows AJCC classification and NCCN recommendations for surgical margins (19, 20). Breslow scores over 9.8 mm were reported as 9.8 mm in the SEER database. Breslow scores reported as greater than 0.0 mm and less than or equal to 0.1 mm were described as 0.1 mm in this study. Mitotic rate analysis was reported from 1 to 10, then as more than 11 mitoses per square mm. We further subdivided it into three categories according to NCCN risk stratification: less or equal to 2 mitoses per square mm, 3 to 10 mitoses per square mm, 11 or more mitoses per square mm (13).

Tumor stage was based on the SEER summary stage variable as the AJCC stage was in-consistently reported, despite being validated for prognostic value (14). Localized disease was defined as a tumor confined to the epidermis and dermis corresponding to AJCC stage I and II, whereas regional diseases required subcutaneous invasion, in transit metastases, satellite lesions or/and positive regional lymph nodes (AJCC stage III). Distant disease encompassed all metastases, including distant lymph node groups (AJCC stage IV).

Table I. *Patients' characteristics*.

	N (%)
Age	
Mean (SD)	62.37 (16.94)
<50 years	92 (23.8)
50 to 69 years	155 (40.1)
≥70 years	139 (36.1)
Sex	
Male	242 (62.7)
Female	144 (37.3)
Histologic subtype	
8720/3 Malignant melanoma, NOS	166 (43)
8721/3 Nodular melanoma	22 (5.7)
8742/3 Lentigo maligna melanoma	51 (13.2)
8743/3 Superficial spreading melanoma	45 (11.7)
8745/3 Desmoplastic melanoma, malignant	56 (14.5)
8772/3 Spindle cell melanoma, NOS	35 (9.1)
Other subtypes	11 (2.8)
Stage	
Localized	260 (67.4)
Regional	75 (19.4)
Distant	23 (6)
Unknown	28 (7.2)
Surgical procedure	
No surgery	21 (5.4)
Tumor resection/destruction without margin	50 (13)
Mohs surgery	24 (6.2)
Surgery with <1 cm margin	259 (67.1)
Surgery with 1 to 2 cm margins	20 (5.2)
Surgery with >2 cm margins	8 (2.1)
Unknown	4 (1)
Radiotherapy	
Yes	51 (13.2)
No/Unknown	335 (86.8)
Chemotherapy	
Yes	9 (2.4)
No/Unknown	377 (97.6)
Breslow N=180	
Mean (SD)	2.1 mm (2.6)
0.1-1 mm (T1)	98 (25.4)
1.1-2 mm (T2)	24 (6.2)
2.1-4 mm (T3)	21 (5.4)
>4 mm (T4)	37 (9.6)
Unknown	206 (53.4)
Ulceration	
Yes	39 (10.1)
No	145 (37.6)
Unknown	202 (52.3)
Mitotic rate (mitosis per mm^2)	
2 or less	90 (23.3)
3 to 10	37 (9.6)
11 or more	14 (3.6)
Unknown	245 (63.5)

NOS: Not otherwise specified.

