Dermatology Practical & Conceptual

The Frequency of Microsatellite Metastases, Satellite Metastases, and Residual Tumor in Thin Melanomas: A Retrospective Cohort Study

Ebba Wennberg[1,2], Rudy Bittar[1], Helena Svensson[1,2], John Paoli[2]

1 Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden
2 Region Västra Götaland, Sahlgrenska University Hospital, Department of Dermatology and Venereology, Gothenburg, Sweden

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Corresponding Author: John Paoli, M.D., Professor. Department of Dermatology, Gröna stråket 16, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden. ORCID ID: 0000-0003-1326-8535. E-mail: john.paoli@vgregion.se

ABSTRACT

Introduction: Thin invasive melanomas (Breslow thickness ≤1.0 mm) are increasing in incidence in Sweden, but notably also have a favorable prognosis. Treatment typically involves complete diagnostic excision followed by wide local excision (WLE) to eliminate potential microsatellite and satellite metastases along with residual melanoma.

Objectives: This study aimed to investigate the frequency of microsatellite and satellite metastases in diagnostic excision specimens and residual melanoma in WLE specimens from thin melanomas.

Methods: This was a retrospective cohort study including consecutively collected primary thin melanomas excised at Sahlgrenska University Hospital (Gothenburg, Sweden) between January 2014 and December 2020.

Results: Among 1,012 cases, no microsatellites were observed in the diagnostic excisions. Meanwhile, macroscopic satellite metastases were only present in 0.2% of the cases (N=2). Among 887 melanomas undergoing WLE with available data (87.6%), no microsatellites or satellite metastases were found in the extra tissue removed. Of the completely excised melanomas (N=936, 92.5%), only 0.2% (N=2) exhibited residual melanoma in the WLE.

Conclusions: Our findings align with previous studies suggesting that WLE may result in excessive and unnecessary treatment for completely excised thin melanomas. The requirement of performing WLEs following complete excision of thin melanomas needs to be reevaluated.

Introduction

Cutaneous melanoma is increasingly prevalent in Sweden, emerging as the third most frequently diagnosed cancer type in males and the fourth among females in 2022, a year in which over 5,400 new cases of invasive melanoma and over 7,300 cases of melanoma in situ were reported [1,2]. In invasive melanoma, the Breslow thickness correlates with mortality rates, with thicker melanomas generally having poorer prognosis [3]. Thin invasive melanomas (Breslow thickness ≤1.0 mm), which constitute about 65% of all diagnosed invasive melanomas in Sweden, exhibit excellent prognosis, with 5-year and 10-year melanoma-specific survival rates of 98.3% and 96.7%, respectively [4]. Traditionally, surgical approaches for melanoma involve a 2-step procedure: diagnostic excision followed by wide local excision (WLE). WLE aims to eliminate potential microsatellites and residual melanoma, which in theory would prevent locoregional recurrence and improve survival [5]. However, recent research questions the necessity of WLE for thin invasive melanomas, given their favorable prognosis, minimal risk of microsatellitosis, and low rates of residual melanoma found in WLE tissue specimens [6-8]. Moreover, postoperative complications are not uncommon, with 25% of patients with thin invasive melanomas undergoing WLE experiencing issues related to wound healing, scarring, and anxiety compared to 0% in a control group undergoing only diagnostic excisions [9].

Objectives

The primary objective of this study was to investigate the frequency of satellite and microsatellite metastases in the diagnostic excision specimens and residual melanoma in the WLE specimens of thin melanomas.

Methods

Patients

This was a retrospective cohort study including consecutively collected primary thin melanomas (Breslow thickness ≤1.0 mm) excised at Sahlgrenska University Hospital (Gothenburg, Sweden) between January 2014 and December 2020. Data from the diagnostic and subsequent wide local excisions (WLE) were collected. Diagnostic excision was defined as the initial excision aiming to completely remove the lesion. The exclusion criteria were lesions treated with curettage or shave biopsy, lesions initially diagnosed with a punch biopsy without data regarding the WLE, lesions with Breslow thickness ≤1.0 mm in the punch biopsy but exceeding 1.0 mm in the subsequent WLE as well as recurrent melanomas. Melanomas were identified at the hospital's Department of Pathology using SNOMED code M87203 and filtered using 'pT1a' and 'pT1b' to exclude melanoma in situ and invasive melanoma with a Breslow thickness >1.0 mm.

