

Risk factors for visceral metastases in cutaneous melanoma: insights from a clinical cohort

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Abstract

Introduction: Cutaneous melanoma, a malignancy originating from melanocytes, is characterized by a high propensity for metastatic spread. It commonly affects the lungs, liver, brain, lymph nodes, and skin.

Aim: This study examines a cohort of cutaneous melanoma patients diagnosed with metastatic disease at our institution, aiming to identify patterns and risk factors associated with metastatic spread.

Materials and methods: A retrospective analysis was conducted on 49 patients treated for cutaneous melanoma in our plastic surgery ward between 2017 and 2022 who subsequently developed metastatic disease.

Results: Over six years, 49 of 130 melanoma cases progressed to metastases. T4 lesions predominated (55.1%). Metastases involved multiple organs in 42.9% of cases. Males had more advanced disease compared to women, with a higher mean Breslow Index, higher ulceration rates, greater metastatic burden.

Despite being a visible tumor, cutaneous melanoma can remain undetected until advanced stages, emphasizing the need for public awareness and early screening. Our study confirms that even thin melanomas (<1 mm) can metastasize, particularly to the lungs, challenging the assumption that low Breslow index ensures favorable prognosis. The high incidence of multiorgan involvement, especially in male and nodular melanoma patients, highlights the aggressive nature of certain subtypes and the importance of personalized follow-up strategies.

Conclusions: Male patients demonstrated more aggressive disease patterns, highlighting the need for early detection and tailored management. Subtype-specific metastatic patterns warrant further investigation to improve prognostic and therapeutic strategies.

Keywords

cutaneous melanoma, distant metastases, risk factors, tertiary prevention

Introduction

Cutaneous melanoma is a melanocytic skin cancer with a high risk of metastatic dissemination.^[1] Unlike other types of malignant tumors, the incidence of cutaneous melano-

ma has demonstrated a steady upward trend, with an annual increase rate of 4.1% over the past four decades.^[2]

Cutaneous melanoma cells can metastasize hematogenously or lymphogenously. The dissemination pattern of cutaneous melanoma cells is explained through one of

three conceptual frameworks.^[3] The stepwise model posits that melanomas progress via the lymphatics in a station-wise pattern. The simultaneous spread model posits that metastatic cells will metastasize simultaneously via hematogenous and lymphatic routes. The model of differential spread posits that different melanoma tumor types have different metastatic capabilities.

Evidence indicates that melanoma metastasis often occurs many months before the primary melanoma is excised. Research on sentinel lymph node metastasis suggests that the initial metastatic cell typically reaches the node about 18 months before the clinical diagnosis of the primary melanoma. Once metastasis is clinically detectable, the tumor volume increases exponentially with a median tumor doubling time (TDT) of 49 days, giving the impression of rapid growth.^[4]

Metastatic melanoma remains a challenging clinical diagnosis, despite substantial progress in the understanding and treatment of this disease.^[5] Among patients with unresectable stage III/IV melanoma, a disease that was previously considered almost invariably incurable, prolonged and sustained complete responses to immunotherapy are now observed in up to 30%–50% of cases.^[6]

Poor prognostic factors in melanoma include tumor thickness, regional lymph node involvement (stage III disease), a higher number of positive lymph nodes, and distant metastasis (stage IV disease). Lesions located on the trunk or face, ulceration, regression on histologic examination (though controversial), and male sex are also associated with worse outcomes.^[7]

This article aims to examine the demographic characteristics of patients diagnosed with cutaneous melanoma who subsequently developed metastases.

Aim

This study examines a cohort of cutaneous melanoma patients diagnosed with metastatic disease at our institution, aiming to identify patterns and risk factors associated with metastatic spread.

Materials and methods

The present work is a retrospective cohort study that analyzes demographic and histopathological characteristics of patients with metastatic cutaneous melanoma, objectivated by imaging modalities such as PET-CT, MRI, CT, and conventional radiography. The study sample consists of individuals treated for cutaneous melanoma and later diagnosed with metastases at the Plastic Surgery Department of Prof. Dr. Agrippa Ionescu Clinical and Emergency Hospital, Bucharest, from January 1, 2017, to December 31, 2022.

