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BRIEF REPORT

Clinical Features and Survival of Multiple Primary Melanoma: A Belgian Single Center Cohort

G. Absil · P. Collins · L. Seidel · T. Damsin · A. F. Nikkels

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ABSTRACT

Introduction: It remains unclear whether multiple primary melanoma (MPM) patients have a worse survival prognosis compared with single primary melanoma (SPM) patients.
Objectives: To investigate the demographics, histological features, and survival of MPM versus SPM patients.
Methods: Cox regression analyses compared survival between SPM and MPM patients. Furthermore, demographics and histological features of the MPM cohort were compared with the SPM patients retrieved from dermatopathology files between 2000 and 2019.
Results: Out of 3853 melanoma patients, 95 MPM patients were retrieved: 81 with two primary melanomas (85.2%) and 14.8% with three or more. Mean Breslow of the first melanoma was 0.84 mm [minimum (min): 0 mm, maximum (max): 16 mm, standard deviation (SD) 1.77] versus 0.37 mm (second MPM) (min: 0 mm, max: 2.5 mm, SD 0.50) and 0.33 mm (third MPM) (min: 0 mm, max: 0.6 mm, SD 0.22). The mean Breslow for the second MPM was significantly higher for men than women (0.59 mm versus 0.27 mm). First and second melanoma in MPM patients developed on pre-existing melanocytic nevi in 13% and 12%, respectively. In contrast with the mean age of primary melanoma in Belgium for women (58.2 years) and men (63.3 years), MPM patients developed their first melanoma earlier, at 44.8 years and 54.6 years, respectively. The mean distribution of anatomical localization of primary and secondary melanoma was highly similar in women, whereas in men a shift towards lower extremities was observed (19% versus 28%). The thicker the primary melanoma was, the sooner the second appeared. Follow-up (2–4/year) versus (1/year) yielded a mean Breslow of 0.29 mm and 0.55 mm, respectively. Cox regression analysis with time-varying covariate revealed a tendency for a worse prognosis in 5-year survival rates, but this was not statistically significant ($p = 0.09$). Patient phenotypes were not available on the histological reports.
Conclusion: A closer follow-up regimen of MPM versus SPM patients is probably justified.

Keywords: Multiple primary melanomas; Melanoma; Survival; Follow-up

G. Absil · T. Damsin · A. F. Nikkels (✉)
Department of Dermatology, CHU du Sart Tilman, University of Liège, 4000 Liège, Belgium
e-mail: Af.nikkels@chuliege.be

P. Collins
Department of Dermatopathology, CHU du Sart Tilman, University of Liège, 4000 Liège, Belgium

L. Seidel
Department of Biostatistics, CHU du Sart Tilman, University of Liège, 4000 Liège, Belgium

Key Summary Points

Why carry out this study?

It remains unclear whether patients with a history of multiple primary melanomas (MPM) have a worse survival prognosis compared with single primary melanoma (SPM) patients. This study investigates the demographics, histological features, and survival of MPM versus SPM patients to determine if (1) some subgroups are more at risk to develop MPM, (2) MPM patients present a worse survival compared with SPM patients, and (3) adaptations of the follow-up protocols of CM patients are required.

What was learned from the study?

A younger age at first diagnosis was identified as a risk factor for developing MPMs. Furthermore, the results sustain the hypothesis that MPM patients might have a worse overall survival compared with SPM patients, and that an increased follow-up is recommended.

INTRODUCTION

Cutaneous melanoma (CM) represents a significant health burden, especially in fair-skinned populations [1]. The incidence of CM is steadily increasing throughout the world [2]. In Belgium, CM represents the fourth and sixth most frequent cancer in women and men, all ages considered, respectively [3]. Approximately 3500 new CM cases are diagnosed each year, but these numbers are steadily rising, with an annual increase of approximately 5% [4].

Patients with a history of CM are at risk of developing subsequent melanomas. The risk of developing a second primary melanoma in CM patients is higher than the risk of developing a first CM in the general population [5]. The frequency of multiple primary melanomas (MPM) ranges from 0.2% to 12.7% of CM patients [5–24].

