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Clinical-Dermoscopic and Histopathologic Markers of Metastatic Risk in Early-Stage Thin Melanoma

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ABSTRACT

Although considered early lesions, thin cutaneous melanomas still account for a notable portion of melanoma-related deaths, and their incidence continues to rise. We carried out a retrospective case-control analysis to determine which clinical-dermoscopic and histologic variables correlate with local or distant spread in melanomas measuring ≤0.8 mm. Records from 1 January 2000 through 22 June 2022 were reviewed from two specialized Italian dermatologic oncology centers. Sixteen individuals with metastasizing ≤0.8 mm melanomas were compared with controls who remained metastasis-free for at least 5 years. Statistical testing used Pearson's chi-square or Fisher's exact test. Out of 1396 eligible melanomas, 1.1% eventually metastasized. The median age at diagnosis was 49 years (range 28-83), with 56.3% male and 43.7% female. Tumors most often arose on the trunk (43.7%). Clinically, lesions were predominantly pigmented and frequently >10 mm (73.3%) with ≥3 hues (80%). Dermoscopy most commonly showed white areas (73.3%), atypical vascular structures (66.5%), blue-gray zones (60%), and an absent pigment network (60%). Histopathology revealed universally unfavorable traits, including regression (87.4%), mitoses within the dermis (50%), vertical growth (62.5%), and ulceration (12.5%). All of these differed significantly from controls ($p < 0.05$). For melanomas ≤0.8 mm, certain clinical and dermoscopic indicators, when combined with adverse tissue findings, may point toward a greater chance of metastatic behavior.

Keywords: Dermatoscopy, Dermoscopy, Skin cancer, Early-stage melanoma, Tumor thickness, Metastasis

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Introduction

Melanoma incidence is accelerating across the globe and is among the most frequent malignancies in younger populations. Within Italy, it ranks as the second most common cancer in men under 50 and the third in women under 50, with estimated lifetime melanoma risks of 1.5% for men and 1.2% for women, while mortality rates have not shown major changes. A large proportion of the rise in invasive tumors is attributed to thin melanomas (Breslow ≤ 1 mm), which now constitute roughly 70-80% of new diagnoses. The widespread use of dermoscopy and other non-invasive tools, such as reflectance confocal microscopy—now standard in dermatologic practice—has increased the detection of these early lesions. Growing public awareness and national screening initiatives have also promoted earlier evaluation.

Yet, the exact drivers behind the surge in thin melanoma diagnoses remain partly unresolved, and the overall death rate from melanoma has remained relatively steady [1-4]. According to the AJCC 8th Edition staging guidelines, melanoma-specific survival for stage IA is 99% at 5 years and 98% at 10 years [5], reflecting excellent outcomes for pT1 melanomas. Still, 5-20% can progress to nodal or distant disease, and a small subset (~5%) may be fatal. Because thin tumors occur so frequently, they account for nearly 30% of melanoma-related mortalities [4, 6-8].

This retrospective case-control work summarizes 22 years of experience with metastatic thin melanomas (MTMs) and outlines their demographic, clinical, dermoscopic, and histopathologic features. Although these patients initially received a low-risk diagnosis, many evolved similarly to thicker tumors, despite thin melanomas generally being considered highly curable. This highlights the heterogeneous risk profile of thin melanoma and the need for

refined staging and surveillance approaches. Current national and international guidelines provide no definitive recommendations regarding optimal follow-up intensity for thin melanomas, including whether short-interval monitoring or long-term observation is appropriate for detecting late metastatic events in high-risk individuals, while maintaining real-world cost-effectiveness.

Prompt recognition of metastatic disease is critical for this group, particularly since advances in systemic therapy over the last decade have dramatically improved survival for metastatic patients. Therefore, we compared MTMs with non-MTM controls to pinpoint predictive characteristics. Ultimately, defining reproducible prognostic markers based on easily obtained data—clinical appearance, dermoscopy, and pathology—together with deeper insight into melanoma progression, may guide clinicians in designing more personalized management strategies.

