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Impact of reducing the deep excision margin in the 5-year local and locoregional recurrence and 5-year overall and local recurrence-free survival of patients with primary cutaneous melanoma

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Abstract

Introduction: Wide local excision is the surgical treatment of election for primary cutaneous melanoma, but no practice guidelines recommend a specific depth of excision. Some studies suggest that resection of the deep muscular fascia is associated with an increased locoregional recurrence rate. The aim of this study is to compare the 5-year local and locoregional recurrence and 5-year overall and local recurrence-free survival rates of patients submitted to melanoma excision with a depth > 10 mm or ≤ 10 mm.

Methods: We performed a retrospective review of pathology, clinical and surgical records from the year of 2017 of the Multidisciplinary Skin Cancer Board in IPO Lisboa.

Results: A comparison between patient groups was not possible. However, in the group submitted to WLE with a depth ≤ 10 mm, we estimated 5-year local and locoregional recurrence rates of 12,2% and 41,5%, respectively. The 5-year overall and local recurrence-free survival rates were 70,7% and 93,1%, respectively.

Discussion: The inferior outcomes in this study compared to the literature are limited by selection bias and reduced statistical power. We suggest conducting additional research about the deep excision margin of melanoma until specific recommendations can be issued.

Keywords: melanoma; excision; margins; recurrence; survival.

Resumo

Introdução: A excisão local alargada é o tratamento cirúrgico de eleição do melanoma cutâneo primário, mas as diretrizes práticas não recomendam uma profundidade de excisão específica. Alguns estudos sugerem que a ressecção da fascia muscular profunda associa-se a um aumento da taxa de recidiva locoregional. Este estudo tem como objetivo comparar as taxas de recidiva local e locoregional a 5 anos e as taxas de sobrevivência global e sobrevivência livre de recidiva local a 5 anos de doentes submetidos a excisão local de melanoma com uma margem profunda > 10 mm ou $\leq$ 10 mm.

Métodos: Foi efetuada uma revisão retrospectiva dos registos patológicos, clínicos e cirúrgicos do ano de 2017 do Painel Multidisciplinar de Cancro Cutâneo do IPO Lisboa.

Resultados: A comparação entre os grupos de doentes não foi possível. No entanto, no grupo de doentes submetidos a excisão local alargada com margem profunda $\leq$ 10 mm, observámos uma taxa de recidiva local e locoregional a 5 anos de 12,2% e 41,5%, respetivamente. A taxa de sobrevivência global e sobrevivência livre de recidiva local a 5 anos foi de 70,7% e 93,1%, respetivamente.

Discussão: Os resultados deste estudo mostraram-se inferiores em comparação com a literatura, se bem que a sua interpretação é limitada por um viés de seleção e reduzido poder estatístico. Sugerimos a realização de estudos adicionais acerca da margem profunda de excisão do melanoma, de modo a que no futuro se possam formular recomendações específicas.

Palavras-chave: melanoma; excisão; margens; recidiva; sobrevivência**.**

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Introduction

Wide local excision (WLE) is the standard surgical treatment for primary cutaneous melanoma and comprises the removal of skin and subcutaneous tissue down to the level of the fascia at the site of the previous skin biopsy.(Barria & Mammen, 2022) The resulting pathology report describes the lateral and deep excision margins, which represent the smallest distance between the tumor border and the lateral and deep specimen edge, respectively. However, while the lateral excision margin has been a subject of extensive research and is defined in guidelines according to melanoma thickness, the current recommendations regarding the deep margin are somehow vague and based on few evidence.