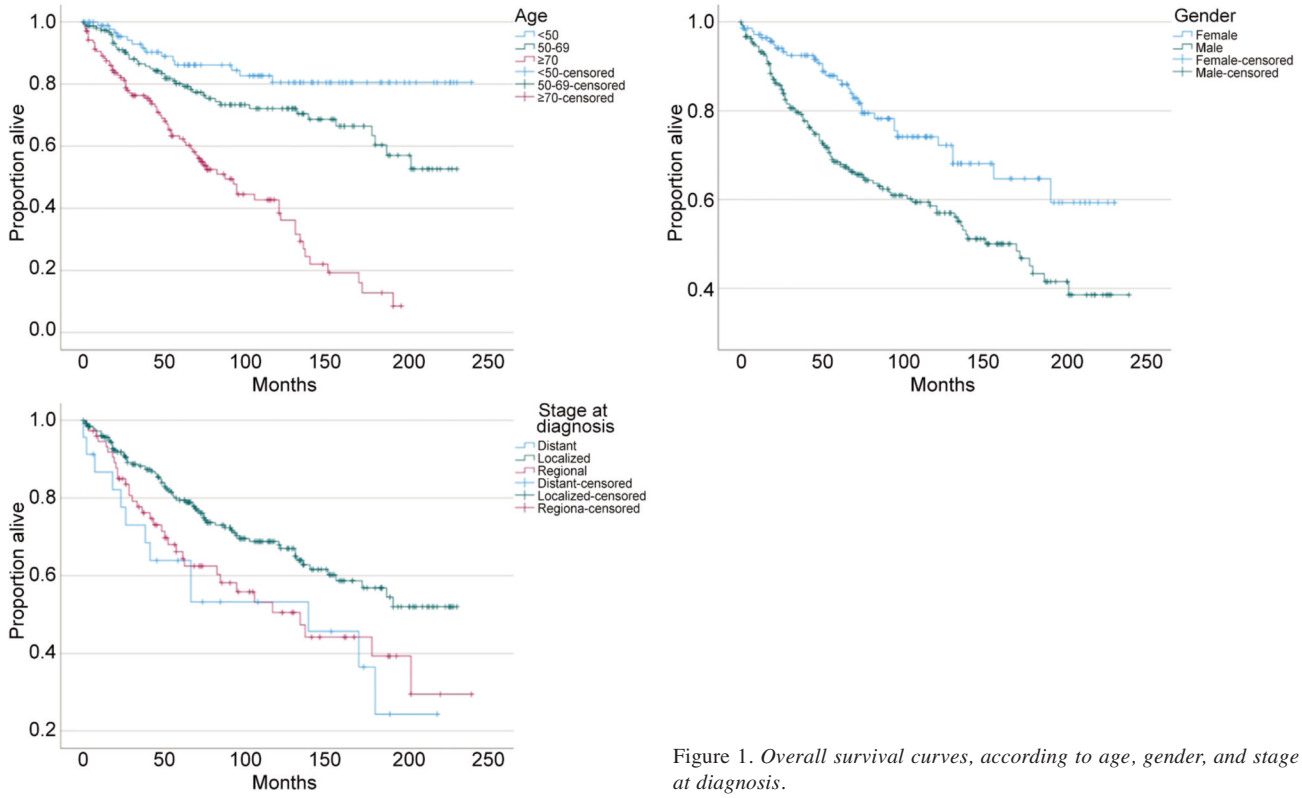

Figure 1. *Overall survival curves, according to age, gender, and stage at diagnosis.*

Statistical analysis. Data were gathered from SEER*stat version 8.4.0.1 and processed using IBM SPSS version 27 (IBM, Armonk, NY, USA). The Kaplan-Meier model was used to analyze the overall survival (OS) of the study population, and survival curves were modelled. Univariable analysis between subgroups was carried out using the log-rank test. In variables with multiple subgroups, subgroups with less than 20 occurrences were reported as "other". Mean OS (mOS) was reported with a 95%CI. Surgery was further assessed with a multi-variable cox regression analysis, where the surgical procedure was adjusted for Breslow thickness. Statistical significance was defined as a p-value <0.05.

Results

A total of 386 LM were identified according to the selection criteria. The mean age at diagnosis was 62.4 years (SD=16.9) on average, and most of the patients were males (62.7%). Demographic data are reported in Table I.

The average Breslow index value was 2.1 mm (SD=2.6). Due to a sporadic report of tumor thickness in the SEER database, caution should be used when analyzing these findings (15, 22).

