

SECOND PRIMARY CUTANEOUS MELANOMA: INCIDENCE AND ANALYSIS OF RISK FACTORS FROM A SINGLE REFERENCE UNIT IN BUENOS AIRES

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Glossary of abbreviations: cutaneous melanoma (CM), subdistribution hazard ratios (sHRs), confidence intervals (CIs)

Abstract

Introduction: Patients with a history of cutaneous melanoma have an increased risk of developing a second primary melanoma. However, epidemiological data from Argentina is limited.

Materials and methods: We conducted a retrospective study including patients with primary cutaneous melanoma between January-2010 and December-2025. Adult patients with clinically localized melanoma and at least 12 months of follow-up were included. The cumulative incidence of second primary melanoma was estimated using competing risks analysis, accounting for death as one. Factors associated with the development of a second melanoma were evaluated using Fine-Gray subdistribution hazard models.

Results: Of 638 patients included, 31 (4.8%) developed a second primary melanoma. The median time to diagnosis was 59 months (IQR 12–165). The cumulative incidence was 2.1% (95% CI 1.2–3.6) at 1 year, 4.8% (95% CI 3.1–7.2) at 3 years, 6.7% (95% CI 4.6–9.5) at 5 years, and 14.3% (95% CI 10.2–19.6) at 10 years. Increasing age was associated with a higher risk of developing a second primary melanoma (sHR 1.02 per year, 95% CI 1.01–1.03; $p = 0.004$). Patients older than 50 years had a significantly higher risk compared with those aged 50 years or younger (sHR 1.64, 95% CI 1.12–2.39; $p = 0.011$) whereas sex was not found to be associated.

Conclusion: In our series, approximately 5% of patients with cutaneous melanoma developed a second primary melanoma during follow-up. Older age was associated with an increased risk, supporting the importance of long-term surveillance in melanoma survivors.

Key words: cutaneous melanoma, second primary, incidence, risk factors

Resumen

Melanoma primario múltiple: incidencia y análisis de factores de riesgo de una única unidad de referencia en Argentina

Introducción: Los pacientes con antecedente de melanoma cutáneo tienen mayor riesgo de desarrollar un segundo melanoma primario. En nuestra región son escasos los datos epidemiológicos.

Materiales y métodos: Se incluyeron pacientes adultos operados de melanoma primario cutáneo clínicamente localizado entre enero-2010 y diciembre-2025, con seguimiento mínimo de 12 meses. La incidencia de segundo melanoma primario se estimó mediante análisis de riesgos competitivos (considerando el evento muerte). Los factores de riesgo asociados se evaluaron mediante modelos de riesgo de subdistribución de Fine-Gray.

Resultados: De 638 pacientes incluidos, 31 (4.8%) desarrollaron un segundo melanoma primario (SMP).

La mediana de tiempo al diagnóstico fue de 59 meses (RIC, 12-165). La incidencia acumulada fue del 2.1% (IC 95%, 1.2-3.6) al año, 4.8% (IC 95%, 3.1-7.2) a los 3 años, 6.7% (IC 95%, 4.6 – 9.5) a los 5 años y 14.3% (IC 95%, 10.2-19.6) a los 10 años. La edad avanzada se asoció con un mayor riesgo de desarrollar un SMP (HRs = 1.02/año, IC 95%: 1.01-1.03, $p = 0.004$). Los pacientes mayores de 50 años tuvieron un riesgo significativamente mayor en comparación con aquellos de 50 años o menos (sHR 1.64, IC 95%: 1.12-2.39, $p = 0.011$); no se encontró asociación con el sexo.

Conclusión: En nuestra serie, aproximadamente el 5% de los pacientes con melanoma cutáneo desarrollaron un segundo melanoma primario durante el seguimiento. La edad avanzada se asoció con un mayor riesgo. Se enfatiza la importancia del seguimiento a largo plazo.

Palabras clave: melanoma cutáneo, segundo primario, incidencia, factores de riesgo

KEY POINTS

Current knowledge

- Patients with a history of cutaneous melanoma have an increased risk of developing a second primary melanoma. However, epidemiological data from Latin American countries remains limited.

