International Journal of
Translational Medicine

MDPI

Article

Prognostic Value of the Width of Invasion in pT3 Cutaneous Melanomas

Dana Antonia Țăpoi [1,2], Ancuța-Augustina Gheorghișan-Gălățeanu [3], Laura Maria Gosman [3,4,*], Adrian Vasile Dumitru [1,2], Ana Maria Ciongariu [1,2] and Mariana Costache [1,2]

1 Department of Pathology, Carol Davila University of Medicine and Pharmacy, 020021 Bucharest, Romania; dana-antonia.tapoi@drd.umfcd.ro (D.A.Ț.); vasile.dumitru@umfcd.ro (A.V.D.); ana-maria.ciongariu@drd.umfcd.ro (A.M.C.); mariana.costache@umfcd.ro (M.C.)
2 Department of Pathology, University Emergency Hospital, 050098 Bucharest, Romania
3 Doctoral School, Carol Davila University of Medicine and Pharmacy, 020021 Bucharest, Romania; ancuta.gheorghisan@umfcd.ro
4 Department of Pathology, Saint Pantelimon Clinical Emergency Hospital, 021659 Bucharest, Romania
* Correspondence: laura.gosman@drd.umfcd.ro; Tel.: +40-751779966

Abstract: Intermediate-thickness melanomas display highly variable outcomes influenced by both clinical and histopathological characteristics. This study investigates several clinicopathological prognostic factors for pT3 cutaneous melanomas, focusing on a novel parameter, the width of invasion. This is a retrospective study of 49 patients diagnosed with cutaneous melanoma between 2012 and 2018 who were followed up for at least five years. We evaluated the age, gender, tumor location, Breslow depth of invasion, width of invasion, mitotic index, the presence/absence of ulceration, regression, microsatellites, lymphovascular invasion, and perineural invasion for their association with disease progression and survival. Cox univariate analysis revealed that progression-free survival (PFS) was significantly associated with age, depth of invasion, width of invasion, lymphovascular invasion, microsatellites, and perineural invasion. Overall survival (OS) was significantly associated with age, depth of invasion, width of invasion, microsatellites, and perineural invasion. Through multivariate Cox proportional hazards regression, the only factor associated with both PFS and OS was the width of the invasion. This is one of the few studies to assess the width of invasion and we have demonstrated that this parameter could become an important prognostic factor for cutaneous melanomas.

Keywords: cutaneous melanoma; width of invasion; Breslow depth; survival; prognosis

Citation: Țăpoi, D.A.; Gheorghișan-Gălățeanu, A.-A.; Gosman, L.M.; Dumitru, A.V.; Ciongariu, A.M.; Costache, M. Prognostic Value of the Width of Invasion in pT3 Cutaneous Melanomas. *Int. J. Transl. Med.* **2024**, *4*, 1–14. https://doi.org/10.3390/ijtm4010001

Academic Editor: Joan Oliva

Received: 6 November 2023
Revised: 18 December 2023
Accepted: 25 December 2023
Published: 26 December 2023

1. Introduction

Cutaneous melanoma is a highly aggressive malignancy, causing the vast majority of skin-cancer-related deaths and displaying rising incidence globally [1]. Nevertheless, the prognosis has improved significantly due to advances in treatment options [2]. In this context, early diagnosis and prompt identification of adverse prognostic factors are of the utmost importance for choosing the best therapeutic approach.

Cutaneous melanoma progression can be unpredictable and is influenced by several clinical and histopathological factors. The most frequently discussed clinical prognostic factors for cutaneous melanoma are age, gender, and the location of the primary tumor. However, their prognostic value is still a matter of debate. Some studies correlated older age and male gender with decreased survival [3–5], while others found no association [6,7]. The primary location of the melanoma also has debatable prognostic value, but it appears location on the lower limbs is associated with a more favorable outcome [8] in comparison to an acral location [9] or head and neck location [10].

Among the histopathological prognostic factors, the Breslow depth of invasion remains the most significant and is used to stage cutaneous melanomas [11]. Patients with

thin cutaneous melanomas (pT1, with Breslow depth less than 1 mm, and pT2, with Breslow depth between 1 and 2 mm) usually have excellent prognosis and patients with thick melanomas (pT4) still present high mortality rates. In contrast, patients with intermediate thickness (pT3) display highly variable outcomes [12]. In addition to the Breslow depth of invasion, other factors influence the prognosis of primary cutaneous melanomas, including ulceration, mitotic count, regression, microsatellites, lymphovascular invasion, and perineural invasion [12–16]. Recent research has shown that a new parameter, the width of invasion, could also be an independent prognostic factor [17,18], but the evidence is still limited.

In this context, we conducted a study on the aforementioned clinical and histopathological prognostic factors, including the width of invasion, for evaluating the progression-free survival (PFS) and overall survival (OS) in primary cutaneous melanomas with depth of invasion between 2 and 4 mm (pT3).

2. Materials and Methods

2.1. Study Participants

This is a retrospective study analyzing 49 cases of with primary cutaneous melanomas diagnosed at the University Emergency Hospital of Bucharest, Romania, between 2012 and 2018. The sample initially included all the cases of intermediate-thickness melanomas (n = 58) diagnosed at the University Emergency Hospital of Bucharest during the study period, but 9 were excluded because no follow-up was available. The cases meeting the inclusion criteria were identified by performing a retrospective chart review. The criteria of inclusion were:

- Patients with pT3 cutaneous melanomas (Breslow depth between 2 and 4 mm) confirmed by histopathological analysis, regardless of lymph node invasion;
- Patients with whole-body CT scans after the initial diagnosis to evaluate metastatic spread;
- Patients were followed-up for at least five years, or until death if it occurred sooner, in order to evaluate the PFS and OS. PFS was defined as the time in months between the date of the initial diagnosis and the date of metastasis diagnosis. OS was defined as the time between the date of the initial diagnosis and the demise of the patient.

This study received the approval of the Ethics Committee at the University Emergency Hospital of Bucharest, Romania. The study followed the principles of the Helsinki Declaration. In order to be included in this study, every patient included in this research signed an informed consent form.

2.2. Histopathological Analysis

Standard histopathological methods were used to process the tissue samples. At the beginning of the study, two pathologists (A.V.D. and D.A.Ț.) examined all the slides to reconfirm the cutaneous melanoma diagnosis and evaluate the depth and width of the invasion. The invasion width was measured as the distance between the two outermost invasive melanoma cells in a plane approximately parallel to the epidermis and perpendicular to the Breslow depth axis (Figure 1), according to the method described by Saldanha G. et al. [17]. TMN staging was determined by consulting the eighth edition of the cancer staging manual of the American Joint Committee on Cancer (AJCC) [11]. In cases of differences in opinion between the two pathologists, a third pathologist (M.C.) was consulted to establish the final diagnosis.