The overall mOS was 155.1 months (95%CI=144.2-166); median OS was 187 months. The one, three-, and five-year OS rates were 94.7%, 84.1%, and 75.2%, respectively. OS was lower in men (mOS 142.3; 95%CI=128.7-156) than in women (mOS 174; 95%CI=157.7-190.2; p<0.05; Figure 1). Increasing age was substantially related to a decrease in OS (p<0.05; Figure 1). Mean OS for <50 years was 203 m (95%CI=186-220.2), 167.4 m (95%CI=152.1-182.8) for patients aged 50 to 69 years, and 93.3 m (95%CI=80.8-105.7) for those aged 70 or more. Significantly lower OS was associated with more advanced stages (p<0.05; Figure 1). Localized disease had a mOS of 161 m (95%CI=148.6-173.3), regional had a mOS of 131.6 m (95%CI=107.5-155.7), and distant disease had a mOS of 115.7 m (95%CI=79.3-152.1). Our survival analysis showed that the best OS according to histologic subtypes was in patients diagnosed with malignant melanoma, NOS (8,720/3; mOS 159.1; 95%CI=143.5-174.8), followed by lentigo maligna melanoma (8,742/3; mOS 155.3; 95%CI=127.0-183.7), whereas nodular melanoma was associated with the lowest OS (8,721/3; mOS 106.3; 95%CI=60.0-152.7). Significant OS differences between malignant melanoma 8,720/3 and nodular melanoma 8,721/3 as well as with spindle cell melanoma, NOS (8,772/3; mOS 118; 95%CI=85.4-150.5) were evidenced. Other significant differences in OS were found between nodular melanoma 8,721/3 and lentigo maligna melanoma 8,742/3 and superficial spreading melanoma (8,743/3; mOS 152.7; 95%CI=126.2-179.3). Compared to all other surgical procedures, surgery with