This study was approved by the Ethics Commission of Prof. Dr. Agrippa Ionescu Clinical and Emergency Hospital, Bucharest (Approval No 21126, January 17, 2022).

Before hospital admission, the medical team informed patients about participation in medical education activities and obtained their written consent upon admission.

The demographic data were compiled and organized within a spreadsheet using Microsoft Excel for Microsoft 365 MSO version 2405. Statistical analysis was carried out using IBM SPSS Statistics Version 29.0.2.0 (20). A chi-square test was employed to assess the relationships among categorical data, and Pearson's correlation test was employed to assess the relationships among interval data. A threshold of $p < 0.05$ was utilized to determine statistical significance.

A literature search was performed using PubMed and Web of Science to identify pertinent articles regarding the occurrence and implications of metastases in individuals with cutaneous melanoma. The search encompassed articles published from the inception of these databases to the current date. The gathered information was analyzed to compare with our cohort's parameters, emphasizing the incidence, clinical characteristics, treatment modalities, and survival outcomes related to brain metastases in patients with cutaneous melanoma.

Results

During the six-year study period, 149 patients were treated for cutaneous melanoma, with 19 patients excluded due to incomplete data. Metastases were identified in 49 of the remaining 130 cases (**Table 1**).

The distribution of male and female patients was approximately equal, with 25 male and 24 female patients. The mean age of the patients was 59.78 years (range 26–81 years), with a median age of 60 years. Patients were represented across all age groups, with the majority in the 51–80 age range: 17 (34.7%) cases in the 51–60 age group, 12 (24.5%) cases in the 61–70 age group, and 10 (20.4%) cases in the 71–80 age group. Analysis by sex showed that male cases steadily increased beginning in the 41–50 age group, with peaks in the 61–70 and 71–80 age groups (28% in each category), while female cases peaked in the 51–60 age group (45% of cases) (**Fig. 1**). The majority of patients (81.6%, $n=40$) resided in urban areas.

Tumor location analysis revealed that 65.3% of cases were located in two areas: the posterior thorax (18 cases, 36.7%) and the lower limbs (14 cases, 28.6%). The remaining 34.7% were distributed among the head, neck, upper limbs, and anterior thorax. Significant differences in tumor location by sex were noted: in male patients, 52% of tumors were on the posterior thorax and 20% on the head, whereas in female patients, 41% were on the lower limbs, followed by the posterior thorax and upper limbs (20.8% each) (**Fig. 2**).

Histologically, two types predominated: superficial spreading melanoma (22 cases, 44.9%) and nodular melanoma (21 cases, 42.9%). There was an inverse sex distribution, with superficial spreading melanoma comprising

Table 1. The demographic and clinical characteristics of the study cohort comprised 49 cutaneous melanoma patients diagnosed with metastatic disease within the six-year timeframe