Data Collection Procedure

The data collected included patient characteristics (sex and age), clinical details (tumor diameter, localization, presence/absence of satellite metastases, and clinical excision margins), and histopathological information (melanoma subtype, Breslow thickness, presence/absence of ulceration, mitosis, regression or microsatellite metastases using the diagnostic excision samples, and residual melanoma using the WLE tissue samples). Instances where melanomas were initially excised with wide clinical margins without a subsequent WLE were considered diagnostic excisions. For such cases, data regarding residual melanoma could not be assessed.

Melanoma Characteristics

Melanoma subtypes included superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), acral lentiginous melanoma (ALM), nevoid melanoma, spitzoid melanoma, desmoplastic melanoma, and others (i.e., difficult to classify). Tumor diameter represented the maximum lesion diameter, sourced from pathology reports if missing in referral or medical records. Breslow thickness was approximated to the nearest decimal. In cases of punch biopsy or excision, the largest Breslow thickness from either biopsy or diagnostic excision was recorded. Clinical excision margins were documented as the narrowest measurement, rounding down if reported as an interval. For punch excisions of smaller lesions, the clinical excision margin was estimated assuming perfect centering (e.g., 2 mm margins if a lesion with a maximum diameter of 4 mm was excised with an 8-mm punch). Histopathological margins were rounded to the nearest decimal.

Statistical Analysis

The obtained data was analyzed using R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). Only descriptive statistics were used due to the limited number of events.

Results

The pathology registry search identified 1,857 melanoma cases. Excluding melanoma in situ and invasive melanomas with a Breslow thickness >1.0 mm left 1,075 thin melanomas. After applying the exclusion criteria, 1,012 cases were included in the analyses (Figure 1). The 1,012 cases of thin melanoma included in this study were identified across 963 patients, among whom 54.5% were females. The median age of the patients was 65.6 years (range 19 to 99 years). Table 1 illustrates categorical clinicopathological characteristics

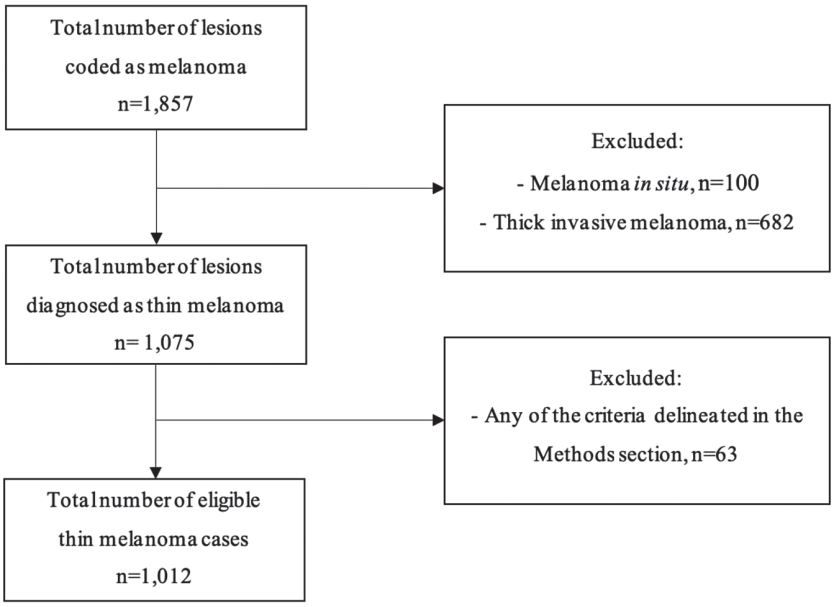

Figure 1. Flowchart illustrating the inclusion and exclusion process.

Table 1. Categorical clinicopathological characteristics.