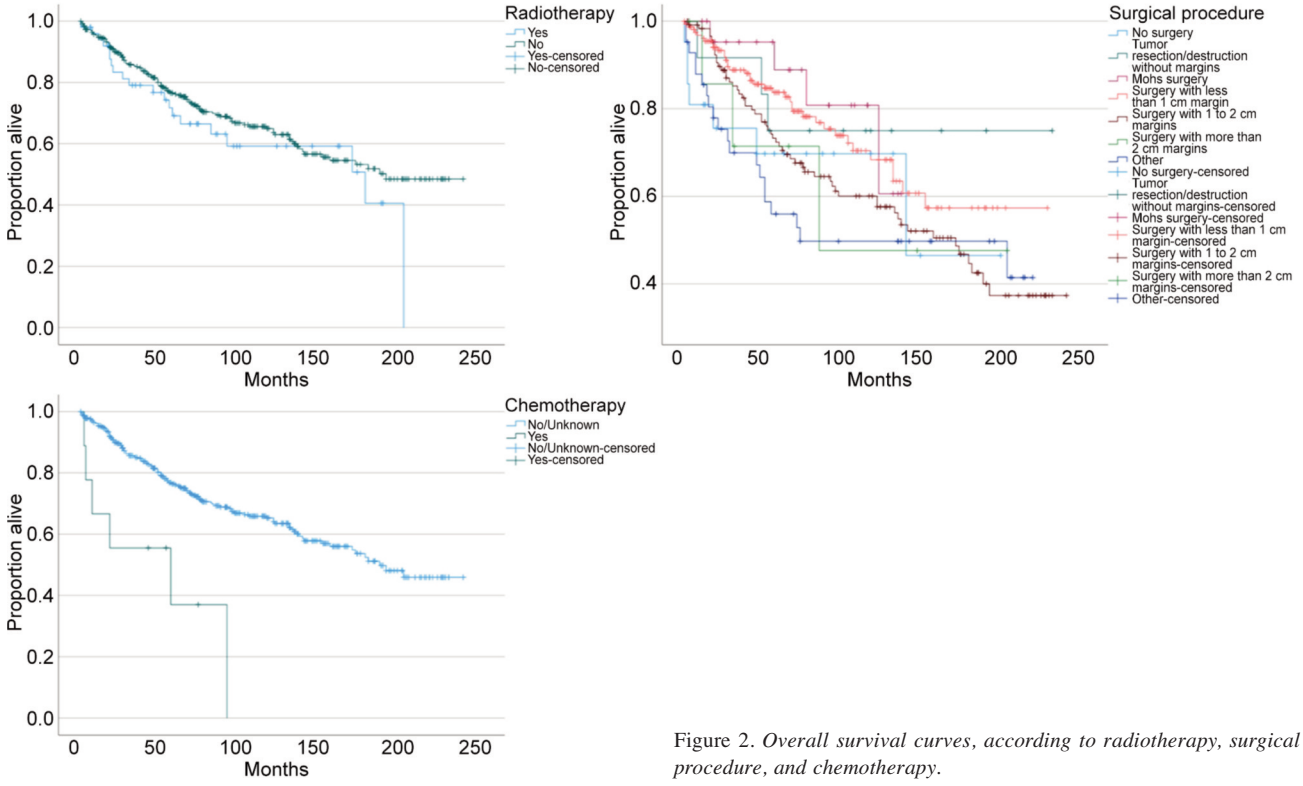

Figure 2. *Overall survival curves, according to radiotherapy, surgical procedure, and chemotherapy.*

less than 1 cm margins was associated with a higher OS (mOS 158.49; 95%CI=145.45-171.52; Figure 2). When comparing how different surgical strategies affected OS, a significant difference was observed in favor of Mohs surgery (mOS 117.5; 95%CI=101.4-133.6) and tumor resection/destruction with no margins (mOS 133.7; 95%CI=105.1-162.4; $p<0.05$) in comparison to surgery with margins of 1 to 2 cm (mOS 102.6; 95%CI=74.3-131) and surgery with margins of more than 2 cm (mOS 122.6; 95%CI=57.4-187.7; $p<0.05$). Chemotherapy was included in the survival analysis even though there were only 9 patients since, despite its restricted use mostly in palliative or stage IV cases, it is still employed regardless of its minor application. Comparing those who were classified as no/unknown (mOS 157.1; 95%CI=146.1-168.1) to those who had had chemotherapy, the use of chemotherapy (mOS 48.4; 95%CI=20.3-76.5) was not linked to a significantly poorer OS ($p>0.05$). No significant difference in OS was seen between patients who received radiotherapy (mOS 131.5; 95%CI=106.8-156.2) and those who were categorized under no/unknown (mOS 157.5; 95%CI=145.8-169.2).

Between 0.1 and 1 mm Breslow thickness (mOS 104.3; 95%CI=97.1-111.5), there was a significant difference in OS compared to 2.1 to 4 mm (mOS 69.8; 95%CI=53.3-86.4) and more than 4 mm (mOS 79.7; 95%CI=65.5-94) Breslow thickness in favor of the former. Breslow depths of 2.1 to 4 mm ($p<0.05$; Figure 3) and greater than 4 mm ($p<0.05$) were also significantly different in terms of survival. No significant differences were seen between 1.1 to 2 mm Breslow thickness (mOS 83.3; 95%CI=62.7-104) and the other Breslow categories. In contrast to tumors without ulceration (mOS 98.0; 95%CI=91.2-104.7); $p<0.05$), those with ulceration had a considerably lower OS (mOS 72.4; 95%CI=57.7-87.4; Figure 3). In univariable analysis, an increase in mitotic rate was significantly associated with a decrease in OS ($p<0.05$; Figure 3). Patients with 2 or less mitosis per square mm had a mOS of 97.7 m (95%CI=89.5-105.8), those with 3 to 10 mitosis/mm^2 had a mOS of 81 m (95%CI=67-95), and those with 11 or more had a mOS of 66.3 m (95%CI=46.1-86.5). When adjusted for Breslow thickness, no significant difference in hazard ratio was seen between surgical therapies in multivariable cox-regression (Table II). When assessing distribution of surgical modalities by Breslow thickness, surgery with less than 1 cm margins remains the most frequent modality even for deeper Breslow thickness (Table III).