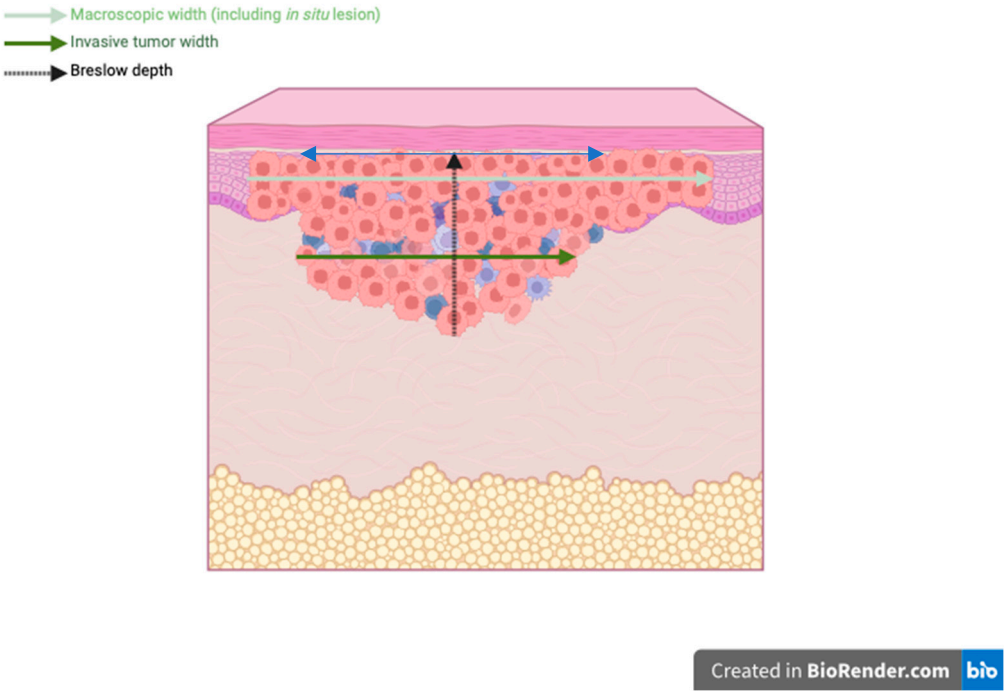

Figure 1. Measurement of tumor width (created in Biorender).

2.3. Data Collection and Analysis

In order to assess the clinical and demographic characteristics of the study population, the following variables were collected: age, gender, and primary tumor localization. The histopathological features collected for analysis included Breslow depth, width of invasion, mitotic index, the presence/absence of ulceration, regression, microsatellites, lymphovascular invasion, and perineural invasion. For each patient, the presence/absence of metastatic lesions was recorded as well as the time until disease progression and/or death. Descriptive statistics were performed for continuous variables including mean, standard deviation (SD), median, minimum and maximum values, and 95% confidence intervals (CI). Univariate and multivariate Cox proportional hazards regression analyses were performed on all the aforementioned clinicopathological variables, using PFS and OS as the outcomes. This method provided hazard ratios (HR) with 95% confidence intervals and p values, regarded as significant at a p value < 0.5. The Kaplan–Meier product limit method was employed for estimating survival probabilities, and log-rank test comparisons were made. GraphPad Prism 10.0 (Graphpad Software Inc., San Diego, CA, USA) was used to perform the statistical analyses.

3. Results

3.1. Demographic and Clinical Characteristics of the Study Population

The mean age of the entire group at the time of the diagnosis was 55.78 years (standard deviation 12.57; range 24–86). Females were more affected than males, as 59.18% (n = 29) of the patients were women and 40.82% (n = 20) were men. In the follow-up time, 30.61% (n = 15) developed metastases, and 22.45% (n = 11) died.

The mean age of the patients in the progression-free survival (PFS) group (n = 34) was 52.15 years (SD 12.01; range 24–78), and 64.7% (n = 22) were female, while 35.3% (n = 12) were male. The mean age of the patients who developed metastatic disease was 64 years (SD 9.88; range 41–86), and 46.67% were female (n = 7), while 53.33% (n = 8) were male. The patients who died during follow-up had a mean age of 65.91 (SD 8.27; range 54–86), and 36.36% (n = 4) were female, and 63.64% (n = 7) were male. These demographic features are summarized in Table 1.

Table 1. Demographic features of the study population.

	Entire Group (n = 49)	Progression-Free Group (n = 34)	Progressive Disease Group (n = 15)	Deceased Group (n = 11)
Age	55.78 years	52.15 years	64 years	65.91 years
Male	40.82% (n = 20)	35.3% (n = 12)	53.33% (n = 8)	63.64% (n = 7)
Female	59.18% (n = 29)	64.7% (n = 22)	46.67% (n = 7)	36.36% (n = 4)

We also assessed the location of the primary tumor, and the most affected site was the limbs, followed by the trunk (Figure 2).

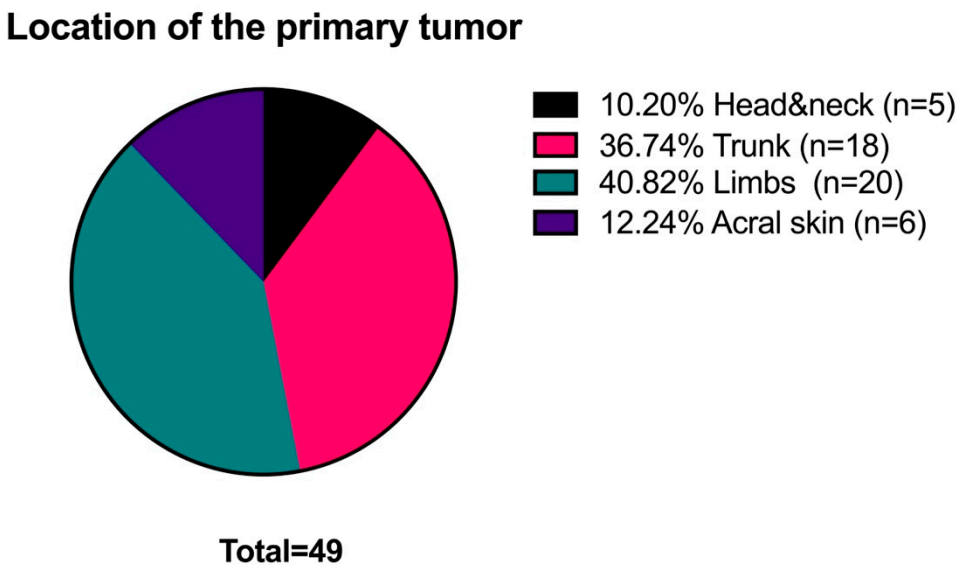

Figure 2. Number of cases based on primary tumor location. Most of the cases were located on the limbs (n = 20) and trunk (n = 18), while the least number of cases were located on acral skin (n = 6) and on the head and neck (n = 5).

Furthermore, we analyzed the distribution of the cases based on tumor location for each of the three groups: patients without progressive disease, patients with progressive disease, and deceased patients. The results are summarized in Table 2.

Table 2. Primary tumor location and disease evolution.

	Progression-Free Group (n = 34)	Progressive Disease Group (n = 15)	Deceased Group (n = 11)
Head and neck	8.82% (n = 3)	13.33% (n = 2)	9.09% (n = 1)
Trunk	32.35% (n = 11)	46.67% (n = 7)	54.55% (n = 6)
Limbs	47.06% (n = 16)	26.67% (n = 4)	27.27% (n = 3)
Acral skin	11.77% (n = 4)	13.33% (n = 2)	9.09% (n = 1)

Cox univariate analysis for PFS and OS was performed considering all the above clinical characteristics (Table 3). Age was the only factor significantly associated with both PFS and OS. As highlighted in Tables 1 and 2, disease progression and death tend to be more often encountered in male patients and in melanomas located on the trunk, while melanomas located on the limbs appear to have the best prognosis. Nevertheless, on Cox univariate analysis, the gender of the patients and primary tumor location were not associated with either PFS or OS.

Table 3. Cox univariate analysis of clinical prognostic factors.