Clinical characteristics	Total (%) N=1,012	95% CI
Localization:		
Trunk	453 (44.8%)	41.7-47.9
Lower extremities	217 (21.4%)	19.0-24.1
Upper extremities	190 (18.8%)	16.4-21.3
Head & neck	118 (11.7%)	9.7-13.8
Feet/toes	17 (1.7%)	1.0-2.7
Buttocks/genitals	12 (1.2%)	0.6-2.1
Hand/fingers	5 (0.5%)	0.2-1.1
NA	0 (0.0)	0.0-0.4
Prescence of satellite metastases:		
Yes	2 (0.2%)	0.02-0.7
No	1009 (99.7%)	99.1-99.9
NA	1 (0.1%)	0.0-0.5
Histopathological characteristics	Total (%) N=1,012	95% CI
Melanoma subtype:		
SSM	737 (72.8%)	70.0-75.5
Other	168 (16.6%)	14.4-19.0
LMM	73 (7.2%)	5.7-9.0
ALM	12 (1.2%)	0.6-2.1
Nevoid	12 (1.2%)	0.6-2.1
NM	7 (0.7%)	0.3-1.4
Spitzoid	3 (0.3%)	0.1-0.9
Prescence of ulceration:		
Yes	23 (2.3%)	1.4-3.4
No	988 (97.6%)	96.5-98.5
NA	1 (0.1%)	0.0-0.5
Presence of mitosis:		
Yes	223 (22.0%)	19.5-24.7
No	781 (77.2%)	74.5-79.7
NA	8 (0.8%)	0.3-1.6

Table1 continues

Table 1. Categorical clinicopathological characteristics. *(continued)*

Histopathological characteristics	Total (%) N=1,012	95% CI
Signs of regression:		
Yes	188 (18.6%)	16.2-21.1
No	816 (80.6%)	78.1-83.0
NA	8 (0.8%)	0.3-1.6
Complete diagnostic excision:		
Yes	936 (92.5%)	90.7-94.0
No	55 (5.4%)	4.1-7.0
NA	21 (2.1%)	1.3-3.2
Prescence of microsatellite metastasis in diagnostic excision:		
Yes	0 (0.0%)	0.0-0.0
No	1011 (99.9%)	99.5-100
NA	1 (0.1%)	0.0-0.5
Prescence of microsatellite metastasis in WLE:		
Yes	0 (0.0%)	0.02-0.7
No	887 (87.6%)	85.5-89.6
NA	125 (12.4%)	10.4-14.5
Melanoma remnants in WLE despite complete diagnostic excision:		
Yes	2 (0.2%)	0.02-0.71
No	934 (92.3%)	90.5-93.9
NA	76 (7.5%)	6.0-9.3

Abbreviations: ALM = acral lentiginous melanoma; CI = confidence interval; LMM = lentigo maligna melanoma; NA = data not available; NM = nodular melanoma; SSM = superficial spreading melanoma; WLE = wide local excision.

Table 2. Numerical clinicopathological features.

Variables	Median (range)	Mean	SD	95% CI
Tumor diameter (mm)	10 (2-85)	11.04	6.5	10.6-11.4
Breslow thickness (mm)	0.6 (0.2-1)	0.57	0.20	0.56-0.58
Clinical surgical margins (mm)	5 (0.5-10)	4.6	2.2	4.5-4.8
Histopathological margins (mm)	3 (0.1-20)	3.2	1.8	3.1-3.3

Abbreviations: CI = confidence interval; SD = standard deviation.

Table 3. Characteristics of the thin melanomas with satellite metastases.

Case	Sex	Histopatho-logical subtype	Diameter (mm)	Localization	Breslow (mm)	Histopatho-logical characteristics	Clinical margin (mm)	Histopatho-logical margin (mm)
1	Male	Other	NA*	Trunk	0.8	Mitosis	5	5.0
2	Female	LMM*	17	Head and neck	0.6	Regression	NA*	1.0

Abbreviations: LMM = lentigo maligna melanoma; NA = data not available.