The matters of the depth of excision and whether the fascia itself should be removed or not has been approached by few studies in the past, which yielded contradictory results. The first study concerning the deep margin reported an increased proportion of regional nodal recurrence following deep fascia resection (Olsen, 1964), while a subsequent study found no significant difference in the regional recurrence rate when the fascia was resected instead of conserved.(Kenady et al., 1982) For many years, the depth of melanoma excision remained a decision uniquely of the physician due to lack of consensus. Consequently, a significant variability in the depth of excision of thin ($\leq$ 1mm) invasive melanomas has been reported between physicians, with specialist non-dermatologists excising more frequently in greater depth and to the fascia than both specialist and non-specialist dermatologists.(DeFazio et al., 2010) These differences were not observed in the case of in situ and thick (> 1mm) melanomas.(DeFazio et al., 2010)

More recently, one study reported an increased in-transit and nodal locoregional recurrence after fascia resection.(Grotz et al., 2013) Other authors' research suggested that deep fascia resection does not lead to improved outcomes for patients with primary cutaneous melanoma thicker than 2 mm and therefore recommended its preservation.(Hunger et al., 2014) Also, a study assessing whether pathological excision margins influence the prognosis and survival of patients with 1,01 to 2,00 mm thick

primary melanoma found a positive association between an increasing deep margin and the local and in-transit recurrence-free survival.(Haydu et al., 2016) Despite these findings, until now no study has been able to recommend a specific excision depth, although a recent review concluded that the resection of the fascia itself does not lead to an improvement of locoregional recurrence or survival.(Barria & Mammen, 2022)

Furthermore, it needs to be taken into consideration that the thickness of the subcutaneous fat varies according to the location and that an excision down to the level of the muscular fascia leads to a larger defect, which is more prone to impaired wound healing.(Burger et al., 2022) Hence a proper in depth removal of both skin and subcutaneous tissue is more suitable in the case of lesions located on the trunk, limbs and scalp.(Katz, 2018)

In this study, our primary and secondary outcomes are to determine the 5-year local and locoregional recurrence rate, as well as the 5-year overall and local recurrence-free survival rate of patients with primary cutaneous melanoma of the trunk, arm or thigh submitted to WLE in our institution, respectively. A comparison of these outcomes will be made between the groups of patients with lesions excised with a deep margin > 10 mm or $\leq$ 10 mm. We expect to find no association between a reduced deep margin ($\leq$ 10 mm) and poorer survival and recurrence outcomes.

Methods

We performed a retrospective review of pathology and clinical records from the year of 2017 of the Multidisciplinary Skin Cancer Board in *IPO Lisboa* available in the program *SClinic®*. This is a board held by specialist dermatologists and surgeons for patients with skin tumors diagnosed through biopsy, which are then referred to our institution for treatment. For this study we selected patients diagnosed with primary cutaneous melanoma of the trunk, arm or thigh and submitted to WLE at our institution.

Data collection was carried out from January 1st, 2017, onwards and included only patients with melanoma diagnosed in 2017 or in previous years, in order to assure a follow-up period of $\geq$ 5 years. Data prior to 2017 is scarce, since at that time patient's records were not stored digitally, but only on paper. Follow-up comprised of appointments at our institution and, when adequate, imaging exams or further surgical procedures.

The collected patients characteristics included age, sex, number of melanomas, location of the tumor, histologic melanoma type (superficial spreading, nodular, lentigo maligna or other), pathologic T and N stage, occurrence of local or locoregional recurrence, systemic progression and survival. Patients with T4 stage melanoma were considered to have a high-risk tumor, while Tis and T1 - T3 stage lesions were considered low-risk. We defined locoregional recurrence as either nodal or in-transit, that is, in the regional lymph node group or between the primary melanoma and the regional lymph nodes, respectively. Included surgical data were performance of sentinel lymph node biopsy (SLNB) and lymphadenectomy.

The evaluated tumor variables were Breslow thickness, ulceration, number of mitosis, regression, lateral margin and deep margin. The follow-up period was calculated since the date of WLE until the last day of data collection, which was April 1st, 2023. Patients with two or more primary cutaneous melanomas were also included in the analysis, although in reduced numbers. Exclusion criteria were anatomical locations other than the trunk, arm or thigh, as well as history of non-cutaneous tumors, unless cured or in remission. Patients with insufficient pathology data or lost to follow-up were

excluded from the statistical analysis. The obtained patient and pathology variables and follow-up data were used to assess the outcomes of 5-year local and locoregional recurrence rate and 5-year overall and local recurrence-free survival of our patient sample.