Materials and Methods

We conducted an observational, retrospective case-control study between January 2000 and June 2022 at two referral centers (Dermatology Unit, Azienda USL Toscana Centro; and Medical Oncology Unit, Careggi University Hospital, Florence, Italy). Both facilities employ routine clinical and dermoscopic imaging for ambiguous lesions before biopsy or excision. Cases consisted of consecutive patients with primary cutaneous melanomas ≤0.8 mm (Breslow) who later developed regional and/or distant metastases. Controls were consecutive patients with primary melanomas ≤0.8 mm who remained metastasis-free for at least 5 years. All participants provided consent for the use of de-identified data and images. Individuals with other malignancies or multiple primary melanomas were excluded.

Primary tumor information was collected retrospectively from two institutional databases and included demographic details, clinical appearance, dermoscopy, histopathology, and standard prognostic parameters. All cases were re-classified according to AJCC 8th Edition criteria. Original tissue slides were available for reassessment in 14 of 16 metastatic cases, reviewed by two dermatopathologists with expertise in skin malignancies.

Dermoscopy was performed using a handheld device (Heine Delta 20; Heine Optotechnick, Herrsching, Germany). Both clinical and dermoscopic photographs were acquired using a high-resolution digital camera (Olympus E-520, 7.1-megapixel sensor, 3.8× optical zoom, 28-105 mm focal range in 35 mm format, maximum aperture f/2.8-f/5.8).

In vivo dermoscopic evaluation employed the Dermaphot system (Heine Optotechnick), which links a dermatoscope to the camera, enabling uniform 10× magnified dermoscopic photographs saved in JPEG format. All dermoscopic and clinical images, along with associated data, were archived on a Windows-based workstation.

A team of dermoscopy specialists from the University of Florence reviewed the stored images without access to diagnostic or follow-up information. Each reviewer filled out a printed assessment form to classify lesions using widely accepted dermoscopic pattern frameworks. All evaluators had comparable backgrounds, including more than 5 years of continuous dermoscopy experience. The dermoscopic items assessed followed internationally endorsed algorithms.

Primary lesions underwent standard excision followed by re-excision determined by Breslow depth (0.5 cm for in situ; 1 cm for pT1 tumors). Each case was evaluated by a multidisciplinary board, which confirmed treatment planning. When appropriate under the relevant edition of the AJCC system, sentinel lymph node biopsy (SLNB) was offered and discussed with patients.

Information on where metastases emerged, the therapies administered, and the eventual clinical evolution was compiled. Metastatic findings detected at diagnosis or later were termed regional when confined to lymph nodes, and distant when involving visceral organs, skin far from the original tumor, bone, or the brain. Local or regional spread was verified by tissue examination, while distant metastases were demonstrated through imaging with or without histologic confirmation.

Statistical testing was performed using IBM SPSS 25 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using Pearson's chi-squared or Fisher's exact test, depending on cell counts. A p-value < 0.05 (two-tailed) was considered significant.

Results and Discussion

From January 2000 to June 2022, 1396 out of 1864 (75%) melanoma diagnoses were classified histologically as in situ or thin lesions measuring ≤0.8 mm. Within this group, 16/1396 (1.1%) progressed to either regional nodal

disease or distant spread. In four individuals (three women, one man), metastasis was the first identified manifestation. Two of these showed nodal involvement, while two had distant lesions, including central nervous system (CNS) spread. In four metastatic patients, the Breslow depth was ≤0.6 mm. For comparison, a control set of 100 thin melanoma patients without metastasis and with ≥5 years of follow-up was selected from the same database. Summary characteristics for both groups appear in **Table 1**. Among the metastatic cases, the median age was 49 (range 28-83), with 56.3% diagnosed before age 50. Sex distribution included nine males (56.3%) and seven females (43.7%).