Article contribution to current knowledge

- In our series, approximately 5% of patients with cutaneous melanoma developed a second primary melanoma during follow-up. Older age was associated with an increased risk. Long-term surveillance in melanoma survivors is encouraged.

Management of patients with cutaneous melanoma (CM) has undergone substantial changes over the past decades¹. Improvements in treatment, together with increased detection of melanomas at earlier stages, have resulted in a growing population of melanoma survivors. Patients with a history of primary cutaneous melanoma have a significantly increased risk of developing a second primary melanoma. Reported incidence rates of a second (metachronous) primary melanoma after an initial diagnosis vary considerably between studies, ranging from ap-

proximately 2% to 10%²⁻⁶. This risk appears to be highest during the first year after diagnosis and remains elevated thereafter.

Several patient-related factors have been associated with an increased risk of developing a second primary melanoma, including older age, male sex, a high number of atypical nevi, and a family history of melanoma^{7,8}. Among these subsequent melanomas, *in-situ* lesions are reported more frequently than invasive melanomas. However, the incidence and cumulative risk of second primary invasive melanomas are not negligible and may have important prognostic implications^{9,10}. In this context, the rationale for structured and individualized follow-up programs becomes evident, as careful surveillance may facilitate earlier detection of new primary melanomas and allow potentially curative treatment.

The epidemiology of cutaneous melanoma in Latin America presents some challenges. The region is characterized by considerable geographic diversity and a heterogeneous population composed of individuals with indigenous, European, and African origins. In addition, epidemiological information and systematic data collection on melanoma remains limited in many Latin American countries, which complicates the generation of reliable information and a better understanding of disease patterns in this population.

Therefore, the aim of this study was to estimate the cumulative incidence of second primary melanoma and to identify risk factors associated with its development in an Argentinian single-centre cohort of patients with cutaneous melanoma.

Materials and methods

This was a single-center retrospective evaluation of patients with primary cutaneous melanoma treated between January 2010 and December 2025 at the Sarcoma and Melanoma Unit of our General Surgery Department (Hospital Británico, Buenos Aires). We included patients aged ≥ 18 years with clinically localized cutaneous melanoma and a minimum follow-up of 12 months. Second primary cutaneous melanoma was defined as a new primary cutaneous melanoma occurring at a different site from the previous tumor and confirmed histologically. Patients with synchronous melanoma (defined as diagnosis of a second cutaneous melanoma within the first 30 days of the first primary melanoma), melanoma of unknown

origin, metastatic disease at diagnosis or with loss of follow-up before 12 months were excluded.

The primary outcome was the incidence of second primary melanoma. Death from any cause was considered as a competing event. Secondly, demographic and pathological characteristics were compared between patients with single and multiple primary melanomas. Institutional Review Board permission was obtained for this study.

Patient characteristics (age at diagnosis, sex and phototype according to Fitzpatrick classification)¹¹ and primary tumor features (histologic subtype, Breslow thickness, ulceration, mitotic rate and lympho-vascular invasion) were recorded. Follow-up was calculated in months from the date of diagnosis of the first primary melanoma to the last date of outpatient clinic visit or death. The time interval between the first and second primary melanoma was calculated from the date of the first cutaneous melanoma diagnosis to the date of diagnosis of the second primary melanoma in months. Patients were followed according to institutional and guidelines recommendations: every 3 months the first 2 years, then every 6 months until the year 5 and annually thereafter with physical examination, chest radiography and hepatic ultrasound. Additionally, a dermatologic examination every 6-12 months was performed.

The relationship of categorical clinic-pathologic parameters between the different groups was assessed initially. Continuous variables are presented as mean (standard deviation) or median (interquartile range), as appropriate, and categorical variables as counts and percentages. Comparisons between groups were performed using Student's t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

The cumulative incidence of second primary melanoma was estimated using competing risks methodology, accounting for death as a competing event. This type of analysis was selected because death may preclude the occurrence of a second primary melanoma. Factors associated with the development of a second primary melanoma were assessed using Fine-Gray subdistribution hazard models, and results are reported as subdistribution hazard ratios (sHRs) with 95% confidence intervals (CIs). Variables included were based on clinical relevance and results from univariate analysis. All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

Due to the retrospective nature of this study, the Ethics Committee waived the requirement for written informed consent: however, all patients signed the surgical consent form.