	Both sexes		Male		Female	
	Total	Percentage of total	Total	Percentage of male cases	Total	Percentage of female cases
Sex						
Male	25	51%				
Female	24	49%				
Age (years)						
Mean	59.78		62.36		57.08	
Median	60		63		58	
Minimum	26		26		27	
Maximum	81		81		75	
Age groups						
21-30	2	4.1%	1	4%	1	4.2%
31-40	3	6.1%	0	0%	3	12.5%
41-50	4	8.2%	3	12%	1	4.2%
51-60	17	34.7%	6	24%	11	45.8%
61-70	12	24.5%	7	28%	5	20.8%
71-80	10	20.4%	7	28%	3	12.5%
81-90	1	2%	1	4%	0	0%
Residence						
Rural	9	81.6%	5	20%	4	16.7%
Urban	40	18.4%	20	80%	20	83.3%
Anatomical distribution						
Head	8	16.3%	5	20%	3	12.5%
Neck	1	2%	1	4%	0	0.0%
Anterior trunk	2	4.1%	1	4%	1	4.2%
Posterior trunk	18	36.7%	13	52%	5	20.8%
Upper limbs	6	12.2%	1	4%	5	20.8%
Lower limbs	14	28.6%	4	16%	10	41.7%
Melanoma histological types						
Superficial spreading melanoma	22	44.9%	8	32%	14	58.3%
Nodular melanoma	21	42.9%	15	60%	6	25%
Acral melanoma	3	6.1%	0	0%	3	12.5%
Naevoid melanoma	1	2%	1	4%	1	1.6%
Desmoplastic melanoma	1	2%	0	0%	1	4.2%
Melanoma - no other classification	1	2%	1	4%	0	0.0%
Breslow index (mm)						
Mean	6.549		7.128		5.946	
Median	4.60		5		4.3	
Minimum	0.6		0.6		0.6	
Maximum	32		32		21	
Primary tumor ulceration						
Non-ulcerated	19	38.8%	7	28%	12	50%
Ulcerated	30	61.2%	18	72%	12	50%
TNM T classification						
T1	4	8.2%	2	8%	2	8.3%
T2	8	16.3%	2	8%	6	25%
T3	10	20.4%	7	28%	3	12.5%
T4	27	55.1%	14	56%	13	54.2%
Sentinel lymph node biopsy						
Negative	16	32.7%	4	16%	12	50%
Positive	33	67.3%	21	84%	12	50%
Metastases						
Locations involved						
Singular location	28	57.1%	9	36%	19	79.2%
Multiple locations	21	42.9%	16	84%	4	20.8%
Location of metastases						
Lungs	30	60%	16	64%	14	58.3%
Liver	12	24%	7	28%	5	20.8%
Skin	5	10%	3	12%	2	8.3%
Skeletal	5	10%	4	16%	1	4.2%
Brain	3	6%	1	4%	2	8.3%
Spleen	3	6%	2	8%	1	4.2%
G.I. tract	1	2%	1	4%	0	0%

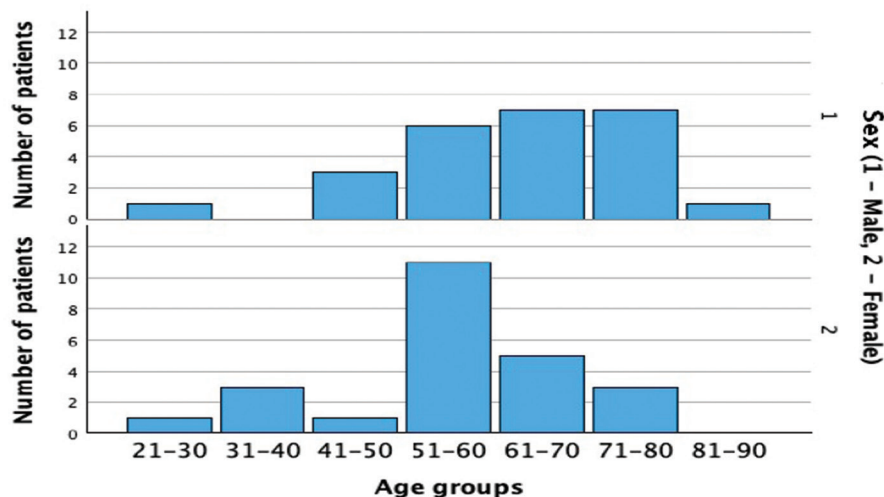


Figure 1. Histogram illustrating the distribution of age groups stratified by sex.