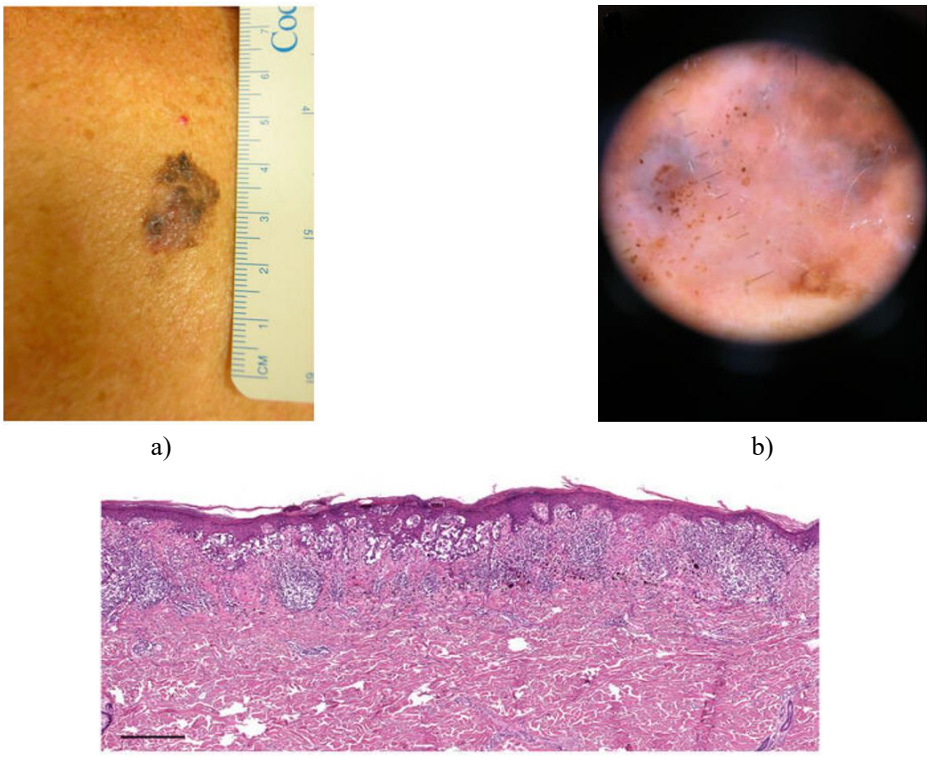
Table 1. Demographic, clinical, and pathological details for case and control groups.

Patients			
	Cases N = 16	**Controls** N = 100	**p-Value**
Age at diagnosis (yr)			
Median (IQR)	49 (28-83)	64 (27-91)	
≤50	9 (56.3%)	19 (19%)	0.003
>50	7 (43.7%)	81 (81%)	0.003
Gender			
Female	7 (43.7%)	45 (45%)	0.926
Male	9 (56.3%)	55 (55%)	0.926
Anatomical site			
Torso	7 (43.7%)	45 (45%)	0.926
Upper limbs	6 (37.5%)	22 (22%)	0.211
Lower limbs	2 (12.5%)	25 (25%)	0.354
Head/neck	1 (6.3%)	8 (8%)	1.000
Histological subtype			
SSM a/Low-CSD melanoma	14 (87.5%)	93 (93%)	0.609
LM b/High-CSD in situ melanoma	2 (12.5%)	7 (7%)	0.609
Breslow thickness (mm) c			
Median (IQR)	0.6 (0.2-0.8)	0.15 (0-0.7)	
<0.5	5 (31.2%)	81 (81%)	<0.001
≥0.5	9 (56.2%)	9 (9%)	<0.001
Ulceration			
Present	2 (12.5%)	1 (1%)	0.044
Absent	13 (81.2%)	99 (99%)	0.044
Missing	1 (6.3%)	0	
Mitotic rate/mm²			
0	5 (31.5%)	97 (97%)	<0.001
1	4 (25%)	3 (3%)	0.003
2-4	4 (25%)	0	<0.001
Missing	3 (18.5%)	0	
Growth phase			
Vertical growth phase (VGP)	10 (62.5%)	27 (27%)	0.002
Radial growth phase (RGP)	4 (25%)	73 (73%)	0.002
Missing	2 (12.5%)	0	
Regression			
Present	14 (87.4%)	53 (53%)	0.003
<75%	9 (64.3%)	34 (64.2%)	
≥75%	4 (28.5%)	19 (35.8%)	
Missing	1 (7.2%)	0	
Absent	1 (6.3%)	47 (47%)	0.003
Missing	1 (6.3%)	0	
Pathological Stage (AJCC 8th Ed.) c			
pTx	2 (12.5%)	0	0.016
pTis	0	58 (58%)	<0.001
pT1a	8 (50%)	41 (41%)	0.368
pT1b	5 (31.2%)	1 (1%)	<0.001
Missing	1 (6.3%)	0	

SLNB d		
Not performed	12 (75%)	99 (99%)
Negative	4 (25%)	1 (1%)

[a] SSM: superficial spreading melanoma; CSD: cumulative sun damage; [b] LM: lentigo maligna; [c] AJCC: American Joint Committee on Cancer; d SLNB: sentinel lymph node biopsy. Significance threshold: two-tailed $p < 0.05$.