Results

During the study period, 638 patients with non-metastatic first primary cutaneous melanoma were treated. A total of 31 patients (4.8 %) developed a second primary melanoma during follow-up. In 51% (16/31) of cases, diagnosis was performed after a dermatologic examination. The median time to diagnosis of a second melanoma was 59 (IQR: 12 – 165) months. Twelve patients (39%) were diagnosed within the first three years of follow-up, and another 8 patients developed a second melanoma more than 10 years after their first melanoma. Most second primaries were invasive melanomas (55%, 17/31) with a median Breslow thickness of 1.2 mm, while *in-situ* lesions accounted for 45% (14/31) of cases. Of note, 70.5% (12/17) of patients who presented a second invasive melanoma had initially an *in-situ* melanoma. Three patients developed more than two melanomas. Baseline characteristics of patients with solitary and multiple primary melanomas are shown in Table 1.

With a median follow-up of 24 months (IQR: 12-48) months, the cumulative incidence of second primary melanoma was 2.1% (95% CI 1.2-3.6%) at 1 year, 4.8% (95% CI 3.1-7.2) at 3 years, 6.7% (95% CI 4.6-9.5) at 5 years and 14.3% (95% CI 10.2-19.6) at 10 years, accounting for death as a competing risk.

In univariate analysis (Table 1), age > 50 years was significantly associated with the development of a second primary melanoma ($p < 0.05$). In Fine-Gray competing risks regression analysis, increasing age was associated with higher risk of second primary melanoma (sHR 1.02 per year, 95% CI 1.01-1.03; $p = 0.004$). When categorized, patients aged > 50 years had a significantly higher risk compared to those aged ≤ 50 years (sHR 1.64, 95% CI 1.12 – 2.39; $p = 0.011$). Male sex (sHR 1.26 for males vs. females, 95% CI 0.89 – 1.79; $p = 0.19$) and initial melanoma type (*in-situ* vs. invasive) (sHR 1.15; $p = 0.61$) were not independently associated with the development of additional primary melanomas (Table 2).

Table 1 | Characteristics of patients with and without multiple melanoma

Parameter	Multiple melanoma n = 31	Solitary melanoma n = 611	p
Sex, n (%)			0.48
Male	17	328	
Female	14	283	
Age, mean (SD), ys	74 (+/- 13.4)	62 (+/- 15.7)	< 0.001
>50 years	27	386	
≤50 years	4	225	
Tumor location			0.09
Head and neck	0	31	
Trunk	13	291	
Upper extremity	6	106	
Lower extremity	11	183	
Phototype, n (%)			1
I-II	17	130	
III-IV	7	55	
No data	7	333	
Breslow thickness, mm			0.08
Median (IQR)	1 (0.6-2)	1.5 (0.76-3)	
Tumor staging (AJCC8), n (%)			0.27
T0 (<i>in-situ</i>)	15	96	
T1	7	196	
T2	5	113	
T3	3	102	
T4	1	77	
No data	0	27	
Histological Subtype, n (%)			0.15
SSM	13	348	
LMM	1	17	
NM	2	92	
ALM	0	21	
IS	15	93	
Others	0	40	
Tumor ulceration			0.64
Present	3	132	
Absent	28	405	
No data	0	74	
Mitotic rate			0.41
0	21	244	
1-2 /mm ²	6	194	
≥ 3 /mm ²	4	61	
No data	0	113	
Lymphovascular invasion			0.08
Present	3	13	
Absent	28	598	
Follow up, median, months	34 (21-63)	24 (12 – 48)	