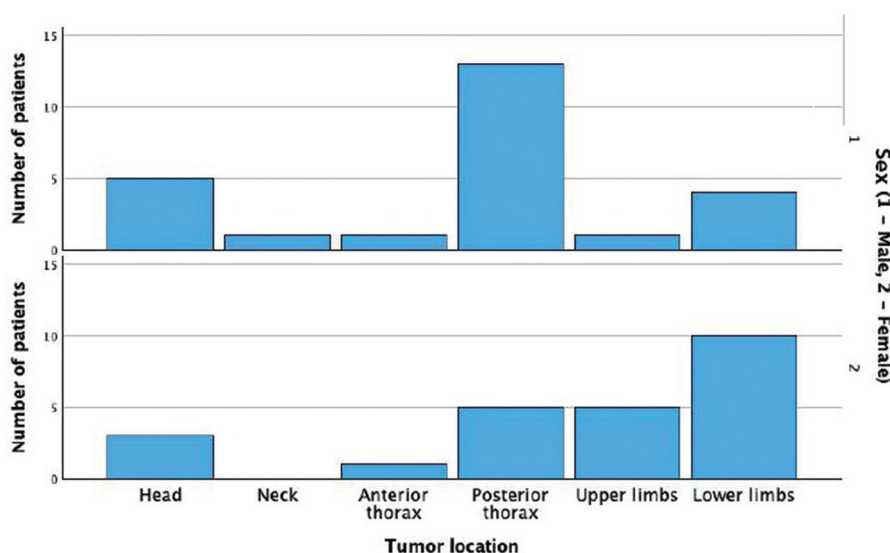


Figure 2. Histogram illustrating the distribution of anatomical segment locations of cutaneous melanoma stratified by sex.

58.3% of female cases and nodular melanoma comprising 60% of male cases (chi-square test $p=0.43$). Nodular melanoma exhibited a positive association with ulceration, with 85.7% of patients with this histopathological subtype presenting ulcerated tumors (chi-square test, $p=0.024$).

The mean Breslow Index across all patients was 6.549 mm, with a higher average in male patients (7.128 mm) compared to female patients (5.946 mm). Ulceration was present in 61.2% of all cases, occurring in 72% of male cases and 50% of female cases.

Regarding TNM T classification, patients ranged from T1 to T4 categories, with the majority in the T4 category (27 cases, 55.1%). The T4 stage was predominant in both sexes (56% in males and 54.2% in females). Sentinel lymph node biopsy was positive in 33 patients (67.3%), with a higher positivity rate in males (84%) compared to females (50%) (Fig. 3).

Statistical analysis revealed that the TNM T stage exhibited a positive association with ulceration, as higher T stages were associated with ulceration (chi-square test, $p=0.008$). Additionally, the risk of positive sentinel lymph nodes increased with T stage in metastatic patients (TNM – sentinel lymph node, chi-square test, $p=0.032$).

Metastatic analysis indicated that 57% of patients had metastases to a single organ, while 42.9% had metastases to multiple sites. Sex analysis revealed that 84% of male patients had metastases to multiple sites, compared to 20.8% of female patients (chi-square test, $p=0.002$).

The most common sites of metastases were lymph nodes (68%), lungs (60%), and liver (24%). Skin and skeletal metastases each accounted for 10% of cases, while cerebral and spleen metastases each accounted for 6% and gastrointestinal tract metastases were observed in only one case. Male patients exhibited a higher percentage of metastases at each location, except for cerebral metastases.