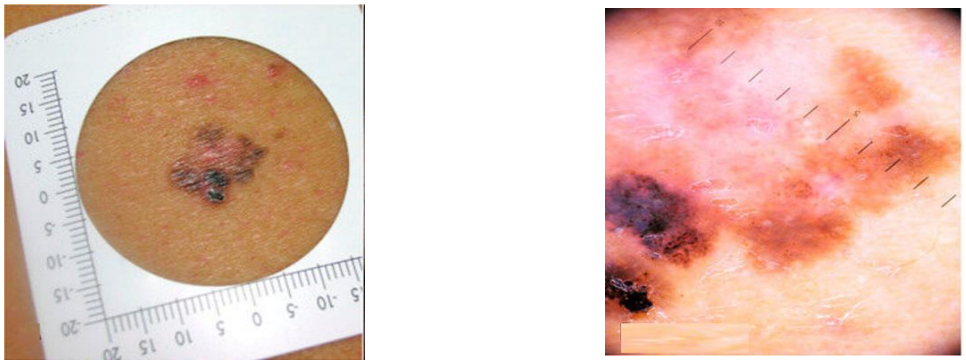
The most common location for the primary tumor was the torso (n = 7, 43.7%), followed by the upper extremities (n = 6, 37.5%), lower extremities (n = 2, 12.5%), and the head/neck (n = 1, 6.3%).
Clinical and dermoscopic images were available for all 16 metastatic thin melanomas (MTMs) and for 100 non-metastatic lesions. Their descriptive features are shown in **Table 2**.



a) b)

c)

Figure 1. (a) Clinical photo of a pT1a melanoma (>10 mm; Breslow 0.6 mm, no ulceration) on the torso of a 62-year-old man. (B) Dermoscopic view: missing pigment network, presence of more than three colors, atypical vessels, and a peripheral blue-white veil. (c) Thin superficial spreading/low-CSD melanoma with regression (partial substitution of tumor by fibrous tissue with vascularity, macrophages containing pigment, and chronic inflammatory infiltrate). Magnification 4×, scale 250 µm, H&E.



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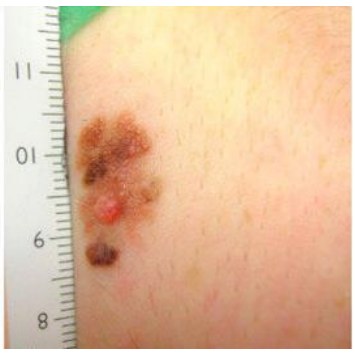

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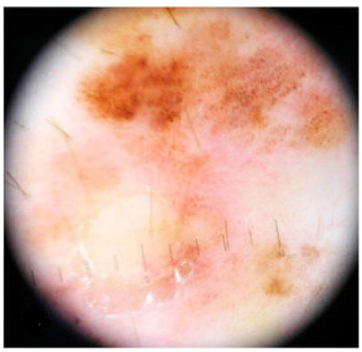

d)

Figure 2. (a) Clinical image of a pT1a melanoma (>10 mm; Breslow 0.2 mm) on the torso of a 40-year-old man. (b) Dermoscopic findings: absent network, ≥3 colors, irregular vessels, and a central white patch. (c) pT1a melanoma (>10 mm; Breslow 0.6 mm) on the neck of a 29-year-old woman. (d) Dermoscopy: missing network, >3 colors, atypical vascular structures, and widespread white patches.

Table 2. Dermoscopic and clinical observations in MTMs vs non-MTMs.

Clinical-Dermoscopic Features	Cases N = 16	Controls N = 100	p-Value
≥3 colors	12 (80%)	3 (3%)	<0.001
Diameter > 10 mm	11 (73.3%)	29 (29%)	0.002
White patch	11 (73.3%)	43 (43%)	0.055
Atypical vascular patterns	10 (66.5%)	15 (15%)	<0.001
Blue-gray areas	9 (60%)	27 (27%)	0.038
Absence of pigment network	9 (60%)	15 (15%)	0.001
Blue-white veil	3 (20%)	5 (5%)	0.079
Regression structures (white patch or blue-gray areas)	16 (100%)	45 (45%)	<0.001

A p-value < 0.05 (two-tailed) was regarded as significant.

