

Clinicopathological Factors Predicting Melanoma Recurrence: A Study From South East Ireland

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ABSTRACT Introduction: Cutaneous malignant melanoma is a neoplastic transformation of melanocytes and a major cause of skin cancer-related mortality. Ireland, with its fair-skinned population, continues to see rising incidence rates, highlighting the importance of identifying clinicopathological predictors of recurrence.

Objectives: To assess the relationship between excision margins and melanoma recurrence, with emphasis on anatomical distribution and clinicopathological features.

Methods: This retrospective observational study analyzed 565 patient records from University Hospital Waterford, Ireland, meeting predefined criteria. Data collected included age, sex, primary tumor site, disease stage, Breslow thickness, Clark level, mitotic figures, ulceration, lymphovascular invasion, sentinel lymph node involvement, and adequacy of excision margins. Statistical analysis was conducted using SPSS 26.0.

Results: Significant predictors of recurrence included age ≥ 65 years, Breslow thickness > 4.0 mm, Clark level IV–V, ulceration, lymphovascular invasion ($P < 0.001$), and positive sentinel lymph node biopsy ($P = 0.004$). Inadequate excision margins were also linked to increased recurrence. Conversely, early-stage disease, thin Breslow lesions (≤ 1.0 mm), and Clark level II were associated with lower recurrence risk.

Conclusions: This study demonstrates a significant association between narrow excision margins and melanoma recurrence, particularly in anatomically complex areas like the head and neck. The findings underscore the importance of individualized surgical planning to ensure oncological safety while preserving function and appearance. Adherence to excision margin guidelines and long-term follow-up are essential, especially in patients with high-risk histological features.

Introduction

Malignant melanomas represent a neoplastic conversion of the neural crest-derived melanocyte [1]. The year 2018 saw malignant melanoma afflicting approximately a third of a million people globally, while 57,000 died as consequence of the disease, with both these numbers expected to double by 2040 [2]. The disease is known to be more common in fair-skinned individuals, and Ireland is no exception. Malignant melanoma is reported to be the fifth most frequently occurring invasive malignancy in the country, with a steadily increasing incidence [3]. This surge is attributed to an increased exposure to ultraviolet radiation whether through the sun or tanning salon exposure [4]. However, other factors have also been implicated and include variables such as immunosuppressive states (drugs, virus, genetic conditions, and neoplastic disease), history of combination therapy with psoralen and ultraviolet A light (PUVA), and a history of the neoplasm in a first-degree relative [5].

Evaluation includes not only establishing the diagnosis but also staging the disease. Using a combination of history/examination, biopsies, and imaging, the managing team has to establish the presence of melanoma and its subtype, the site of the disease, presence of ulceration, the degree of tumor thickness, spread to regional lymph nodes, number of lymph nodes involved, and the presence of distant metastasis, all of which have a direct impact on prognosis [6,7]. The five-year survival rate for stage 1 disease is over 90%, but rapidly drops to 45%–77% and to 27%–70% in those suffering from stage 2 and 3 disease, respectively, while patients with stage 4 disease have a five-year survival rate of below 20% [8].

Management of malignant melanomas centers around wide local excision, with sentinel lymph node biopsy (SLNB) and/or lymph node dissection when the disease is diagnosed at an early stage, while more advanced disease is managed with a combination of surgery and adjuvant treatment or even radiotherapy [9,10]. An essential requirement from successful surgery is the need for margins clear of neoplastic cells on excision [9,10]. We conducted this study with the express purpose of determining the outcomes of management for malignant melanoma in our setup, recurrence, and clinicopathological markers associated with its increased risk.