The sample size was restricted by the number of patients followed at our institution at least since 2017 and which fulfilled the selection criteria mentioned above. Due to the size of the sample and to the fact that all patients were followed in one center, this study might be subject to a selection bias. Furthermore, loss to follow-up, missing data and measurement bias of the pathology variables are also significant sources of bias. Unfortunately, the group of patients with a lesion excised with a deep margin > 10 mm comprised of only 3 patients, hence the comparison between groups was unfeasible due to a too small sample size and this group was excluded from statistical analysis.

Categorical variables were handled using frequency and percentage, while numeric variables were summarized using mean, standard deviation, as well as minimal and maximal value. Statistical analysis was performed with the software IBM SPSS® Statistics. The 5-year local and locoregional recurrence rate and 5-year overall and local recurrence-free survival rates estimated in our study were compared to the available scientific literature.

Results

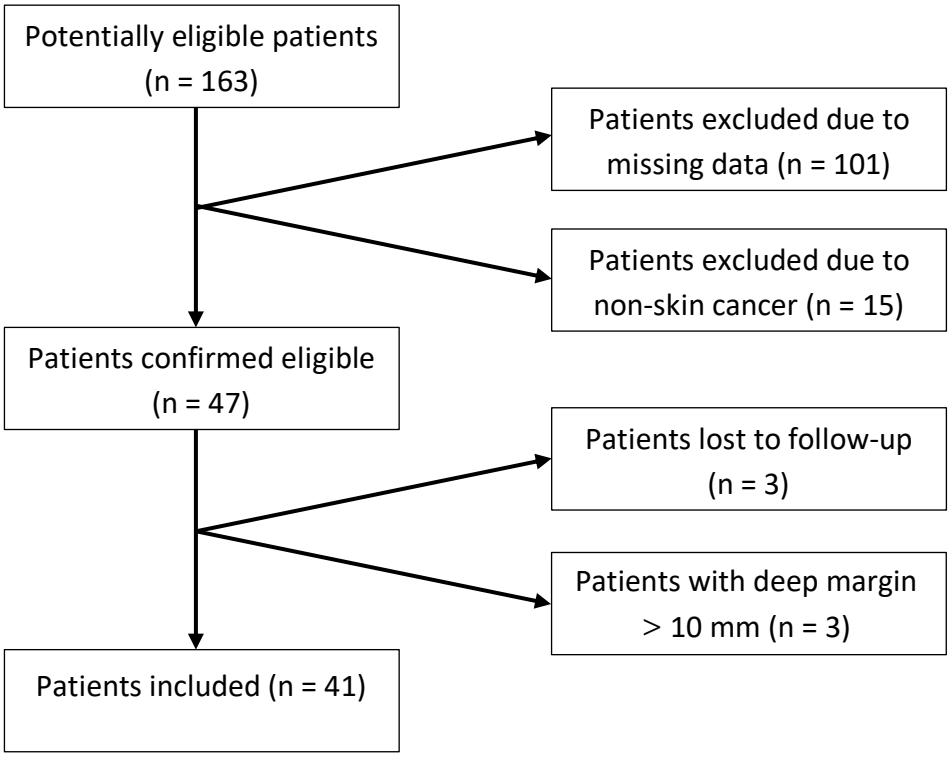

Figure 1. Study flow diagram

From 163 patients examined for eligibility, 101 were excluded due to missing data and 15 patients were excluded due to history of untreated non-cutaneous cancer. Patients with a missing deep margin value in the pathology report were excluded since this information is vital for the purpose of this study and is usually not included in the report, even when the other variables of interest were available.