	PFS			OS		
	HR	**95%CI**	***p* Value**	**HR**	**95%CI**	***p* Value**
Age	1.06	1.02–1.1	0.0053	1.07	1.02–1.13	0.0045
Gender (male)	1.81	0.65–5.17	0.2520	2.8	0.84–10.71	0.1017
Tumor location						
Limbs	Ref.					
Head and neck	2.54	0.35–13.03	0.2821	1.52	0.07–11.99	0.7187
Trunk	2.15	0.65–8.22	0.2211	2.4	0.63–11.36	0.2170
Acral skin	1.63	0.23–8.32	0.5738	1.11	0.05–8.67	0.9305

3.2. Histopathological Characteristics of the Study Population

3.2.1. The Depth and Width of Invasion

The mean Breslow depth for the pT3 melanomas included in this study was 2.941 mm and the median was 2.95 mm (range 2.1–3.9, 95%CI = 95.56%). The mean Breslow depth in patients with PFS was 2.73 mm and the median was 2.65 mm (range 2.1–3.75, 95%CI = 97.57%). The mean Breslow depth in patients with metastases was 3.41 mm and the median was 3.6 mm (range 2.2–3.9, 95%CI = 96.48%). The mean Breslow depth in patients who died during follow-up was 3.48 mm and the median was 3.6 mm (range 2.2–4, 95%CI = 98.83%) (Figure 3).

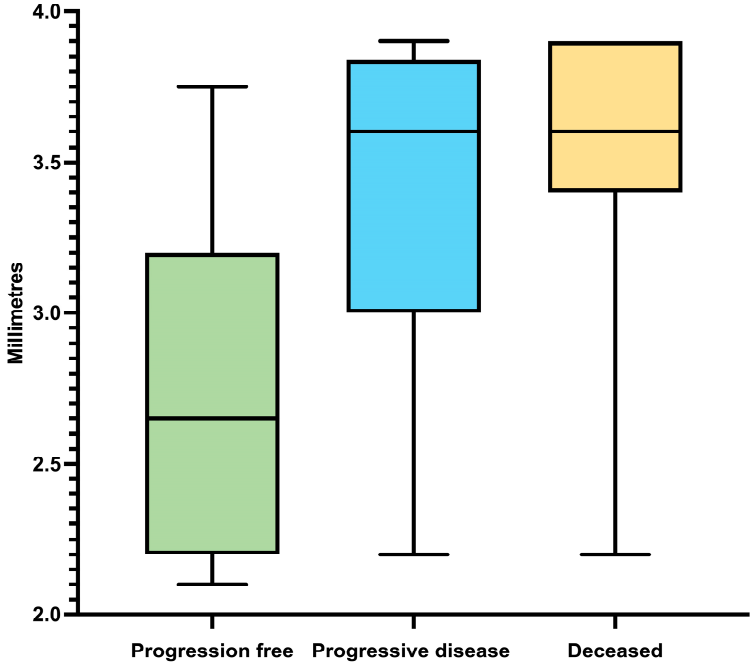

Figure 3. Breslow depth and patient outcome. The median, minimum, and maximum values are displayed. The depth of invasion is significantly associated with both progressive disease ($p = 0.0011$) and death ($p = 0.0034$).

The mean width of invasion in the whole study population was 6.76 mm and the median was 5 mm (range 1–19, 95%CI = 95.56%). The mean width of invasion in the group with PFS (n = 34) was 4.47 mm and the median was 4 mm (range 1–14, 95%CI = 97.57%). The mean width of invasion in cases with metastatic disease (n = 15) was 11.93 mm and the median was 12 mm (range 2–19, 95%CI = 96.48%). Additionally, the mean width of

invasion in patients who died during follow-up (n = 11) was 13.09 mm and the median was 12 mm (range 8–19, 95%CI = 98.83%) (Figure 4).

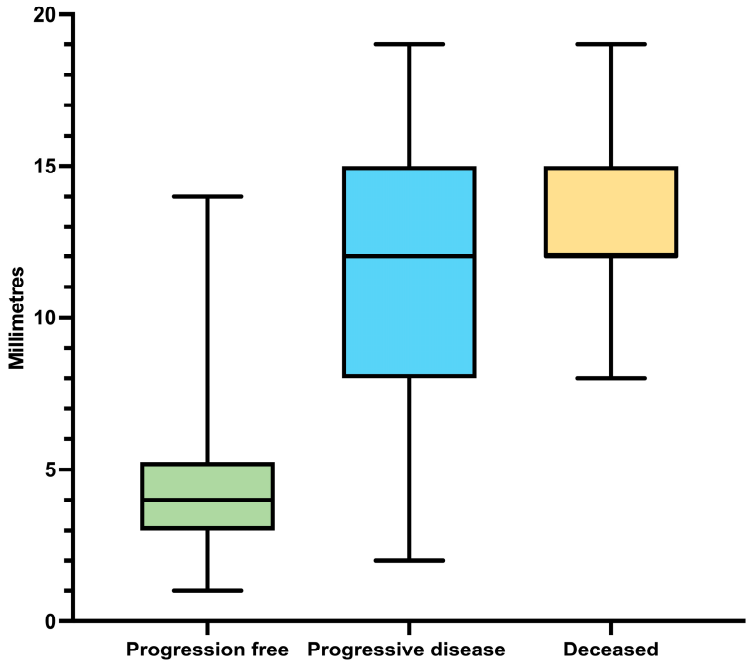

Figure 4. Width of invasion and patient outcome. The median, minimum, and maximum values are displayed. The width of invasion is significantly associated with progressive disease ($p < 0.0001$) and death ($p < 0.0001$).

The results of Cox univariate analysis for the depth of invasion and the width of invasion are presented in Table 3. The depth of invasion and the width of invasion are significantly associated with both PFS and OS on univariate analysis (Table 4).

Table 4. Cox univariate analysis of the depth and width of invasion.

	PFS			OS		
	HR	**95%CI**	***p* Value**	**HR**	**95%CI**	***p* Value**
Depth of invasion	6.8	2.4–24.8	0.0011	8.81	2.48–48.92	0.0034
Width of invasion	1.27	1.16–1.4	<0.0001	1.35	1.32–1.5	<0.0001

3.2.2. Mitotic Index

The mean mitotic index in the whole group was 5.14 and the median was 4 (range 1–21, 95%CI = 95.56%). The mean mitotic count in the PFS group was 5.12 and the median was 3.5 (range 1–21, 95%CI = 97.57%), while the mean mitotic index in patients with metastatic disease was 5.2 and the median was 5 (range 1–17, 95%CI = 96.48%). In deceased patients, the mean mitotic index was 5.64 and the median was 5 (range 1–17, 95%CI = 98.83%) (Figure 5).

Even though mitotic counts were slightly elevated in patients with metastatic disease and in patients who died during follow-up in comparison to patients without progressive disease, on Cox univariate analysis, this parameter was not associated with either PFS (HR = 1.007; 95%CI: 0.88–1.11; $p = 0.9015$) or OS (HR = 1.04; 95%CI: 0.9–1.16; $p = 0.5171$).