Methods

We conducted a retrospective study of patients reporting to University Hospital Waterford, Ireland, with melanomas from January 2016 to February 2023. The study sample was based on 565 records extracted from the hospital's database. Data were coded in the Statistical Package for Social Sciences (SPSS) version 26 (Armonk, NY: IBM Corp) and analyzed

for accuracy. Partial records were completed using the hospital medical records database. Records that could not be completed were excluded from statistical analysis. An audit team re-verified all histopathology reports for the biopsy of the primary lesion as well as the SLNB, and the data pertaining to total margins with operation notes. Ethical approval was sought and received. Data were analyzed using Statistical Package for the Social Sciences version 26.0. Mean and standard deviation (SD) were calculated for quantitative variables, specifically age, Breslow thickness, and number of mitotic figures per high-power field. Melanoma in situ cases were under-represented in this dataset because the hospital registry records them under dermatopathology follow-up and minor procedure categories. Our study extracted only surgically managed melanomas from the oncology surgery department, so most in situ cases were not captured. Recurrence was defined as any reappearance of melanoma after primary treatment, including local recurrence, regional lymph node recurrence, or distant recurrence.

Qualitative variables like year of diagnosis, sex, site of primary disease, stage of the disease at the time of presentation, degree of Breslow thickness, Clark stage, ulceration, lympho-vascular invasion, whether sentinel lymph node biopsy was done and its results, and whether the melanoma was excised with adequate margins as per the British Association of Dermatologists (BAD) guidelines were recorded in terms of frequency and percentage. The chi-square test was used for qualitative variables, while the independent samples t-test was used for quantitative variables for comparison between cases where recurrence developed or those where it did not, and a p-value of ≤ 0.05 was considered significant. Multivariate analysis was performed using binary logistic regression for variables which were found to be significant on univariate analysis.

Results

A general increase in the number of cases of melanoma was seen over the study period, with the highest number of cases seen in 2018, 2021, and 2022, accounting for 99 (17.3%), 95 (16.6%), and 98 (17.1%) cases, respectively. Details for the distribution of cases over the years is displayed in Figure 1.

The mean age of our study sample was 60.00 ± 18.03 years, with a slight female majority: 292 (51.0%). Of the 565 cases for whom data for site of primary lesion were available, 156 (26.7%) had trunk involvement, the upper and lower limbs were affected in 148 (26.4%) and 147 (26.2%) cases, respectively, while the head and neck were the least frequently affected: 114 cases (20.7%). We recorded the disease stage in the same number of patients (565 patients): 257 (44.7%) were stage T1a, and 45 (7.8%) were stage

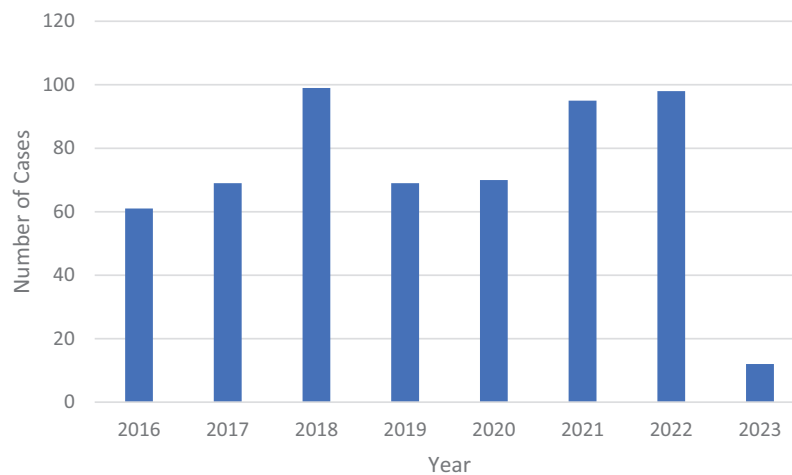


Figure 1. Distribution of cases by year.

T1b, while stages T2a, T2b, T3a, and T3b accounted for 88 (15.5%), 14 (2.7%), 42 (7.2%), and 36 (6.4%), respectively. Advanced disease in the form of stages T4a and T4b were found in 32 (6.0%) and 50 (9.5%) cases, respectively, while in situ disease was found in one (0.2%) case. The distribution of cases on the basis of patient and disease characteristics according to recurrence is displayed in Table 1.