A total of 47 patients were confirmed eligible, from which 3 patients were lost to follow-up, mainly because they were residents in districts other than Lisbon and preferred to be followed at a hospital closer to their residence, from which data is not accessible. Further 3 patients with a deep margin > 10 mm were excluded, since this group is too small to allow for a significant statistical comparison with the group of 41 patients with inferior excision depth. Thus, we analyzed 41 patients, from which 6 (14,6%) were diagnosed with two or more cutaneous melanomas each and 35 (85,4%) with only one melanoma. From the group of patients with multiple cutaneous melanomas diagnosed during or prior to 2017, it was only possible to analyze the data

of only one of the tumors for 5 patients due to missing pathology data of the remaining histology slides. Only 1 patient had enough available data to allow for the analysis of two lesions, therefore we included 42 cutaneous melanomas in the analysis. The mean follow-up period for our sample of patients was 60 months ($\bar{x}$ = 60,41; σ = 26,29).

From the 41 analyzed patients, the age average was 56 years of age (σ = 16,433) at the time of WLE, with the youngest patient being 30 and the oldest 87 years old. 19 patients (46,3%) were female and 22 patients (53,7%) were male. 28 lesions were located on the back (66,7%), 7 on the upper arm (16,7%), 4 on the thigh (9,5%), 2 on the anterior chest wall (4,8%) and 1 on the abdominal wall (2,4%).

The most frequent histologic melanoma types were superficial spreading melanomas in 30 cases (71,4%), followed by 9 nodular melanomas (21,4%) and 2 melanomas from other types (4,8%), from which 1 was an animal-type melanoma and the other a Spitzoid melanoma. No histologic subtype was reported for 1 lesion (2,4%).

Table 1. Age distribution

	N	Minimum	Maximum	Mean	Std. Deviation
Age	41	30	87	56,27	16,43

Table 2. Patient characteristics

		Frequency	Percent
Sex	Female	19	46,3
	Male	22	53,7
Location of lesion	Abdominal wall	1	2,4
	Anterior chest wall	2	4,8
	Back	28	66,7
	Arm	7	16,7
	Thigh	4	9,5
Histologic type	Superficial spreading	30	71,4
	Nodular	9	21,4
	Other	2	4,8

The Breslow thickness of the lesions varied between 0,28 mm and 18,30 mm and the average was 3,10 mm (σ = 3,14 mm). Breslow thickness was not reported in 1 case (2,4%). Ulceration was absent in 26 tumors (61,9%) and present in 15 tumors (35,7%). Ulceration was not evaluated in 1 case (2,4%). The number of mitosis ranged from 0 to 21, with a mean of 4 mitosis (σ = 5,26). Mitosis was not evaluated in 9 lesions (21,4%).

Table 3. Tumor characteristics: Breslow thickness, mitosis, lateral and deep margin

	N	Minimum	Maximum	Mean	Std. Deviation
Breslow thickness	41	0,28	18,3	3,10	3,14
Mitosis	33	0	21	4,12	5,26
Lateral Margin	41	0	12	2,88	2,29
Deep Margin	42	0,7	10	5,20	2,85

Regression was absent in 34 lesions (81%), present in 4 lesions (9,5%) and was not evaluated in 4 cases (9,5%). The lateral excision margin ranged from 0 mm until 12 mm, with an average of 2,88 mm (σ = 2,30 mm). The lateral excision margin was not reported for 1 patient (2,4%). The deep margin values of the 42 analyzed lesions ranged from 0,70 mm to 10 mm, with an average of 5,20 mm (σ = 2,85 mm).