Clinically, every MTM lesion showed pigmentation and uneven coloration. A diameter > 10 mm appeared in 11 cases (73.3%, p = 0.002), while 12 cases (80%, p ≤ 0.001) exhibited three or more colors (black, brown, gray, blue, red, and white). In contrast, only 3% of control lesions had at least three colors, and only 29% exceeded 10 mm.

Dermoscopic elements, including blue-gray areas, white patches, and atypical vessels, were documented in 9 cases (60%, p = 0.038), 11 cases (73.3%, p = 0.055), and 10 cases (66.5%, p ≤ 0.001), respectively. Among controls, the same traits appeared far less often: 27%, 43% and 15%, respectively **(Table 2)**.

Furthermore, additional dermoscopic signs—specifically the blue-white veil and loss of a pigment network—appeared in 20% (p = 0.079) and 60% (p = 0.001) of the lesions, respectively. In contrast, these same findings occurred in only 5% and 15% of the controls.

Histologically, two melanomas in the case group displayed regression with a remaining intraepidermal/in situ portion. Among MTM cases, 14 (87.5%) tumors were classified as invasive SSM/low-CSD melanomas per the WHO 4th edition [9], and 5 of these 14 retained remnants of a nevus. Mean Breslow depth measured 0.6 mm (range 0.2-0.8 mm), with 56.2% exhibiting a value ≥0.5 mm (p ≤ 0.001). Ulceration occurred in two tumors (12.5%, p = 0.044). Vertical growth phase (VGP) was observed in 10 samples (62.5%, p = 0.002). Mitotic counts ranged from 1-4 mitoses/mm² in invasive lesions: one case showed 4 mitoses/mm² (6.3%, p ≤ 0.001), two showed 3 (12.5%), one showed 2 (6.3%), four showed 1 (25%), and five had 0 (31.5%, p ≤ 0.001) **(Table 1)**. Regression—early, intermediate, or late—was documented in 14/16 MTMs (87.4%, p = 0.003), distributed as 2 cases (14.2%), 7 cases (50%), and 4 cases (28.5%), respectively. According to CAP criteria, regression involved <75% of the lesion in nine cases (64.2%) and ≥75% in four (28.5%).

Using the AJCC 8th edition, the pathological stage at diagnosis was pTx in two regressed melanomas (12.5%), pT1a in eight cases (50%), pT1b in five cases (31.3%), and undetermined in one patient (6.3%). Four pT1b MTM patients (25%) underwent SLNB, all returning negative. Three were male, with the oldest being 52 years old. Sentinel nodes were located in the axilla in two cases and the groin in two others. One pT1b patient did not receive SLNB because metastasis had already been identified during staging.

Table 1 outlines the control group's histopathology. When contrasted with non-MTMs, MTMs displayed greater thickness at presentation, markedly higher mitotic activity (50% vs. 3%), and more frequent regression (87.4% vs. 53%). All differences reached statistical significance ($p \leq 0.05$).

For MTM patients, median follow-up lasted 58.1 months (range 1.6-174 months). The interval between primary tumor diagnosis and first metastatic event had a median of 30.1 months (range 2.6-93.2 months). No case showed local recurrence, in-transit disease, or satellitosis. Altogether, regional nodal involvement occurred in five patients (38.4%), and distant metastases in eight (61.5%). Distant metastatic sites included lungs (43.7%), brain (43.7%), liver (25%), adrenal gland (12.5%), non-regional lymph nodes (12.5%), skin (6.2%), and bone (6.2%).

Most metastatic cases (56.2%) received multimodal therapy involving surgery, radiation, and systemic agents. Surgery alone, radiotherapy alone, and systemic therapy alone (chemotherapy, targeted therapy, or immune checkpoint inhibitors) were used in 25%, 6.2%, and 12.5% of patients, respectively. At the final assessment, five individuals (31.2%) remained alive, while ten (62.5%) had died from melanoma. A single death was unrelated to melanoma.

Younger age correlated with worse outcomes: the median age at melanoma-related death was 47 years, slightly below the median diagnostic age of 49 years.

In this cohort, thin melanomas constituted the majority (75%), and 1.1% progressed to regional or distant disease—representing 15.4% of all metastatic melanomas, independent of tumor thickness. These observations align with earlier publications [10-12]. Dermoscopy remains the central tool for evaluating suspicious skin lesions, and numerous investigations have attempted to associate dermoscopic patterns with the histology of thin melanomas [13-22]. To date, no analyses have focused on whether MTMs demonstrate distinct dermoscopic signatures. Our retrospective case-control design aimed to explore whether certain clinical or dermoscopic elements might flag lesions with metastatic potential by comparing MTMs to a demographically matched non-MTM cohort.