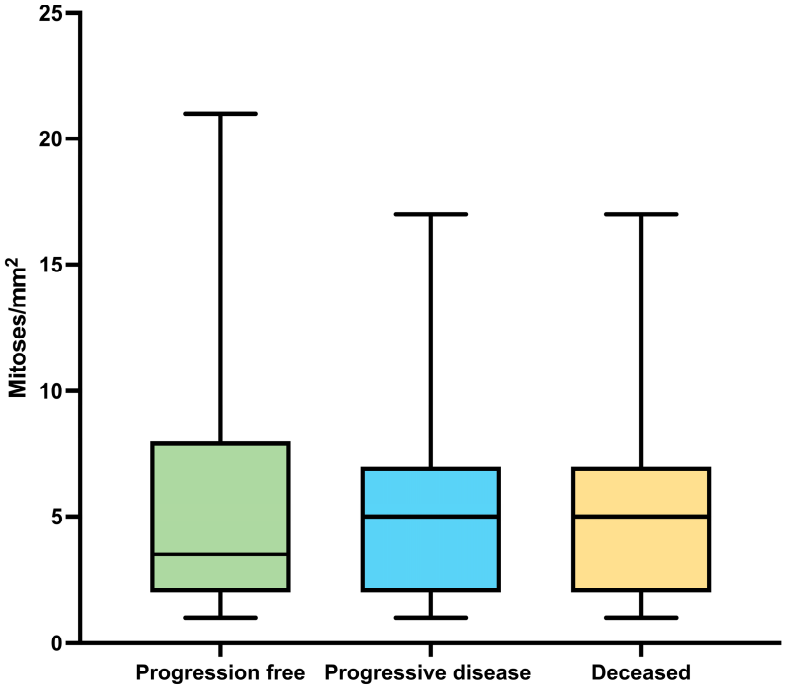

Figure 5. Mitotic counts and patient outcome. The median, minimum, and maximum values are displayed. The mitotic counts were not associated with either progressive disease (p = 0.9015) or death (p = 0.5171).

3.2.3. Ulceration, Regression, Microsatellites, Lymph-Vascular Invasion, and Perineural Invasion

On Cox univariate analysis, PFS was correlated with the microsatellites, lymphovascular invasion, and perineural invasion, but it was not correlated with ulceration or regression. However, both ulceration and regression were more frequently noted in patients with progressive disease (Table 5).

Table 5. Cox univariate analyses on the presence of ulceration, regression, microsatellites, lymphovascular invasion, neurotropism, and PFS.

	No Progression	Disease Progression	HR (95%CI)	p Value
Ulceration	44.12% (n = 15)	53.33% (n = 8)	1.35 (0.48–3.84)	p = 0.5666
Regression	11.76% (n = 4)	20.00% (n = 3)	1.513 (0.34–4.77)	p = 0.5214
Microsatellites	0% (n = 0)	26.67% (n = 4)	12.86 (3.24–45.19)	p < 0.0001
Lymphovascular invasion	8.82% (n = 3)	40.0% (n = 6)	5.57 (1.84–15.7)	p = 0.0013
Perineural invasion	8.82% (n = 3)	33.33% (n = 5)	3.99 (1.24–11.36)	p = 0.0122

On Cox univariate analysis, OS was correlated with the microsatellites, and perineural invasion, but it was not correlated with ulceration, lymphovascular invasion, or regression. Nevertheless, these features were more frequently observed in patients who died during follow-up (Table 6).

Table 6. Cox univariate analyses on the presence of ulceration, regression, microsatellites, lymphovascular invasion, neurotropism, and OS.

	Alive	Deceased	HR (95%CI)	*p* Value
Ulceration	47.37% (n = 18)	45.45% (n = 5)	0.97 (0.28–3.23)	$p = 0.9632$
Regression	10.53% (n = 4)	27.27% (n = 3)	2.5 (0.54–0.74)	$p = 0.1785$
Microsatellites	2.63% (n = 1)	27.27% (n = 3)	8.48 (1.76–32.96)	$p = 0.0029$
Lymphovascular invasion	15.79% (n = 6)	27.27% (n = 3)	2.07 (0.45–7.27)	$p = 0.2887$
Perineural invasion	10.53% (n = 4)	36.36% (n = 4)	3.96 (1.03–13.28)	$p = 0.0295$

3.3. Multivariate Analysis for PFS and OS

Cox multivariate analysis revealed that lymphovascular invasion and the width of invasion are independently associated with PFS. In contrast, the only factor independently associated with OS is the width of invasion (Table 7).

Table 7. Cox multivariate analysis for PFS and OS.

	PFS			OS		
	HR	**95%CI**	***p* Value**	**HR**	**95%CI**	***p* Value**
Age	1.04	0.96–1.15	0.3373	1.2	1.02–1.57	0.0787
Gender (male)	2.04	0.5–14.68	0.3794	14.22	0.03–11,769	0.3134
Location						
Limbs	Ref					
Head and neck	1.6	0.07–19.5	0.7345	2.03	0.0005–76,544	0.8447
Trunk	0.58	0.07–4.33	0.5761	30.82	0.21–10,036	0.1668
Acral skin	0.57	0.04–7.04	0.6637	6.17	0.0004–5719	0.5872
Depth of invasion	2.06	0.45–12.00	0.3746	28.09	0.14–8252	0.1891
Width of invasion	1.3	1.09–1.6	0.0057	2.08	1.28–10.96	0.0280
Mitoses	0.85	0.62–1.1	0.2753	1.35	0.63–3.375	0.4135
Ulceration	3.63	0.57–30.76	0.1947	0.01	0.81–20,607	0.1362
Regression	2.28	0.32–19.94	0.4038	25.01	8.328×10^{-6}–4.1	0.0911
Microsatellites	6.88	0.62–75.9	0.1099	7.56	0.0008–89,652,594	0.9967
Lymphovascular invasion	6.85	1.81–101.1	0.0153	0.06	8.463×10^{-9}–4.22	0.3341
Perineural invasion	1.19	0.19–12.41	0.8620	1.35	0.15–18,375	0.4005

3.4. Survival Analysis

Since the width of invasion was the strongest predictor for both PFS and OS, we analyzed the survival rates based on this parameter considering the following cut-off values: width < 5 mm, width between 5 and 10 mm, and width > 10 mm (Figure 6).

The mean follow-up time for the whole group was 64.41 months (median 60, range 16–120). The group with invasive width < 5 mm encompassed 27 patients, of which none died during follow-up. The group with invasive width between 5 and 10 mm encompassed 10 patients, out of which 20% (n = 2) died during follow-up. The median survival for this group was 80 months. Finally, there were 12 patients with invasive width > 10 mm, and 81.82% (n = 9) died during follow-up. The median survival time for this group was 27 months. These differences were highly significant ($p < 0.0001$, log-rank test).

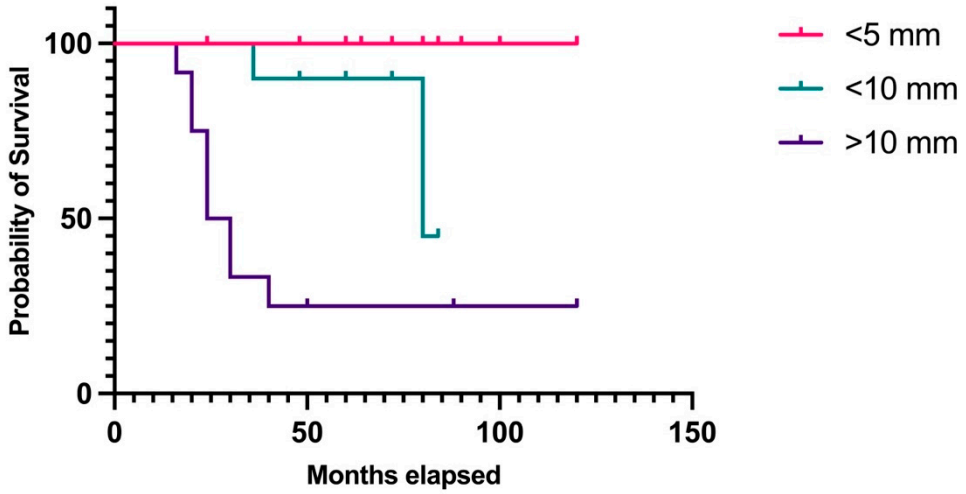

Figure 6. OS stratified by invasive width. The survival rate was 100% in patients with invasive width < 5 mm. Survival rates decreased to 80% in patients with invasive width between 5 and 10 mm and to 18.18% in patients with invasive width > 10 mm, while the median survival time also decreased significantly ($p < 0.0001$, log-rank test).