Table 4. Tumor characteristics: pT staging, ulceration, regression, risk

		Frequency	Percent
pT Staging	T1a	6	14,3
	T1b	2	4,8
	T2a	8	19
	T2b	2	4,8
	T3a	6	14,3
	T3b	9	21,4
	T4a	3	7,1
	T4b	5	11,9
Ulceration	Absent	26	61,9
	Present	15	35,7
Regression	Absent	34	81
	Present	4	9,5
Risk	Low	9	21,4
	Intermediate	25	59,5
	High	7	16,7

6 lesions were staged as T1a (14,3%), 2 lesions as T1b (4,8%), 8 lesions as T2a (19,0%), 2 lesions as T2b (4,8%), 6 lesions as T3a (14,3%), 9 lesions as T3b (21,4%), 3 lesions as T4a (7,1%) and 5 lesions as T4b (11,9%). Regarding the risk stratification according to T stage, 9 patients (21,4%) were considered to have a low-risk tumor, 25 patients (59,5%) had an intermediate-risk tumor and 7 patients (16,7%) had a high-risk tumor. There was no T staging and risk classification reported for 1 case (2,4%).

Table 5. Local recurrence, locoregional recurrence and systemic progression

		Frequency	Percent
Local recurrence	No	36	87,8
	Yes	5	12,2
Locoregional recurrence	No	24	58,5
	Nodal	12	29,3
	In transit and nodal	5	12,2
Systemic progression	Absent	27	65,9
	Present	14	34,1

The estimated 5-year local recurrence rate for our sample of patients is 12,2% (n = 5), from which 3 patients initially presented with a stage T3a lesion and 2 patients had a stage T4b lesion. The remaining 36 patients (87,8%) presented no signs or pathology evidence of local melanoma recurrence.

33 patients (80,5%) were submitted to SLNB, while 8 patients (19,5%) were not. From the patients who performed SLNB, 12 patients (36,4%) had a positive sentinel lymph node (SLN) and 21 patients (63,6%) had a negative pathology result.

Lymphadenectomy was performed in 17 patients (41,5%), whilst 24 patients (58,5%) were not submitted to this surgical procedure. From the group of 17 patients submitted to lymphadenectomy, there were 12 positive pathology results (70,6%) and 5 negative results (29,4%).

The estimated 5-year locoregional recurrence rate in this study is 41,5% (n = 17), from which 12 patients (29,3%) presented with nodal recurrence and 5 patients (12,2%) presented with both nodal and in transit recurrence.

Systemic progression occurred in 14 patients (34,1%) and was absent in 27 cases (65,9%). Most patients presented with multiple distant metastasis sites. The most common locations of metastasis were the brain (n = 7; 50%), followed by the lung (n = 5; 35,7%), distant lymph nodes (n = 5; 35,7%), liver (n = 4; 28,6%), skin and subcutaneous tissue (n = 4; 28,6%), muscle (n = 2; 14,3%), bone (n = 2; 14,3%), adrenal glands (n = 1; 7,1%) and the retroperitoneum (n = 1; 7,1%).

Table 6. Sites of distant metastasis

	Metastasis sites		
	N	Percent	Percent of Cases
Brain	7	22,60%	50,00%
Lung	5	16,10%	35,70%
Skin or subcutaneous tissue	4	12,90%	28,60%
Muscle	2	6,50%	14,30%
Lymph nodes	5	16,10%	35,70%
Adrenal glands	1	3,20%	7,10%
Liver	4	12,90%	28,60%
Bone	2	6,50%	14,30%
Retroperitoneum	1	3,20%	7,10%

a. Dichotomy group tabulated at value 1.

At the end of the follow-up period, the estimated 5-year overall survival rate in our study sample was 70,7% (n = 29). 12 patients (29,3%) died during the follow-up period. The 5-year local recurrence-free survival rate was 93,1% (n = 27), having only 2 (6,9%) from the surviving patients presented a local melanoma recurrence.