The mean Breslow thickness of the sample was 2.28 ± 3.40 mm. The Clark Level was recorded for 565 patients; only one (0.2) patient had Stage 0 (melanoma in situ). Multiple Stage 1 cases (pT1a= 245, pT1b= 44) were identified, while the bulk of cases were almost evenly distributed across Stages 2, 3, and 4, with 179 (32.0%), 174 (30.9%), and 184(32.4%) cases, respectively. A total of 27 (4.5% of cases) were Stage 5 at presentation. The mean mitotic count per high-power field for the sample was 2.18 ± 3.96 per high-power field. A total of 111 (19.4%) cases had ulceration of the primary lesion at the time of presentation, while 28 (4.9%) had lymph vascular invasion. A sentinel lymph node biopsy was done in 134 (26.9%) cases, of which 47 (35.1%) were positive for malignant cells. Out of the total of 565 patients on whom surgery was performed, 504 (89.4%) had adequate margins according to BAD guidelines, while 61 (10.6%) did not. The distribution of cases on the basis of tumor and management characteristics according to recurrence is displayed in Table 2.

Univariate analysis showed that melanomas on the trunk, Clark Stage of II, Breslow thin lesions (≤ 1.00 mm), and a tumor stage 1B were all associated with a decreased chance of recurrence, all of which remained significant on multivariate analysis. Univariate analysis also showed that age ≥ 65 years, lesions on lower limb, stages 4A and 4B disease, Breslow thickness of >4.0 mm, Clark Stages 4 and 5, number of mitotic figures ≥ 1 per high-power field, presence of ulceration, lympho-vascular invasion, positive sentinel

lymph node biopsy, and inadequate margins on excision were all associated with an increased chance of recurrence. However, lower limb lesions, tumor stage 4A, a mitotic rate ≥ 1 per high-power field, and adequate margins on excision lost statistical significance on multivariate analysis.

Discussion

We conducted this retrospective study on patients with melanoma with the aim of determining the association between clinicopathological focus and the development of recurrent disease. Recurrent disease in malignant melanoma is the re-appearance of melanoma after it has been treated and appeared to be gone. This can happen at the original location (local recurrence), in nearby lymph nodes (regional recurrence), or in other parts of the body (distant or metastatic recurrence). The probability and location of recurrence are influenced by clinicopathological factors such as the initial stage of the melanoma, the success of the initial treatment, and specific patient characteristics [2]. Identifying patients who are at high risk of recurrence will help the treating clinician to maintain a higher degree of vigilance. Our data analysis showed that there was a steadily increasing trend in the number of cases of melanoma reporting to our institute every year, in keeping with existing data, making the conclusions of our study even more relevant [3,4].

We found that patients aged 65 years or more had a significantly higher frequency of recurrent disease, which was in keeping with other studies such as that by Fleming et al., where older patients were also found to be at an increased risk (Hazard Ratio HR 3.34; 95% Confidence interval CI: 1.53–7.25; $P < 0.01$) [11]. Univariate analysis showed that lower limb melanomas were associated with a higher risk of recurrence; however, this association became insignificant on multivariate review in this study, while head and neck lesions

Table 1. Distribution of Patient and Disease Characteristics according to Recurrence with Univariate Analysis.

Recurrence	Yes (N=44)	No (N=521)	p-value
Age (Years)	69.77 ± 15.56	59.21 ± 17.99	<0.001
Age ≥ 65 Years	31 (12.1%)	225 (87.1%)	<0.001
Sex			
Male (N [%])	24 (10.6)	203 (89.4)	0.542
Female (N [%])	20 (8.6)	213 (91.4)	
Site of Primary Lesion			
Trunk (N [%])	6 (5.0)	113 (95.0)	0.007
Upper Limbs (N [%])	8 (6.6)	114 (93.4)	0.258
Lower Limbs (n [%])	19 (15.6)	103 (84.4)	0.007
Head and Neck (N [%])	11 (11.8)	82 (88.2)	0.232
Stage at Presentation			
In Situ Disease	-	1 (100)	0.772
pT1a (N [%])	13 (5.0)	232 (95.0)	0.054
pT1b (N [%])	-	44 (100)	0.045
pT2a (N [%])	7 (8.1)	79 (91.9)	0.887
pT2b (N [%])	-	15 (100)	0.255
pT3a (N [%])	3 (7.3)	38 (92.7)	0.912
pT3b (N [%])	3 (8.3)	33 (91.7)	0.895
pT4a (N [%])	7 (20.6)	27 (79.4)	0.004
pT4b (N [%])	10 (19.2)	42 (80.8)	0.001

Table 2. Distribution of Tumor and Management Characteristics according to Recurrence with Univariate Analysis.