In order to properly envision the prognostic value of the width of invasion, a whole-slide image of a superficial spreading melanoma taken from a patient who developed widespread metastatic disease and subsequently died during follow-up is presented in Figure 7.

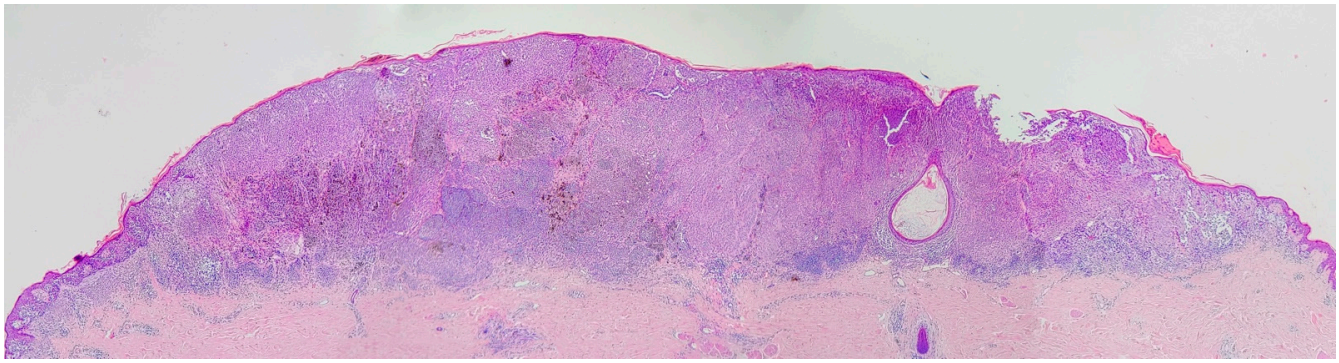

Figure 7. Whole-slide imaging of a superficial spreading melanoma with invasive width of 15 mm and depth of invasion of 3 mm (hematoxylin and eosin, 4× magnification). The patient was diagnosed with metastatic disease concomitant with the initial primary melanoma diagnosis and died 24 months later.

4. Discussion

During the follow-up time, 22.45% of the patients died, which is in concordance with data reported in the literature for pT3 cutaneous melanomas [12]. Among the clinical characteristics, age was the only factor correlated with both PFS and OS on univariate analysis, but not on multivariate analysis. Age is considered an important prognostic factor in melanomas. Still, the poor outcomes of elderly patients may be explained by factors unrelated to the tumor itself, such as age-related comorbidities [5]. Female gender has been associated with increased survival by some authors [19], while, as in our study, others found no correlation between gender and prognosis [20,21]. We found no correlation between the primary tumor location and PFS or OS, and a clear connection is still debatable. A poorer prognosis has been reported in acral locations [20] or the head and neck [22] in comparison to location on the extremities [23]. On the contrary, some studies demonstrated that head and neck location is an adverse prognostic factor only in elderly patients. In contrast,

tumor location does not seem to influence disease evolution in younger individuals [24]. Furthermore, other authors reported no association at all between tumor location and prognosis [25].

The presence of ulceration is used to stage melanomas according to the AJCC Cancer Staging Manual [11]. Interestingly, ulceration was more frequently noted in patients with progressive disease and in patients who died during follow-up, but these associations were not statistically significant. Similar results concerning the lack of association between ulceration and prognosis have been reported for thick cutaneous melanomas (Breslow > 4 mm) [26], and more studies would be beneficial for evaluating this parameter in intermediate-thickness melanomas.

Regression is a controversial parameter associated with both decreased and increased survival [16,27,28]. In the present study, the presence of regression was more often noted in patients with progressive disease and deceased patients than in patients without progressive disease, but the difference was not significant.

The presence of microsatellites was correlated with decreased PFS and OS on univariate analysis, and similar findings are reported in various other studies [15,25,29]. Similarly, perineural invasion was also associated with PFS and OS on univariate analysis. Nevertheless, the impact of perineural invasion on cutaneous melanoma prognosis has not been extensively studied, but recent evidence has shown this parameter to be a significant predictor for poor prognosis [26,29–31]. Therefore, the presence of perineural invasion should be reported as it is also a risk factor for local recurrence, and in some instances, treatment strategies may include wider excision margins and/or radiotherapy [11,32].

Interestingly, lymphovascular invasion was only correlated with PFS on univariate analysis. These results may seem surprising as lymphovascular invasion is widely regarded as an important prognostic factor for cutaneous melanomas [33]. Nevertheless, its predictive impact on pT4 cutaneous melanomas is questionable [34–36], and further studies are needed to better assess the relationship between lymphovascular invasion and pT3 cutaneous melanomas.

Mitotic counts are an important prognostic factor that should be reported according to the AJCC Staging Manual. Nonetheless, the impact of this parameter may vary based on tumor stage and it is no longer used for sub-classifying pT1 tumors [11]. Unexpectedly, in our study, there was no correlation between mitotic index and PFS or OS, even though mitotic figures tended to be slightly more numerous in patients with metastatic disease than in patients with PFS. Furthermore, the highest values were noted in patients who died during follow-up. Even though the lack of correlation between mitotic counts and prognosis might seem surprising, this might be explained by the fact that mitotic counts are correlated with Breslow depth [37]. Since the cases included in our study had similar Breslow depths, there was no significant variation in mitotic counts among the three groups, possibly explaining the unexpectedly insignificant differences. Additionally, mitotic counts have been shown to display significant interobserver variation, which further challenges the value of this parameter [38].

The Breslow depth of invasion is the most important prognostic factor in cutaneous melanomas as it is used for disease staging [39]. Nevertheless, within each particular stage based on Breslow depth, patient outcomes can vary significantly. For instance, in pT4 cutaneous melanomas, increasing Breslow depth continues to be correlated with PFS and OS [26,27,34,40]. For pT3 cutaneous melanomas (Breslow between 2 and 4 mm), we have demonstrated that increasing depth is correlated with PFS and OS on univariate analysis. This is an interesting finding as it could help improve our understanding of disease progression and subsequent staging of cutaneous melanomas.

Finally, the strongest and only independent factor correlated with PFS and OS in multivariate analysis was the width of invasion. Until now, there has been insufficient data regarding the prognostic role of microscopic tumor width in cutaneous melanomas. Various studies have tried to evaluate the macroscopic tumor width and correlated it with Breslow depth [41,42]. A few authors have reported that tumor size and tumor volume