Discussion

Cutaneous LM is a malignant tumor for which research is scarce and mostly based on older small-cohort studies. Furthermore, different published studies primarily focus on

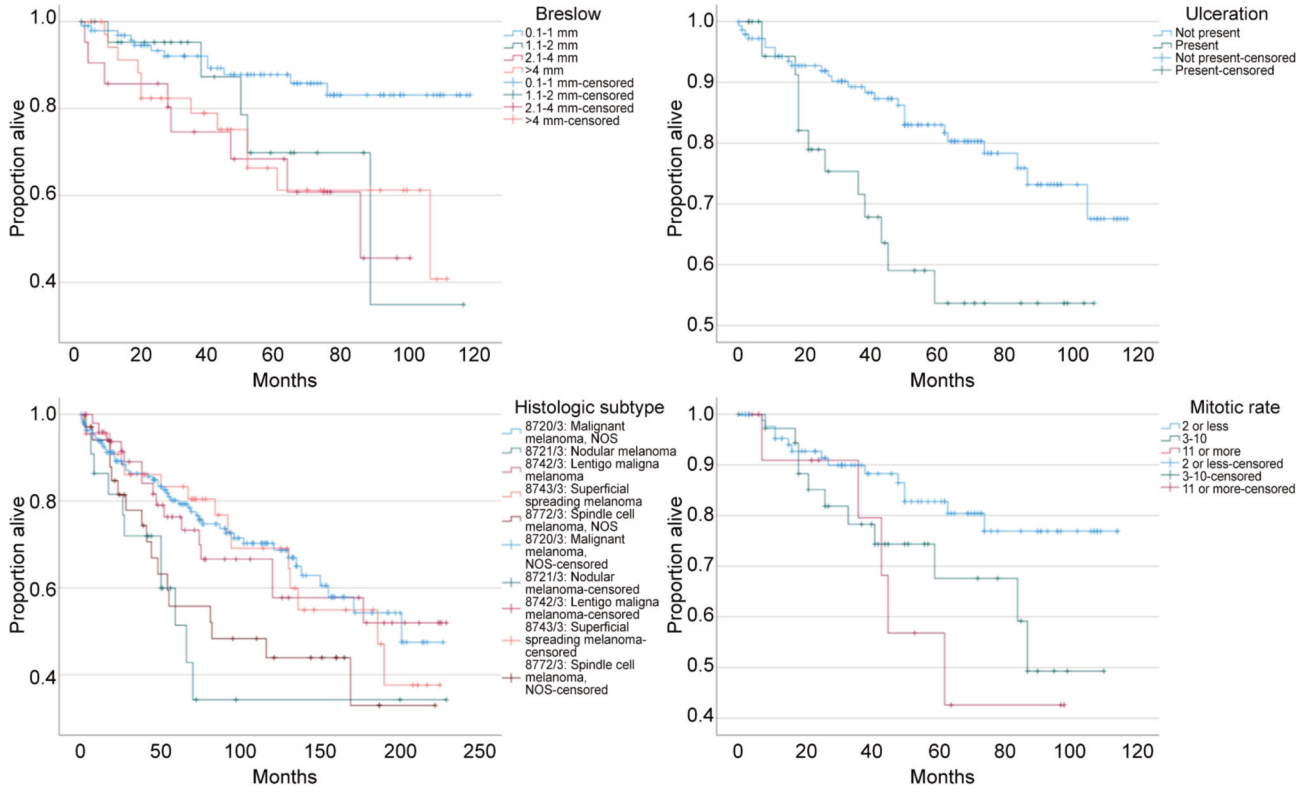

Figure 3. *Overall survival curves, according to Breslow thickness, ulceration, histologic subtype, and mitotic rate.*

mucosal melanoma or do not distinguish between the skin and mucosal melanoma of the lip, which further decrease the real number of studies regarding cutaneous LM. By analyzing data from the U.S. population, this study shows the characteristics of LM patients and their surgical and treatment strategies. To our knowledge, this is the largest and most comprehensive study that focuses exclusively on cutaneous LM. Despite the relatively small number of patients, the possible biases associated with a registry-based study, and a portion of missing or unknown data, we believe that this study can provide a better understanding of LM and, as a result, higher quality patient care. Notwithstanding the rarity of LM, it is important to note that the fundamental distinction between LM and malignant melanoma of the oral mucosa is that the latter is much more uncommon, accounting for just 0.5% of all malignant tumors of the oral cavity and 1-2% of all melanomas (23). Mucosal LM has a worse prognosis with an estimated 5-year survival rate ranging from 12.3% to 16.6% (23-26). Its bad prognosis is probably related to a propensity for local invasion or distant metastases because of late diagnosis, uneven clinical presentation, and persistent trauma given its anatomic location, which hence tends to result in ulcerated lesions (27). The current study population's average age of 62.4 years is consistent with other studies' findings that melanomas of the head and neck are typically diagnosed between the ages of 60 and 70 (28, 29). This mean age was found to be marginally higher than a small series study with 11 patients with LM who showed a mean age of 55.2 years (11).