The torso was the most frequent site (43.7%), consistent with previous literature [23-25], and no clear associations with sex or age were identified. Notably, 73.3% of lesions ($p = 0.002$) exceeded 10 mm in diameter, which is atypical for early melanomas. All tumors were pigmented, exhibited varying degrees of color irregularity, and showed at least three hues (black, brown, gray, blue, red, or white) in 80% of cases ($p \leq 0.001$). None were truly amelanotic. In contrast, the control group showed >10 mm diameter in only 29% of lesions and ≥3 colors in just 3%.

Prior studies have suggested that thinner melanomas (≤1 mm) often display atypical pigment networks and uneven globules [13-15], while thicker lesions (>1 mm) more frequently show atypical vessels, regression structures, and network absence [13-22]. In our MTM series, the pigment network was missing in 60% ($p = 0.001$) versus 15% of controls. Regression-related dermoscopic signs (white areas and/or blue-gray zones) were present in all cases (100%, $p \leq 0.001$), and atypical vessels appeared in 66.6% ($p \leq 0.001$). These findings are highly informative: every thin melanoma that later metastasized exhibited regression patterns, and more than half expressed atypical vasculature and lacked a pigment network—features usually associated with melanomas thicker than 1 mm.

The dermoscopic parameters assessed in this work appeared evenly represented across lesions, independent of tumor thickness. Prior publications have proposed several Breslow thresholds beyond which thin melanomas may behave more aggressively. Some researchers linked thicknesses above 0.75 mm with increased SLN positivity [23, 26, 27], whereas others identified 0.6 mm, 0.76 mm, and ≥0.8 mm as relevant high-risk cut points [10, 11, 28].

Notably, our dataset did not include inherently high-risk melanoma variants such as nodular melanomas. As anticipated, greater tumor depth correlated with poorer outcomes, with 64.2% of MTMs measuring ≥0.5 mm in Breslow thickness. Moreover, every MTM displayed at least one established adverse histologic indicator—regression, VGP, ulceration, or dermal mitoses [29]. These findings lend support to recent discussions proposing that thin melanomas (<0.8 mm) confined to the radial growth phase and lacking adverse attributes (e.g., regression, ulceration, dermal mitoses) might be better classified as "melanocytic proliferations of low malignant potential" [9]. Conversely, most MTMs in our cohort were already in the VGP (62% vs. 27% in controls) and exhibited regression (87.4% vs. 53% in controls).

Importantly, all individuals who underwent SLNB eventually developed distant metastases without prior nodal disease during follow-up. Unlike thicker melanomas, the utility of SLNB for thin lesions remains uncertain, with reported positivity rates around 5% (range 3.2-9.5%) [28, 30, 31]. Thus, an individualized evaluation of risks and benefits is crucial. Based on our observations and the modest negative predictive value of SLNB in thin

melanomas, vigilant observation may be a more appropriate strategy than routinely performing SLNB in all pT1a cases.

The lungs and brain constituted the most frequent sites of distant spread, with correspondingly poor outcomes, mirroring the pattern and aggressiveness documented for thicker tumors [32]. Every patient who developed distant metastases received systemic treatment in the metastatic or adjuvant setting. In our cohort, all individuals initially received chemotherapy before the era of newer agents; among those later treated with modern therapies, two survived, underscoring the transformative impact of contemporary systemic treatments in advanced melanoma.

This study has two primary constraints: the limited patient number and the retrospective nature of the analysis. Future multicenter prospective studies will be essential, ideally incorporating additional prognostic determinants beyond standard histopathology—such as tumor-microenvironment spatial characteristics or intrinsic molecular/genetic features.

Conclusion

In summary, certain clinical-dermoscopic traits—including a diameter >10 mm, the presence of three or more colors within a lesion, loss of a pigment network, dermoscopic signs of regression, and atypical vascular patterns—may indicate heightened metastatic risk in thin melanomas, especially when combined with traditional adverse histologic findings (regression, VGP, dermal mitoses). Accordingly, these patients should undergo careful and extended follow-up.

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Ethics Statement: None

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