can be regarded as independent prognostic factors and may even be superior to Breslow depth [43–45]. However, calculating tumor volume may be time-consuming and prone to interobserver variability as there is no standard for evaluating this parameter, and different authors have reported slightly different methods, also including macroscopic measurements [44,45]. Macroscopic and microscopic tumor dimensions may vary significantly, as shown by Bamford M. et al. in a study on 718 cutaneous melanomas. Both macroscopic and microscopic width of invasion are correlated with survival, but the microscopic analysis is superior in this instance. The median microscopic width was 3.7 mm smaller than the macroscopic width as the former only accounts for invasive width, without in situ lesions [18]. This measurement method was first reported in 2020 by Saldanha G. et al., who demonstrated that the microscopic measurement of tumor width is an independent prognostic factor for PFS and OS, in contrast to Breslow depth, which was not independently associated with any outcome [17]. Our study used the same method for reporting tumor width, and the results confirmed the findings reported by Saldanha G. et al. Furthermore, these authors also addressed the prognostic value of calculated tumor area (CTA), a two-dimensional feature approximating the area of invasive melanoma cells measured on the same slide used for reporting Breslow depth [46]. CTA is a strong independent prognostic factor, superior to Breslow depth [17,46]. Despite the promising results concerning tumor width and CTA, a 2023 study argues that these parameters are not superior to Breslow depth in predicting sentinel lymph node metastases and, hence, the overall outcome of the patients [47]. Additionally, calculating the tumor area is also time-consuming and may be affected by observer estimations. These disadvantages could be solved in the future with the help of digital pathology, as computer-assisted measurement of tumor area has been correlated with recurrence-free survival [48]. In the same context, another related novel parameter, Breslow density, has been shown to be superior to Breslow depth for estimating PFS and OS. Still, this method bears the same disadvantages as CTA: its calculation is tedious and dependent on the observer [49]. Therefore, at present, we believe that tumor width is a more valuable parameter as it is easily determined. Having considered everything, invasive width could become a precious prognostic factor in cutaneous due to its estimated strong association with patient outcome and straightforward estimation. Nevertheless, more studies on larger populations, integrating all stages of cutaneous melanoma, are required to fully validate these findings and potentially integrate the width of invasion in future disease staging.

In spite of the promising results presented in this paper, the study also has some limitations. One such restraint is that the cases included were limited to a single center. A future multi-center study would be beneficial in order to confirm these findings on a significantly higher number of patients. Another limitation is that this study focuses solely on histopathological features of the primary tumor and it does not address the predictive value of lymph node invasion. The patients were included in this study regardless of lymph node invasion due to the fact that over half of them did not benefit from a sentinel lymph node biopsy immediately after their melanoma diagnoses. The future study also intends to address this parameter.

At present, patients with pT3 cutaneous melanomas and lymph node metastasis (stage IIIB/IIIC) are usually treated with neoadjuvant therapy, which may also include BRAF/MEK inhibitors and immune modulators [50–52]. Nevertheless, not all pT3 cases undergo sentinel lymph node biopsy and even among those that do the positivity rate is around 11% [53]. Therefore, a significant number of pT3 CM patients remain untreated after surgical intervention. Still, the mortality rates in pT3 cases are much higher, as proven both by this study and other authors [12]. In this context, identifying high-risk patients regardless of lymph node status is of the utmost importance in order to choose the best therapeutic options. Assessing the width of the invasion may further increase the accuracy of identifying such patients.

5. Conclusions

Intermediate-thickness melanomas are potentially deadly entities requiring prompt identification of adverse prognostic factors to provide the best management for the patients. This study evaluates numerous features traditionally associated with cutaneous melanoma prognosis and a novel parameter, the width of invasion. We have shown that in pT3 tumors, increasing Breslow depth is a significant prognostic factor for PFS and OS, which may help redefine the way we stage cutaneous melanoma. Furthermore, this is one of the very few studies to address the impact of invasive width. We have demonstrated that this parameter is the sole independent prognostic factor for PFS and OS in pT3 cutaneous melanomas. This finding might open new perspectives for diagnosing and treatment of melanoma, which could ultimately lead to increased survival rates.

Author Contributions: Conceptualization, D.A.Ț. and M.C.; methodology, L.M.G. and M.C.; software, D.A.Ț.; validation, A.-A.G.-G. and A.V.D.; formal analysis, D.A.Ț., A.V.D. and A.M.C.; investigation, D.A.Ț. and L.M.G.; resources, M.C.; data curation, A.-A.G.-G. and A.M.C.; writing—original draft preparation, D.A.Ț. and L.M.G.; writing—review and editing, A.-A.G.-G.; visualization, A.V.D.; supervision, A.-A.G.-G.; project administration, M.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of University Emergency Hospital Bucharest (no. 17834/02 February 2012).

Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: All the data processed in this article are part of the research for a doctoral thesis, which is archived in the pathology department at the University Hospital of Bucharest where the interventions were performed. The original data are available upon reasonable request.

Acknowledgments: The authors wish to express their gratitude to Ionel Dandu, for the help provided in capturing the whole-slide image.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Whiteman, D.C.; Green, A.C.; Olsen, C.M. The Growing Burden of Invasive Melanoma: Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031. *J. Investig. Dermatol.* **2016**, *136*, 1161–1171. [CrossRef] [PubMed]
2. Khayyati Kohnehshahri, M.; Sarkesh, A.; Mohamed Khosroshahi, L.; HajiEsmailPoor, Z.; Aghebati-Maleki, A.; Yousefi, M.; Aghebati-Maleki, L. Current status of skin cancers with a focus on immunology and immunotherapy. *Cancer Cell Int.* **2023**, *23*, 174. [CrossRef] [PubMed]
3. Afshar, N.; Dashti, S.G.; Mar, V.; Te Marvelde, L.; Evans, S.; Milne, R.L.; English, D.R. Do age at diagnosis, tumour thickness and tumour site explain sex differences in melanoma survival? A causal mediation analysis using cancer registry data. *Int. J. Cancer* **2023**. *epub ahead of print*. [CrossRef] [PubMed]
4. Huang, J.N.; Yu, H.; Wan, Y.; Ming, W.K.; Situ, F.; Zhu, L.; Jiang, Y.; Wu, U.T.; Huang, W.E.; Chen, W.; et al. A prognostic nomogram for the cancer-specific survival of white patients with invasive melanoma at BANS sites based on the Surveillance, Epidemiology, and End Results database. *Front. Med.* **2023**, *10*, 1167742. [CrossRef] [PubMed]
5. Segura, S.; Podlipnik, S.; Boada, A.; Martí, R.M.; Sabat, M.; Yélamos, O.; Zarzoso-Muñoz, I.; Azón-Masoliver, A.; López-Castillo, D.; Solà, J.; et al. Melanoma-specific survival in worse in the elderly: A multicentric cohort study. *Melanoma Res.* **2023**, *33*, 532–538. [CrossRef] [PubMed]
6. Sharma, N.; Adhikari, R.C.; Sayami, G. Primary Cutaneous Melanoma in a Tertiary Hospital: A Retrospective Study. *J. Nepal. Health Res. Counc.* **2021**, *19*, 300–304. [PubMed]
7. Ferhatoglu, F.; Erturk, K.; Faruk, T. Cutaneous melanoma survival rates of the elderly are not worse than those of the young, yet they have some specific differences. *J. Cancer Res. Ther.* **2023**, *19*, S0. [CrossRef] [PubMed]
8. Walz, S.N.; Martineau, J.; Scampa, M.; Madduri, S.; Kalbermatten, D.F.; Oranges, C.M. Melanoma of the Lower Limbs and Hips: A Surveillance, Epidemiology, and End Results Analysis of Epidemiology and Survival 2000–2019. *Anticancer Res.* **2023**, *43*, 4105–4113. [CrossRef]