Recurrence	Yes (N=44)	No (N=521)	p-value
Breslow Thickness (mm)	4.13 ± 4.51	2.13 ± 3.27	<0.001
Thin (≤1.00 mm)	13 (4.4)	279 (95.6)	0.002
Intermediate (1.01 – 2.00 mm)	7 (7.1)	92 (92.9)	0.772
Intermediate (2.01 – 4.00 mm)	7 (8.8)	73 (91.2)	0.725
Thick (>4.00 mm)	16 (19.5)	66 (80.5)	<0.001
Clark Level			
Stage I (N [%])	-	1 (100%)	0.772
Stage II (N [%])	7 (4.0%)	168 (96.0%)	0.021
Stage III (N [%])	8 (4.8%)	160 (95.2%)	0.073
Stage IV (N [%])	21 (11.7%)	159 (88.3%)	0.021
Stage V (N [%])	7 (29.2%)	17 (70.8%)	<0.001
Mitotic Rate (Per High-Power Field)	4.55 ± 7.07	2.01 ± 3.56	<0.001
Mitotic Rate ≥ 1	32 (10.9%)	263 (89.1%)	0.004
Ulceration (N [%])	14 (12.8%)	95 (87.2%)	0.061
Lymphovascular Invasion (N [%])	7 (25.0%)	21 (75.0%)	0.002
Positive Sentinel Lymph Node Biopsy	8 (17.0%)	39 (83.0%)	0.007
Adequate Margins according to British Association of Dermatologist (BAD) Guidelines			
Yes	31 (5.8%)	469 (94.2%)	<0.001
No	17(22.8%)	48 (77.2%)	

Table 3. Multivariate Analysis of Significant Factors.

Variable	p-value
Variables with Decreased Risk of Recurrence	
Lesions of Trunk	0.008
Clark Stage II	0.022
Tumor Stage 1B	0.042
Breslow Thin Lesions (≤ 1.00 mm)	0.002
Variables with Increased Risk of Recurrence	
Age ≥ 65 Years	0.001
Lower Limb Lesions	0.609
Tumor Stage 4A	0.684
Tumor Stage 4B	<0.001
Breslow Thick Lesions (>4.00 mm)	<0.001
Clark Stage IV	0.029
Clark Stage V	0.035
Mitotic Rate ≥ 1	0.224
Ulceration	<0.001
Lymph vascular Invasion	<0.001
Positive Sentinel Lymph Node Biopsy	0.004

did not appear to have any association with an increased risk of recurrence. Previous studies on the subject such as that by von Schuckmann et al. have demonstrated that head and neck lesions are associated with an increased risk of recurrence (HR 1.67; 95% CI 1.01–2.76; $P<0.05$) [12]. However, it is important to note here that not all studies agree with this result: Lyth et al. demonstrated that the site of lesion, whether head and neck, lower limbs, or any other, was not associated with an increased risk of recurrence [13]. We believe this subject requires further study prior to forming concrete conclusions.

Unsurprisingly, advanced stages of melanoma were associated with a higher rate of recurrence, while the converse was true for earlier stages, in our study. We found that Stage 4B was associated with a statistically significant increase in this risk. Additionally, Stage 1B was associated with good outcomes, while the stages between these two did not appear to have a statistically significant association with recurrence in our sample. Feigelson et al. reported similar results: the more advanced the stage, the higher the risk of recurrence [14]. Von Schumann et al. reported a significant increase in risk of recurrence in stage 4A (HR 1.48; 95% CI: 0.48–4.59; $P<0.05$) and 4B (HR 3.86; 95% CI: 1.40–10.64; $P<0.05$) [12]. Moreover, Liang et al. noted that cases with a more advanced stage at the time of presentation not only had a higher risk of recurrence but were also at an increased risk of developing recurrence earlier than those patients with earlier stage disease at presentation [15].