Table 7. 5-year overall and local recurrence-free survival

		Frequency	Percent
5-year overall survival	Deceased	12	29,3
	Alive	29	70,7
5-year local recurrence-free survival	Local recurrence-free	27	93,1
	Local recurrence	2	6,9

Discussion

Since we were unable to compare the group of patients submitted to melanoma excision with a deep margin > 10 mm or ≤ 10 mm, the interpretation of our results is limited. Although initially 163 patients were eligible for this study, most of them had no documented deep margin in the pathology report since this is not a standard practice. Despite our request, a revision of the histological slides was not possible due to lack of capacity of the Pathology Department in our institution. Furthermore, the study sample is small and from only one center, which is a considerable source of bias in this study. We cannot provide an exact explanation regarding the size difference between groups, but we consider it might reflect the current WLE practice in our institution.

A recent study evaluated the risk of recurrence of 385 patients in which WLE specimens were excised either to the muscular fascia or mid/deep fat. The reported local recurrence rate after a follow-up period of approximately 47 months was of 8,1%, while no locoregional recurrence cases occurred.(Burger et al., 2022) A comparison with the estimated 5-year local recurrence rate of 12,2% in this study is however not reasonable due to different follow-up periods. It is also worth noting that a considerable proportion of local recurrence cases in our study were of high-risk T4b lesions. Furthermore, Burger et al. found no statistically significant association between depth of excision and recurrence.

In another trial with 964 patients in which 278 patients (29%) were submitted to a deeper resection, including the muscular fascia, the reported 5-year local recurrence rate was 6%, while the 5-year in-transit and nodal locoregional recurrence rates were 12% and 24%, respectively. In the remaining group of 686 (71%) of patients submitted to resection with preservation of the muscular fascia, the estimated 5-year local recurrence rate was 6% and the 5-year in-transit and nodal locoregional recurrence rates were 4% and 12%, accordingly.(Grotz et al., 2013) The reported outcomes of local and locoregional recurrence in both groups are comparably better than the ones achieved in this study, although the sample size could be a source of a selection bias. In addition, the authors found that excision of the deep muscular fascia was associated

with an increased risk of locoregional in-transit and nodal recurrence, but it had no association with local recurrence or overall survival.(Grotz et al., 2013)

The 5-year overall survival rate for cutaneous melanoma patients is underreported in the literature, with one study reporting a 5-year overall survival after WLE alone of 86,6% and after WLE plus SLNB of 87,1%.(Eggermont et al., 2014) In the UK, the reported age-standardized 5-year net survival for melanoma patients between 2010-2012 was of 93% for women and 86% for men.(National Collaborating Center for Cancer (UK), 2015) In comparison, our findings show an increased mortality in this study sample, with a 5-year overall survival rate of only 70,7%, which once again might be due to a selection bias.

Regarding the 5-year local recurrence-free survival of cutaneous melanoma patients, we found no other studies reporting this outcome. The validity of our study results is however limited due to the reasons already mentioned above.

Studies regarding the depth of excision of cutaneous melanoma are still underrepresented in the literature, however some studies suggest an association between fascia resection and worse local and locoregional recurrence outcomes. We recommend that further clinical trials with larger sample sizes are conducted before specific recommendations about the deep excision margin of melanoma can be issued.

Conclusion

This is the first retrospective study from a Portuguese institution reporting on melanoma survival and recurrence outcomes after WLE with a reduced deep excision margin. Although the main objective of this study could not be fulfilled due to an inadequate sample size, by comparing our results with previous studies we estimated a slightly inferior overall survival rate and higher local and locoregional recurrence rates in our patient group. The relatively higher local recurrence rate in our study might be related to the proportion of patients who presented initially with a high-risk stage T4b lesion. However, the interpretation of these outcomes is limited due to a possible selection bias and reduced statistical power.

We recommend including the deep excision margin in the biopsy and WLE pathology reports of cutaneous melanoma patients, especially for locations that allow deeper resection margins such as the trunk and proximal limbs. Although some studies report an increased local and locoregional recurrence rate associated to deep fascia resection, we suggest that additional studies emphasizing the importance of the deep excision margin of cutaneous melanoma should be performed in order to issue a practice guideline in the future.

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