9. Pérez-Aldrete, B.M.; Matildes-Mariscal, J.B.; Gómez-Padilla, F.; Guevara-Gutiérrez, E.; Barrientos-García, J.G.; Hernández-Peralta, S.L.; Tlacuilo-Parra, A. Cutaneous melanoma in patients from western Mexico: Clinical pathology characteristics and their relationship to prognosis. *Australas. J. Dermatol.* **2019**, *60*, e298–e303. [CrossRef]
10. Ding, Y.; Jiang, R.; Chen, Y.; Jing, J.; Yang, X.; Wu, X.; Zhang, X.; Xu, J.; Xu, P.; LiuHuang, S.C.; et al. Comparing the characteristics and predicting the survival of patients with head and neck melanoma versus body melanoma: A population-based study. *BMC Cancer* **2021**, *21*, 420. [CrossRef]
11. Gershenwald, J.E.; Scolyer, R.A.; Hess, K.R.; Thompson, J.F.; Long, G.V.; Ross, M.I.; Lazar, A.J.; Atkins, M.B.; Balch, C.M.; Barnhill, R.L.; et al. *AJCC Cancer Staging Manual*, 8th ed.; Springer International Publishing: Cham, Switzerland, 2017; pp. 563–585.
12. Buja, A.; Bardin, A.; Damiani, G.; Zorzi, M.; De Toni, C.; Fusinato, R.; Spina, R.; Vecchiato, A.; Del Fiore, P.; Mocellin, S.; et al. Prognosis for Cutaneous Melanoma by Clinical and Pathological Profile: A Population-Based Study. *Front. Oncol.* **2021**, *11*, 737399. [CrossRef] [PubMed]
13. Mulder, E.E.A.P.; Johansson, I.; Grünhagen, D.J.; Tempel, D.; Rentroia-Pacheco, B.; Dwarkasing, J.T.; Verver, D.; Mooyaart, A.L.; van der Veldt, A.A.M.; Wakkee, M.; et al. Using a Clinicopathologic and Gene Expression (CP-GEP) Model to Identify Stage I-II Melanoma Patients at Risk of Disease Relapse. *Cancers* **2022**, *14*, 2854. [CrossRef] [PubMed]
14. Lee, T.L.; Liao, Y.H.; Liau, J.Y.; Sheen, Y.S. Risk factors of recurrence and distant metastasis in primary cutaneous melanoma in Taiwan. *Sci. Rep.* **2021**, *11*, 21012. [CrossRef] [PubMed]
15. Niebling, M.G.; Haydu, L.E.; Lo, S.N.; Rawson, R.V.; Lamboo, L.G.E.; Stollman, J.T.; Karim, R.Z.; Thompson, J.F.; Scolyer, R.A. The prognostic significance of microsatellites in cutaneous melanoma. *Mod. Pathol.* **2020**, *33*, 1369–1379. [CrossRef] [PubMed]
16. Aivazian, K.; Ahmed, T.; El Sharouni, M.A.; Stretch, J.R.; Saw, R.P.M.; Spillane, A.J.; Shannon, K.F.; Ch'ng, S.; Nieweg, O.E.; Thompson, J.F.; et al. Histological regression in melanoma: Impact on sentinel lymph node status and survival. *Mod. Pathol.* **2021**, *34*, 1999–2008, Erratum in *Mod Pathol.* **2021**, *34*, 2091. [CrossRef] [PubMed]
17. Saldanha, G.; Khanna, A.; O'Riordan, M.; Bamford, M. The width of invasion in malignant melanoma is a novel prognostic feature that accounts for outcome better than Breslow thickness. *Am. J. Surg. Pathol.* **2020**, *44*, 1522–1527. [CrossRef] [PubMed]
18. Bamford, M.; Udensi, L.; Khanna, A.; O'Riordan, M.; Saldanha, G. Comparison of the prognostic value of microscopically measured invasive width versus macroscopic width in cutaneous melanoma shows the superiority of microscopic invasive width measurement. *J. Cutan. Pathol.* **2022**, *49*, 536–542. [CrossRef]
19. Buja, A.; Rugge, M.; Damiani, G.; Zorzi, M.; De Toni, C.; Vecchiato, A.; Del Fiore, P.; Spina, R.; Baldo, V.; Brazzale, A.R.; et al. S. Sex Differences in Cutaneous Melanoma: Incidence, Clinicopathological Profile, Survival, and Costs. *J. Womens Health* **2022**, *31*, 1012–1019. [CrossRef]
20. Adams, B.E.; Peng, P.D.; Williams, M.L. Melanoma of the Foot Is Associated With Advanced Disease and Poorer Survival. *J. Foot Ankle Surg.* **2018**, *57*, 52–55. [CrossRef]
21. Li, S.; Yin, C.; Yang, X.; Lu, Y.; Wang, C.; Liu, B. Risk factors and predictive models for early death in patients with advanced melanoma: A population-based study. *Medicine* **2023**, *102*, e35380. [CrossRef]
22. Shannon, C.M.; Mehta, N.K.; Li, H.; Nguyen, S.A.; Koochakzadeh, S.; Elston, D.M.; Kaczmar, J.M.; Day, T.A. Anatomic Region of Cutaneous Melanoma Impacts Survival and Clinical Outcomes: A Population-Based Analysis. *Cancers* **2023**, *15*, 1229. [CrossRef] [PubMed]
23. Egger, M.E.; Bhutiani, N.; Farmer, R.W.; Stromberg, A.J.; Martin, R.C., 2nd; Quillo, A.R.; McMasters, K.M.; Scoggins, C.R. Prognostic factors in melanoma patients with tumor-negative sentinel lymph nodes. *Surgery* **2016**, *159*, 1412–1421. [CrossRef] [PubMed]
24. Mishra, K.; Barnhill, R.L.; Paddock, L.E.; Fine, J.A.; Berwick, M. Histopathologic variables differentially affect melanoma survival by age at diagnosis. *Pigment. Cell Melanoma Res.* **2019**, *32*, 593–600. [CrossRef] [PubMed]
25. Hwa Lee, S.; Ung Ha, G.; Ji Lee, H.; Yun Chung, H.; Huh, S.; Ha, D.L.; Duck Park, K.; Hyun Jang, Y.; Ju Lee, W.; Lee, S.J.; et al. Survival rates for invasive cutaneous malignant melanoma in South Korea in accordance with the Eighth edition AJCC Cancer Staging Manual: A retrospective single center study. *Indian. J. Dermatol. Venereol. Leprol.* **2023**, *28*, 1–7. [CrossRef] [PubMed]
26. Țăpoi, D.A.; Derewicz, D.; Gheorghișan-Gălățeanu, A.-A.; Dumitru, A.V.; Ciongariu, A.M.; Costache, M. The Impact of Clinical and Histopathological Factors on Disease Progression and Survival in Thick Cutaneous Melanomas. *Biomedicines* **2023**, *11*, 2616. [CrossRef] [PubMed]
27. Ribero, S.; Osella-Abate, S.; Sanlorenzo, M.; Balagna, E.; Senetta, R.; Fierro, M.T.; Macripò, G.; Macrì, L.; Sapino, A.; Quaglino, P. Sentinel Lymph Node Biopsy in Thick-Melanoma Patients (N=350): What is Its Prognostic Role? *Ann. Surg. Oncol.* **2015**, *22*, 1967–1973. [CrossRef] [PubMed]
28. Cintolo, J.A.; Gimotty, P.; Blair, A.; Guerry, D.; Elder, D.E.; Hammond, R.; Elenitsas, R.; Xu, X.; Fraker, D.; Schuchter, L.M.; et al. Local immune response predicts survival in patients with thick (t4) melanomas. *Ann. Surg. Oncol.* **2013**, *20*, 3610–3617. [CrossRef] [PubMed]
29. Bobos, M. Histopathologic classification and prognostic factors of melanoma: A 2021 update. *Ital J. Dermatol Venerol.* **2021**, *156*, 300–321. [CrossRef]
30. Namikawa, K.; Aung, P.P.; Gershenwald, J.E.; Milton, D.R.; Prieto, V.G. Clinical impact of ulceration width, lymphovascular invasion, microscopic satellitosis, perineural invasion, and mitotic rate in patients undergoing sentinel lymph node biopsy for cutaneous melanoma: A retrospective observational study at a comprehensive cancer center. *Cancer Med.* **2018**, *7*, 583–593.