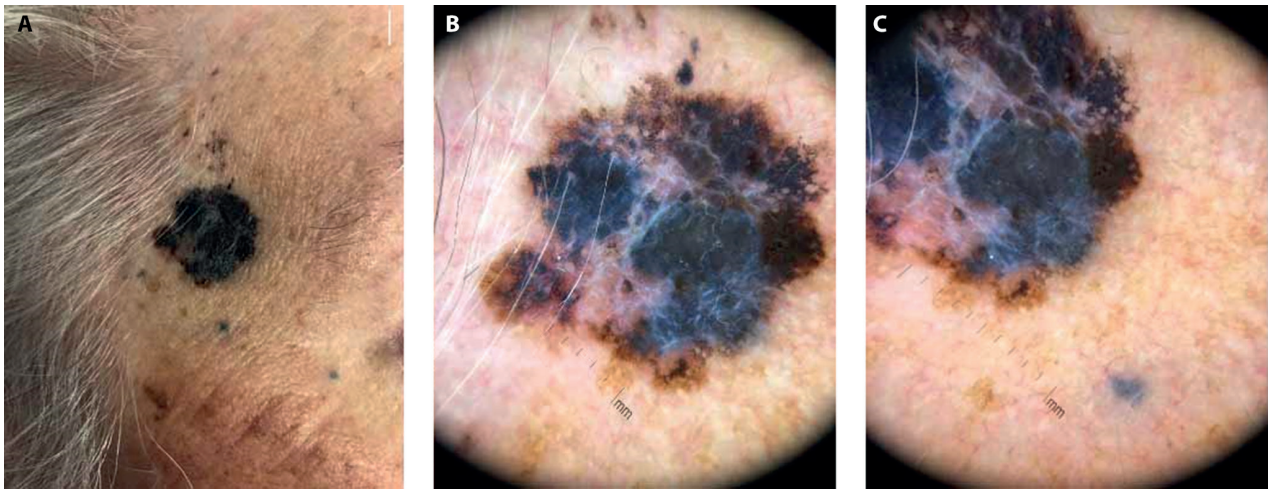

Figure 2. A case of thin melanoma with satellite and in-transit metastases. (A) Macroscopic view and (B, C) dermoscopic views of the lesion and a few of the satellite metastases.

Table 4. Characteristics of the cases with residual melanoma following complete diagnostic excision.

Case	Sex	Histopathological subtype	Diameter (mm)	Localization	Breslow (mm)	Histopathological characteristics	Clinical margin (mm)	Histopathological margin (mm)
1	Male	Other, similar to nevoid melanoma	14	Trunk	0.6	Regression	5	2.0
2	Female	SSM*	35	Head and neck	0.8	Ulceration and mitosis	2	1.0

Abbreviation: SSM = superficial spreading melanoma.

of the included melanomas. The great majority of the thin melanomas were located outside of the head and neck area (N=894, 88.3%). Only two cases (0.2%) exhibited macroscopic satellite metastases. Regarding the histopathological characteristics, SSM was the predominant subtype (72.8%), ulceration was rare (2.3%), while mitoses (22.0%) and regression (18.6%) were more common. No microsatellite metastases were found in any of the 1,011 diagnostic excision specimens nor in the 887 WLE specimens (87.6%) with available data. Among the 991 melanomas with data on complete/incomplete diagnostic excision, 55 were incompletely excised, resulting in an incomplete excision rate of 5.5%. Among the 936 completely excised melanomas, two (0.2%) showed residual tumor in the WLE specimens. Among the 21 cases lacking data regarding the complete/incomplete histopathological margins of the diagnostic excision, none exhibited residual melanoma in the WLE specimens. Table 2 outlines numerical clinicopathological characteristics regarding tumor diameter, Breslow thickness, clinical surgical margins used, and histopathological margins obtained. Table 3 describes the characteristics of the two cases with macroscopic satellite metastases. The first case involved a 49-year-old male with a lesion on the trunk with a single satellite metastasis measuring 1.2 mm in diameter, located approximately 3 mm from the primary tumor. This patient also had a positive sentinel lymph node biopsy. The second case involved an 83-year-old female with a lesion on the temple with multiple macroscopic satellite and in-transit metastases (Figure 2).

Table 4 describes the characteristics of the two cases with residual melanoma despite complete excision during the diagnostic excision. In the first case, residual invasive melanoma with a Breslow thickness of 0.4 mm was found in the WLE specimen, despite a 2.0 mm histopathological margin observed in the diagnostic excision specimen. The second case showed melanoma in situ in the WLE despite a 1.0 mm histopathological margin following the diagnostic excision.