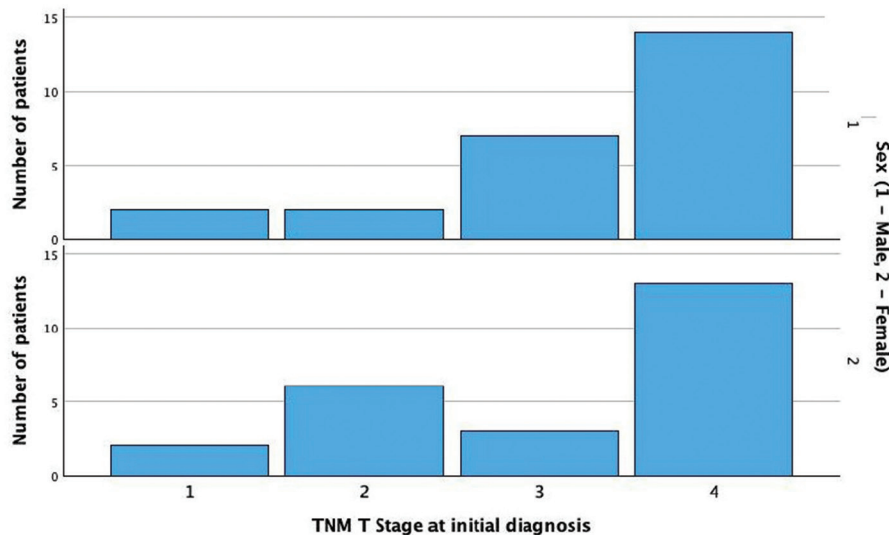


Figure 3. Histogram illustrating the distribution of TNM T stage at initial diagnosis, stratified by sex.

Discussions

For patients diagnosed with cutaneous melanoma, survival is correlated with early diagnosis of thin tumors.^[8] Although cutaneous melanoma is a visible tumor and can be visually identified, in some cases it is still diagnosed and treated after a long period.^[9]

Although prevention and early treatment of melanoma are vital for best outcomes, thin tumors (Breslow Index <1 mm) can metastasize, as a study by Richetta et al. identified metastases in 1.2% of patients with thin melanomas from a cohort of 1851 patients diagnosed with cutaneous melanoma.^[10] In our study cohort, we also observed metastases in patients with thin tumors; specifically, 4 patients (8.2%) had a Breslow Index <1 mm, among whom 3 developed lung metastases and one patient developed cutaneous metastases.

Lung metastases

Metastasis in melanoma frequently targets the skin and subcutaneous tissue, followed by the lungs, liver, bones, and brain. Pulmonary involvement is particularly significant in melanoma: Pulmonary metastases are the primary cause of death in metastatic melanoma, often leading to respiratory failure.^[11] In our study, 60% of patients developed lung metastases, making it the most frequently affected site. Factors associated with lung metastases included body mass index (BMI), age, and sex.^[12] No significant correlation was identified between the presence of lung metastases and any specific demographic or histological factors within our study cohort.

Liver metastases

Only 10% of malignant hepatic neoplasms are primary liver or bile duct carcinomas. The vast majority of malignant

hepatic lesions are metastases originating from primary tumors located outside the liver.^[13]

The occurrence of liver metastases (LM) significantly decreases the 5-year survival rate and quality of life for cancer patients.^[14] Hepatic metastases are diagnosed in 10% to 20% of patients with AJCC stage IV melanoma; however, postmortem examinations often reveal liver involvement in most cases. Despite this, most patients have other metastatic sites, reducing median survival to 4 to 6 months. The median interval from initial melanoma diagnosis to the development of hepatic metastases is 58 months (range, 0–264 months).

In our study cohort liver metastases were the second most common site after lung metastases with 24% of patients presenting liver metastases. Among these patients, 58.3% were presented with tumors located on the posterior thorax, and 66.7% were diagnosed with nodular melanoma. Ulcerated tumors were observed in 9 out of 12 patients. The TNM T stages ranged from T2 to T4.

Metastasis to the liver seems to be inversely correlated with metastases to the brain.^[15,16] In our study cohort, cerebral metastases were identified in 1 out of 12 patients with liver metastases, but no statistically significant association was found. However, statistical analysis revealed a correlation between liver metastases and multimetastatic disease (chi-square test, $p < 0.001$), as 83.3% of patients with liver metastases had multiple organ metastases.

Brain metastases

Intracranial metastases are five times more frequent than primary brain tumors.^[17] The most common cancers metastasize to the brain are lungs, breast, colorectal carcinomas, renal cell carcinoma, and melanoma.^[18]

Research conducted by Davis et al. estimated that 6.9% of patients diagnosed with cutaneous melanoma will develop brain metastases.^[19] Moreover, patients diagnosed with

metastatic melanoma have a 40% probability of developing brain metastases.^[20] For patients diagnosed with cutaneous melanoma, the median time from initial diagnosis to brain metastases is 23 months and the median survival for patients with brain metastases is 7–9 months after initial diagnosis.^[21,22]