31. Vița, O.; Jurescu, A.; Văduva, A.; Cornea, R.; Cornianu, M.; Tăban, S.; Szilagyi, D.; Micșescu, C.; Natarâș, B.; Dema, A. Invasive Cutaneous Melanoma: Evaluating the Prognostic Significance of Some Parameters Associated with Lymph Node Metastases. *Medicina* **2023**, *59*, 1241. [CrossRef]
32. Scolyer, R.A.; Rawson, R.V.; Gershenwald, J.E.; Ferguson, P.M.; Prieto, V.G. Melanoma pathology reporting and staging. *Mod. Pathol.* **2020**, *33*, 15–24. [CrossRef] [PubMed]
33. Matrakool, P.; Chaisrisawadisuk, S.; Vongviriyangkoon, T. Prognostic Factors and Outcomes of Cutaneous Malignant Melanoma: A 174-Patient Cohort Study in a Tertiary Hospital in Thailand. *Ann. Plast. Surg.* **2023**, *90*, 621–625. [CrossRef] [PubMed]
34. Blakely, A.M.; Cohen, J.T.; Comissiong, D.S.; Vezeridis, M.P.; Miner, T.J. Prognosis and Management of Thick and Ultrathick Melanoma. *Am. J. Clin. Oncol.* **2019**, *42*, 824–829. [CrossRef] [PubMed]
35. Bello, D.M.; Han, G.; Jackson, L.; Bulloch, K.; Ariyan, S.; Narayan, D.; Rothberg, B.G.; Han, D. The Prognostic Significance of Sentinel Lymph Node Status for Patients with Thick Melanoma. *Ann. Surg. Oncol.* **2016**, *23*, 938–945. [CrossRef] [PubMed]
36. Gyorki, D.E.; Sanelli, A.; Herschtal, A.; Lazarakis, S.; McArthur, G.A.; Speakman, D.; Spillane, J.; Henderson, M.A. Sentinel Lymph Node Biopsy in T4 Melanoma: An Important Risk-Stratification Tool. *Ann. Surg. Oncol.* **2016**, *23*, 579–584. [CrossRef] [PubMed]
37. Marsch, A.F.; McKee, R.M.; Werbel, T.; Ruo, B.; Hinds, B.R. The Relationship Between Epidermal Mitotic Density, Atypical Mitotic Figure Density, Breslow Depth, Ulceration, and Dermal Mitotic Rate in Cutaneous Melanoma: A Retrospective Cohort Study. *Int. J. Surg. Pathol.* **2021**, *29*, 592–599. [CrossRef] [PubMed]
38. Saldanha, G.; Ali, R.; Bakshi, A.; Basiouni, A.; Bishop, R.; Colloby, P.; Craig, P.; Da Forno, P.; Edward, S.; Espinosa de Los Monteros, O.; et al. Global and mitosis-specific interobserver variation in mitotic count scoring and implications for malignant melanoma staging. *Histopathology* **2020**, *76*, 803–813. [CrossRef]
39. Davis, L.E.; Shalin, S.C.; Tackett, A.J. Current state of melanoma diagnosis and treatment. *Cancer Biol. Ther.* **2019**, *20*, 1366–1379. [CrossRef]
40. Aguilar-Romero, E.; Chávez-Hernández, J.D.; Zepeda-Najar, C.; Salcedo-Hernández, R.A.; Lino-Silva, L.S. Prognostic variables in patients with thick melanomas. Analysis of 362 cases. *Gac. Med. Mex.* **2021**, *157*, 207–211. [CrossRef]
41. Moreno-Ramírez, D.; Ojeda-Vila, T.; Ríos-Martín, J.J.; Nieto-García, A.; Ferrándiz, L. Association between tumor size and Breslow's thickness in malignant melanoma: A cross-sectional, multicenter study. *Melanoma Res.* **2015**, *25*, 450–452. [CrossRef]
42. Crocetti, E.; Fancelli, L.; Caldarella, A.; Buzzoni, C. Thickness and diameter in melanoma: Is there a relation? *Tumori* **2016**, *102*, e1–e3. [CrossRef] [PubMed]
43. Ma, Q.; Suo, H.; Zhu, L.; Qian, Y.; Sun, X.; Xie, J.; Li, Q.; Fu, Y.; Li, J.; Tao, J. Prognostic significance of tumor size for primary invasive cutaneous melanoma: A population-based study, 2004–2016. *Cancer Med.* **2020**, *9*, 4561–4571. [CrossRef] [PubMed]
44. Voss, B.; Wilop, S.; Jonas, S.; El-Komy, M.H.; Schaller, J.; von Felbert, V.; Megahed, M. Tumor volume as a prognostic factor in resectable malignant melanoma. *Dermatology* **2014**, *228*, 66–70. [CrossRef] [PubMed]
45. Walton, R.G.; Kim, J.; Velasco, C.; Swetter, S.M. Tumor volume: An adjunct prognostic factor in cutaneous melanoma. *Cutis* **2014**, *94*, 226–230. [PubMed]
46. Saldanha, G.; Yarrow, J.; Elsheikh, S.; O'Riordan, M.; Uraiby, H.; Bamford, M. Development and Initial Validation of Calculated Tumor Area as a Prognostic Tool in Cutaneous Malignant Melanoma. *JAMA Dermatol.* **2019**, *155*, 890–898. [CrossRef] [PubMed]
47. Meves, A.; Todd, A.; Johnson, E.F. Tumor width and calculated tumor area do not outperform Breslow thickness in predicting sentinel lymph node biopsy positivity. *J. Am. Acad. Dermatol.* **2023**, *89*, 188–190. [CrossRef]
48. Rosenbaum, B.E.; Schafer, C.N.; Han, S.W.; Osman, I.; Zhong, H.; Brinster, N. Computer-assisted measurement of primary tumor area is prognostic of recurrence-free survival in stage IB melanoma patients. *Mod. Pathol.* **2017**, *30*, 1402–1410. [CrossRef]
49. Saldanha, G.; Yarrow, J.; Pancholi, J.; Flatman, K.; Teo, K.W.; Elsheik, S.; Harrison, R.; O'Riordan, M.; Bamford, M. Breslow Density Is a Novel Prognostic Feature That Adds Value to Melanoma Staging. *Am. J. Surg. Pathol.* **2018**, *42*, 715–725. [CrossRef]
50. Zhong, J.; Sun, W.; Hu, T.; Wang, C.; Yan, W.; Luo, Z.; Liu, X.; Xu, Y.; Chen, Y. Comparative analysis of adjuvant therapy for stage III BRAF-mut melanoma: A real-world retrospective study from single center in China. *Cancer Med.* **2023**, *12*, 11475–11482. [CrossRef]
51. Qin, Z.; Zheng, M. Advances in targeted therapy and immunotherapy for melanoma (Review). *Exp. Ther. Med.* **2023**, *26*, 416. [CrossRef]
52. Eggermont, A.M.M.; Blank, C.U.; Mandalà, M.; Long, G.V.; Atkinson, V.G.; Dalle, S.; Haydon, A.M.; Meshcheryakov, A.; Khattak, A.; Carlino, M.S.; et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): Distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol.* **2021**, *22*, 643–654. [CrossRef] [PubMed]
53. Johansson, I.; Tempel, D.; Dwarkasing, J.T.; Rentroia-Pacheco, B.; Mattsson, J.; Ny, L.; Olofsson Bagge, R. Validation of a clinicopathological and gene expression profile model to identify patients with cutaneous melanoma where sentinel lymph node biopsy is unnecessary. *Eur. J. Surg. Oncol.* **2022**, *48*, 320–325. [CrossRef] [PubMed]