A Breslow thickness, a key clinicopathological marker, of ≤ 1.0 mm was associated with a lower chance of recurrence, while for patients in our study sample with a thickness of >4.0 mm, the converse was true. Oh et al. reported that a Breslow thickness of >1.0 mm was associated with a higher risk of recurrence, ($P=0.008$), adding that there is a variation in male and female sex: a thickness of ≥ 2.5 mm in males was associated with higher rates of recurrence, while the value for females was >4.0 mm ($P<0.05$) [16]. Reschke et al. also reported a similar relation between thickness and recurrence, with the addition of an increased risk of metastases in patients who had increased thickness [17], as did von Lyth et al., who noted that a Breslow thickness of 2.01 mm to 4.0 mm was associated with a greatly increased risk of recurrence (HR 4.0; 95% CI: 2.1–7.6; $P<0.05$), while a thickness of >4.0 mm carried an even greater risk (HR 6.7; 95% CI: 3.4–13.0; $P<0.05$) [13].

As with tumor stage, early Clark stages were associated with a significantly lower frequency of recurrence versus advanced Clark stages (e.g., for stages 4 and 5), where recurrence was much more common; these conclusions were shared by Tas et al. [18]. Contrariwise, Kim et al. reported that Clark staging did not appear to have a statistically significant association with the development of recurrence; however, this study was conducted on thin melanomas, with the sample predominantly consisting of advanced Clark stage disease cases and a relatively small number of patients, which may have introduced confounding [19].

A mitotic rate of ≥ 1 per high-power field was not associated with an increased chance of recurrence in our study; using a higher cutoff may have been associated with significant results on multivariate analysis (Table 3). Tas et al. conducted a detailed study on the effect of a high mitotic index in patients with melanoma and found that melanomas with a mitotic count of 0–1/ mm² were associated with higher Clark stages at presentation ($P=0.001$), more aggressive tumor stages ($P=0.003$), ulcerated primary lesion ($P=0.006$), lymphovascular disease ($P=0.0001$), metastatic disease ($P=0.005$), and a higher chance of relapse ($P=0.0001$) [20]. Ulceration of the melanoma and lymphovascular invasion at the time of presentation were associated with a higher frequency of recurrence according to our analysis, which is in keeping with existing literature such as that by von Schuckmann et al. [12], Lyth et al. [13], and Kim et al. [19]—a clear indication that such cases need more aggressive management and surveillance.

A limitation of our study is that local, regional and distant recurrences were analyzed together. While these represent biologically distinct events, our retrospective database did not consistently differentiate between them. Future perspective studies should stratify recurrence by type to examine independent predictive factors for local versus metastatic disease.

This study's strength lies in its comparatively large sample size as well as in the confirmation of recurrence on tissue biopsy. Moreover, the data collected were diverse, broad-based, and covered a wide range of variables based on our institute's robust medical record keeping. Our study was limited by its retrospective nature and carries the restrictions inherent in this study design. In addition, as the patient data were collected from a single center which draws its patients from a specific part of the country, the results may not be generalizable to the whole population. Our findings help identify clinicopathological predictors of recurrence which can guide clinicians in tailoring follow-up intensity and surveillance. However, our study did not consider the variation in treatment modalities offered to each patient, which may have resulted in a degree of confounding within our results.

Conclusion

Advancing age, tumor stage, Breslow thickness, Clark stage, ulceration, and lympho-vascular invasion were all identified as significant clinicopathological factors associated with the increased frequency of melanoma recurrence. Future studies should aim to focus on incorporating these variables into a validated scoring system to predict recurrence and overall prognosis at the time of diagnosis. Such a tool should assist clinicians in tailoring surveillance and management strategies to the individual risk profile of each patient.

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