Table II. *Logistic regression analysis of factors associated with the risk of intubation and/or death.*

	Exp(B)-HR	95%CI	*p*-Value
Surgery[1]			
No surgery	Ref		0.024
Tumor resection/destruction without margins	3.951	0.460-33.906	0.210
Surgery with less than 1 cm margins	1.065	0.136-8.338	0.952
Mohs surgery	0.370	0.023-5.990	0.484
Surgery with 1 to 2 cm margins	0.732	0.043-12.438	0.829
Surgery with more than 2 cm margins	2.613	0.218-31.300	0.448

[1]Adjusted for Breslow thickness.

Table III. *Distribution of surgical modalities according to Breslow thickness values.*

Breslow thickness	No surgery	Tumor resection/destruction without margins	Surgery with less than 1 cm margins	Mohs surgery	Surgery with 1 to 2 cm margins	Surgery with more than 2 cm margins
0.1 to 1 mm	7	7	66	13	2	3
1.1 to 2 mm	0	1	21	1	0	1
2.1 to 4 mm	1	3	11	2	2	1
>4 mm	0	7	25	1	4	0
Unknown	8	18	123	17	8	5

The advanced age of our study cohort could be a reason for the low 5-year OS. Increasing age is correlated with decreased OS due to higher risk of death from natural causes or comorbidities. Furthermore, elderly patients are more susceptible to oncological treatment side-effects.

Considering that the LM that occurred in our cohort was primarily localized (67.4%), this study's 5-year OS figure of 75.2% was low. The percentage of men with LM (62.7%) was higher than that of women, which is consistent with earlier research on melanoma of the head and neck region (17, 30-32).

It is interesting to note that Czerninski *et al.* found that men with increased sun exposure were more likely to develop cancers of the lower lip than women with the same exposure (33). In the SEER database, it was not possible to explore this topic in detail because the difference between upper and lower lip was not indicated. Other research has highlighted this difference, and it has been proposed that it is related to women's potential protective usage of lipstick (34, 35). Furthermore, it has been previously noted that women are diagnosed with melanoma in the head and neck region earlier than men, which leads to an increase in OS (36). Various studies on the difference in OS between men and women hypothesize a biological trait based mostly on the role of androgens and estrogens, whereas other studies have suggested a role of immune homeostasis, vitamin D, as well as psychological factors, but the subject remains controversial, necessitating further investigation (37-45).

Most of the patients (67.1%) underwent surgery with less than 1 cm margins, while Mohs surgery (6.2%), surgery with 1 to 2 cm margins (5.2%), and surgery with more than 2 cm margins (2.1%) were the least common in our study. Surgery with less than 1 cm margins was the most frequent surgical modality in each Breslow category, highlighting an overall trend toward conservative surgery. When assessing survival, surgery with a margin of less than 1 cm was also associated with the best OS (158.48 months) in the univariable analysis. Significant differences between Mohs surgery and tumor resection/destruction with no margins, and between surgery with margins of 1 to 2 cm and surgery with margins of more than 2 cm were found. However, these results might be confounded by the Breslow thickness of the tumor as demonstrated by the multivariable analysis where surgical margins adjusted for Breslow thickness were shown to have no significant difference in HR. While no conclusion can be drawn on optimal resection margins, it remains a hot topic with an ongoing debate about the ideal surgical resection margins (46, 47). Furthermore, the analysis of survival for Mohs surgery was limited because margins were not specified.

Studies on recurrence following surgery are warranted. However, recurrence was not reported in the SEER database, preventing disease-free-survival analysis across surgical treatment groups that could provide more insights on the recurrence rate of less invasive procedures and allow to compare the different surgical strategies. Optimizing surgical strategies is essential for plastic surgeons in order to achieve the best possible oncologic resection outcome while also respecting the many complex subunits that constitute the face.