AJCC8: American Joint Committee on Cancer 8th Edition; SSM: superficial spreading melanoma; LMM: lentigo maligna melanoma; NM: nodular melanoma; ALM: acral lentiginous melanoma; IS: in-situ melanoma

Table 2 | Multivariable Fine-Gray competing risks regression analysis for second primary melanoma

Variable	Subdistribution Hazard Ratio (sHR)	95% Confidence Interval	p-value
Sex (male vs female)	1.26	0.89-1.79	0.19
Age > 50 (vs ≤ 50 years)	1.64	1.12-2.39	0.011
Initial melanoma in-situ (vs. invasive)	1.15	0.66-2.01	0.61

Discussion

In this study of patients with cutaneous melanoma, 4.8% of patients had a second primary melanoma during follow-up. Age greater than 50 years was significantly associated with an increased risk of developing a second melanoma, whereas sex was not significantly associated with the development of additional primary melanomas.

Information on CM in Latin America remains limited. Differences in data collection, the limited number of studies reporting incidence and mortality rates, geographic diversity and the heterogeneous population in the region (native inhabitants and European and African descendants) make it challenging to draw reliable conclusions¹²⁻¹⁶. In this context, our study provides real-world data on the incidence and risk factors for second primary melanoma in our country.

The incidence of second primary melanoma observed in our cohort is consistent with previous studies from different populations, describing rates between 2-10%. Several studies report that most second melanomas are diagnosed during the first year after initial diagnosis and then the incidence remains stabilized thereafter. However, in our study the cumulative incidence increased progressively over time. In fact, 25% of second melanomas were diagnosed more than 10 years after the first melanoma. Other studies have also shown that cumulative incidence continues to increase with longer follow-up periods^{3,8}. Win Myint et al, analyzed the risk of subsequent new invasive melanomas after primary in-situ or invasive cutaneous melanoma in New Zealand. In both cohorts they had 5% incidence rate of second primary invasive melanomas and also reported an increased cumulative incidence over time⁸. Moreover, in our study 70% of patients with multiple primary melanoma developed an invasive melanoma during follow-up

after a first in-situ melanoma. This has relevant clinical and prognostic implications. Some studies or guidelines do not include in-situ melanomas as part of their analysis or surveillance recommendations^{17,18} despite published data reporting that the risk of second invasive melanoma is similar whether the primary lesion was in-situ or invasive^{3,19-21}. Consequently, and based on our results, no patient should be underestimated and be included in a standardized follow-up schedule by a health care physician experienced in melanoma. Additionally, approximately half of second melanomas were detected during dermatologic examinations, highlighting the value of multidisciplinary follow-up involving dermatologists and clinicians experienced in melanoma management.

Several factors have been associated with the development of second primary melanoma. Described risk factors include the presence of numerous or atypical melanocytic nevi, fair skin phototypes, and a family history of melanoma^{7,15,16,22}. Male sex is another risk factor frequently reported although not across all studies such as ours^{4,6}. Competing risk analysis further confirmed age as an independent predictor of second primary melanoma in our study. Increasing age has consistently been identified as a risk factor in other studies, likely reflecting cumulative ultraviolet radiation exposure^{3,6,9}. An additional finding of our study was that the type of the initial melanoma (in-situ vs. invasive) was not associated with the risk of second primary melanoma as described in previous population-based studies^{3,19,20}. This suggests again that surveillance strategies should not be based solely on the type of initial melanoma (in-situ or invasive).

This study has some limitations. First, it is a retrospective single-center analysis, which may limit the generalizability of the findings. Second,

the median follow-up of the cohort was relatively short. However, the use of competing risk analysis allowed a more accurate estimation of cumulative incidence over time. Longer follow-up would further strengthen these findings. Third, our study was not able to account for all the risk factors for second melanoma such as family history or previous dysplastic nevi. However, to the best of our knowledge, this is the first national

study and one of the few analysis addressing this topic using competing risk methodology.

Our results highlight the importance of long-term follow-up and regular dermatologic surveillance in patients with melanoma, particularly in older patients, as second primary melanomas may occur several years after the initial diagnosis.

Conflict of interest: None to declare

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