Conclusions

Our study benefitted from the inclusion of all consecutive cases of thin melanoma over a 7-year period, totaling more

than 1,000 lesions. Only two cases with satellite metastases were observed among the 1,012 diagnostic excision specimens included for analysis; no microsatellite metastases were found in any of the diagnostic excision specimens nor in the WLE specimens for which data were available. Among the completely excised diagnostic excision specimens, only two were identified as having residual melanoma in the WLE. Our research findings align with the few previous studies on the frequency of microsatellite metastases in thin melanoma. In a larger retrospective cohort study on the prognostic role of microsatellites in melanoma, Riquelme-McLoughlin et al. observed only two cases with microsatellites among 2,359 thin melanomas (0.1%), which is consistent with our results [10]. Similarly, Kelly et al. found no microsatellite metastases in 93 thin melanomas [11]. Azimi et al. reported 54 cases of satellite metastases among 1,865 cases of melanoma with a Breslow thickness ≥0.75 mm (2.9%), but only 84 of the melanomas were thin and data regarding microsatellitosis for these specific cases were not available [12]. In a retrospective cohort study, Shaikh et al. found one case of microsatellitosis among 167 (0.6%) thin melanomas [13]. Finally, Day Jr et al. reported no microsatellites in 168 melanomas with a Breslow thickness ≤0.75 mm. In the same study, seven of 144 melanomas (4.9%) with a Breslow thickness of 0.76-1.50 mm had microsatellites, but the authors did not specify if any of these cases belonged to the thin melanoma subgroup (i.e., 0.76-1.0 mm) [14]. In our study, the frequency of residual melanoma in WLE despite complete diagnostic excision was only 0.2%, which was lower than in previous studies. For instance, Jackett et al. observed a frequency of 1.6% among 255 thin melanomas [15], and Bolshinsky et al. reported a frequency of residual melanoma in 34 of 807 melanomas with a median Breslow thickness of 1.05 mm (4.2%), with lentigo maligna melanoma subtype shown to be a risk factor for residual melanoma upon multivariate analysis [8]. Since their study included thicker melanomas, direct comparisons are challenging. The two lesions with residual melanoma in our study both had relatively large diameters (14 mm and 35 mm, respectively), surpassing the cohort's median diameter of 10 mm. This aligns with the study by Jackett et al., in which the median lesion diameter in cases with residual melanoma was 14 mm [15]. Bolshinsky et al. also noted a higher frequency of residual melanoma on the head and neck, consistent with one of our cases occurring on the scalp [8].

The current surgical approach for thin invasive melanomas with diagnostic excision followed by WLE is becoming more questioned given their favorable prognosis, the minimal risk of microsatellitosis, and low rates of residual melanoma found in WLE tissue specimens [6-8]. In an article from 2019, Weyers advocated for personalized excisions of melanoma, highlighting the necessity for a paradigm shift considering the current era of personalized medicine [16]. He further argued that the current surgical treatment method is based on several misconceptions, such as the belief that an extended excision would improve survival. Zijlker et al. also questioned if there is any benefit in continuing the practice of routine WLEs for melanoma [5]. They emphasized that the 2-step approach involving diagnostic excision followed by WLE is not used for other solid tumors such as colorectal and breast cancer, for which a single surgical procedure aiming for complete excision with tumor-free margins is deemed sufficient. In a retrospective Dutch study, no significant difference was seen in overall survival after adjusting for age, sex, Breslow thickness, and tumor location in 182 melanoma patients not undergoing WLE compared to 282 controls [17]. In two studies with large cohorts comparing outcomes for melanoma patients treated with WLE or Mohs micrographic surgery, in which very narrow histopathological margins are deemed sufficient, higher overall survival was observed in melanomas in the head and neck area, and no significant difference in overall survival was observed on the trunk or extremities [18,19]. Dermatopathologists typically examine only one tissue section when analyzing WLE specimens, potentially resulting in overlooked residual melanoma and microsatellite metastases, which may occur beyond the clinical margin used in WLEs, potentially impacting detection. In our cohort, 125 cases lacked WLE data, potentially affecting the accuracy in determining the frequency of microsatellite metastases and residual melanoma in WLEs.

In summary, microsatellite and satellite metastases as well as residual melanoma despite initial reporting of a complete diagnostic excision are exceptionally infrequent findings in thin melanomas. Our study suggests that fewer than one out of every 500 thin melanomas will exhibit satellite metastases, highlighting their relatively low frequency in this subset. Our results also imply that patients with thin melanoma may be subjected to unnecessary WLEs. To delve deeper into this issue, our group has planned a randomized clinical trial to compare recurrence rates and melanoma-specific survival with and without WLE in patients with thin melanoma, the "Wise or wide" (WoW) study (https://clinicaltrials.gov/study/NCT06363591) [20].

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