Several factors seem to be correlated with an increased risk of brain metastases. Primary tumor location on the head and neck or trunk, male sex, superficial spreading histopathological type, and ulceration are independent predictors of brain metastases. Elevated BRAFV600 ctDNA, elevated LDH, and high IGF-1R are markers associated with brain metastases in patients with cutaneous melanoma.^[23] In a study by Zakrzewski et al. from 2020 on clinicopathological characteristics of patients with brain metastases, lymphovascular invasion was absent in 82% of cases.^[24] In our cohort, cerebral metastases showed a positive association with the nodular melanoma histopathological type compared to all other variables (chi-square test, $p=0.004$).

Moreover, it is estimated that between 46% to 82% of individuals diagnosed with brain metastases of cutaneous melanoma also present with metastatic lesions in other anatomical locations.^[25]

Skeletal metastases

The incidence of bone metastases in malignant melanoma was found to be 2.5% at 5 years, higher among patients with more advanced stages of disease at diagnosis.^[26] In our study cohort, 10% (5 out of 49) of patients developed skeletal metastases.

Survival after the detection of bone metastases ranged from 3 to 13 months. Bone metastases are associated with skeletal-related events such as pathological fractures and spinal cord compression. Risk factors for developing bone metastases include elevated LDH levels, younger age at diagnosis, and melanoma located in the trunk, axial, or mucosal areas.^[27]

Statistical analysis revealed an association between skeletal metastases and multiple metastatic sites (chi-square test, $p=0.006$), suggesting that skeletal metastases tend to appear later in the progression of cutaneous melanoma, during the stage of multiple organ dissemination. Notably, all patients with skeletal metastases had plurimetastatic disease.

Skin, subcutaneous tissue, and lymph node metastases

The skin, subcutaneous tissue, and lymph nodes are the most frequent sites for distant recurrence, with skin and lymph node involvement observed in 59% of cases. Given that skin tumors are readily identifiable and amenable to surgical excision, meticulous physical examination is essential.^[28] In our cohort, sentinel lymph node biopsy was positive in 67.3% of cases and skin metastases were identified in 10% of cases.

Spleen metastases

Due to its protective microenvironment, splenic metastases are rare, and cutaneous melanoma is one of the few cancers that metastasizes to the spleen.^[29] In our cohort, three patients had splenic metastases.

Gastrointestinal tract metastases

Melanoma is the most common solid tumor metastasizing to the gastrointestinal tract.^[30] In our study, one patient with metastatic disease involving multiple organs (cerebral, pulmonary, hepatic, and cutaneous) also had metastases in the small intestine and gallbladder.

Conclusions

Male patients exhibited more severe tumors with a higher Breslow Index, ulceration rate, and association with posterior thorax and nodular melanoma, correlating with increased metastatic rates and multiple organ involvement. Nodular melanoma was notably associated with cerebral metastases ($p=0.004$), indicating subtype-specific spread patterns. Statistical analyses also revealed significant associations between multiple metastatic sites and skeletal metastases ($p=0.006$), as well as liver metastases ($p<0.001$). These insights underscore the need for early detection and tailored management strategies, particularly for male patients at higher risk of aggressive disease progression and widespread metastases.

Ethical approval

This study was approved by the Ethics Committee of Prof. Dr. Agrippa Ionescu Clinical and Emergency Hospital, Bucharest (Approval No. 21126, dated January 17, 2022).

Ethical statements

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- The authors declared that written informed consent was obtained from the patients at admission.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

Conflict of interest

The authors have declared that no competing interests exist.

Use of AI

No use of AI was reported.

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Author contributions

LSV: study's conception, design, data acquisition, and interpretation, critically reviewed and approved the manuscript, ensured accountability for its integrity; RD: conducted data analysis and interpretation, contributed to manuscript drafting and critical review, approved the final version; LR: oversaw study design and data acquisition, contributed to data interpretation, and manuscript review, approved the final version; CRJ: supported study design and data interpretation, critically reviewed and approved the manuscript. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work

Data availability

The datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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