In our study, only 51 individuals were treated with radiotherapy, and chemotherapy was used in only nine patients. It should be noted that OS was noticeably lower for the groups receiving these treatments, and one rationale might be that they were only utilized in cases of advanced disease. However, this should be interpreted cautiously, as a high rate of false negatives may exist due to no distinction being made between the patients who did not receive radiation therapy or chemotherapy and those for which the information was missing. Furthermore, no details on the timing of the treatments and regimen are available in the SEER database. These findings are consistent with the literature, which indicates that radiotherapy and chemotherapy for melanoma are rarely used alone and are frequently combined with other treatments (*i.e.*, immunotherapy) (48-50). Interestingly, according to Syrigos *et al.*, chemotherapy and radiotherapy are still considered in elderly and palliative patients when surgery is not an option, with more than 90% of patients over the age of 80 years old successfully completing planned treatment (51).

In the majority of patients, no specification of the histologic subtype was available, with 43% of them being reported as malignant melanoma, NOS. Again, taking into account the small number of current publications mentioning histologic subtypes, it was discovered that desmoplastic melanoma (14.5%) and superficial spreading melanoma (11.7%) rates were in line with what is described in the literature as the most frequent histologic subtypes in LM (11, 52).

Furthermore, given the proportion of malignant melanoma, NOS in our sample, and the known propensity for desmoplastic melanoma misdiagnosis, the latter may be underrepresented (52). Only 53.4% of the cases in the study had a Breslow depth reported; of these, the majority (25.4%) had a depth of 0.1 to 1 mm with a mean value of 2.1 mm, which is higher than that in earlier studies assessing overall locations (17). Univariable analysis in our study revealed a significant difference in OS depending on Breslow thickness. According to Lachiewicz *et al*., this finding revealed a higher Breslow than that demonstrated by earlier investigations. It is consistent with the body of research that shows Breslow to be a predictor of lower OS (53, 54).

The use of techniques such as continuous intra-arterial (IA) administration are not reported in the SEER database. IA is a technique that has shown excellent results in the treatment of SCC in cosmetic areas such as the lips, as demonstrated by Fujimura *et al*. Future research on the use of substances administered *via* continuous intra-arterial infusion in the treatment of LM is required (55).

The univariable analyses revealed that the presence of ulceration and a higher mitotic rate were associated with a significantly lower OS. Furthermore, it was shown that the ulceration and mitosis rate in our study was higher than ulceration and mitosis rates of other head and neck melanomas, a finding that could be further investigated considering the low OS observed in this study (17).

This study has several limitations. The absence of records reporting clinical tumor stage, which has a significant impact on survival, is of specific concern. Lack of data regarding associated risk factors, occupation, lifestyle, and health behaviors hinders optimal interpretation of the results.

The choice of using OS instead of disease-specific survival (DSS) can be a limitation. While DSS reflects the impact of treatments on tumoral response, OS is more representative of real-life conditions. OS and therapeutical choices are influenced by age, patient comorbidities, and overall health status.

Conclusion

External LM is a rare malignancy with a poor prognosis that primarily affects men between the ages of 60 and 70. LM has a better prognosis than oral mucosa melanoma, but it still has a poor prognosis with a 5-year OS of 75.2%. Surgery remains the mainstay of treatment, with less invasive surgical approaches yielding a comparable OS to surgery with greater margins. Further studies exploring differences across surgical strategies are warranted to confirm this finding.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, J.A.V. and C.M.O.; methodology, M.S., S.N.W. and C.M.O.; validation, S.G., D.F.K. and C.M.O.; formal analysis, M.S, J.M. and S.N.W.; investigation, J.A.V.; data curation, M.S., J.M., S.N.W. and J.A.V.; writing—original draft preparation, J.A.V.; writing—review and editing, J.A.V., D.F.K., S.G., P.G.d.S. and C.M.O.; supervision, D.F.K. and C.M.O. All Authors have read and agreed to the published version of the manuscript.

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