Although different scientific societies have published guidelines (including European Society Medical Oncology (ESMO), European Organization for Research and Treatment of Cancer (EORTC), European association of dermato-oncology (EADO), European Dermatology Forum (EDF), and American Academy of Dermatology (AAD)), there is no unanimous consensus for the dermatological follow-up of CM patients, which is mostly based on the initial tumor staging and not on the risk of subsequent melanoma [25–27]. Standard follow-up in our center is, regardless of staging, every 3 months for the first 2 years, followed by twice a year for the next 3 years, and then annually for the long term.

To investigate if MPM patients require a specific follow-up regimen, this study evaluated whether SPM versus MPM patients present different survival rates, and compared the demographics and histological features of SPM and MPM patients.

MATERIAL AND METHODS

Patients

The local university ethics committee approved the design of the study (ref. 2017/334). From the melanoma database from the Dermatopathology Department of the University Hospital Centre of Liège, all patients diagnosed with CM between 1 January 2000 and 31 July 2019 were selected. Among those, MPM patients were identified by matching the names appearing twice or more in the histological records of melanoma. Both in situ and invasive melanomas were included in this study. Metastatic and recurrent CM were excluded.

Demographics

From all the MPM patients, date of birth, gender, age at the diagnosis of the first and subsequent melanomas, the respective anatomical locations, and the delay between the first and

Table 1 Total number of patients and MPM patients, gender, and vital status at the end of the study

Variable	Categories	*N*	Number (%)
Gender		3853	
	F		2363 (61.3)
	M		1490 (38.7)
Vital status		3853	
	Alive		3384 (87.8)
	Dead		469 (12.2)
MPM		3853	
	No		3758 (97.5)
	Yes		95 (2.5)

subsequent melanomas were recorded. The vital status and eventual date of death of all the SPM and the MPM patients at the end of the study (31 July 2019) was identified using the civil registries.

Histology

All the histological slides of the primary and subsequent primary melanomas were reexamined by one dermatopathologist according to the latest staging guidelines, including melanoma subtype, Clark level, Breslow's thickness, mitotic activity, tumor-infiltration lymphocytes (TIL), presence of microscopic satellites, lympho-vascular embolization, neurotropism, presence of ulceration, melanomas developing on previous existing melanocytic lesions, and signs of regression [28]. Furthermore, the expression of immunohistochemical markers, including HMB45, P16, SOX10, Ki-67, and Melan-A were reassessed in the primary and subsequent melanomas.

As the data of the dermatopathology files of the SPM were not always available, we used the mean Breslow index of SPM of 0.90 (IQR 0.52–1.80) mm as the reference population [24].

Survival

Survival probabilities of SPM and MPM patients were represented using Kaplan–Meier curves, yielding global 5-year survival rates. Subsequently, univariate and multivariate Cox regressions were performed, with and without a time-varying covariate to assess the impact of the survival bias of the immortal time for the MPM patients, yielding a hazard ratio (HR) for death risk [24].

Table 2 Age at first melanoma, duration of follow-up since first melanoma diagnosis, and time interval between first and second melanomas

Variable	Mean	SD	*p*-Value
Age at first melanoma (years)			
SPM	53.76 years (n = 3758)	18.739	0.014
MPM	48.98 years (n = 95)	17.667	
Follow-up since first melanoma (months)			
SPM	100.08 months (n = 3758)	65.188	< .0001
MPM	139.48 months (n = 95)	59.280	
Delay between first and second melanoma (months)			
MPM	50.60 months (n = 95)	48.805	NA

Statistics

Continuous variables are presented as means, standard deviations (SDs), or medians (quartiles). Qualitative variables are presented as frequency tables. Quantitative parameters were compared using Student's *t*-tests (Kruskal–Wallis test) and qualitative parameters were compared using chi-squared tests.

RESULTS

Demographics

The total number of patients and MPM patients, gender, vital status at the end of the study, age at first melanoma, time interval between first and second melanoma, and duration of follow-up since first melanoma diagnosis are presented in Tables 1 and 2. Out of the cohort of 95 MPM patients (females: 66.3%; males: 33.7%), 81 presented with 2 (85.2%), 10 with 3 (10.5%), 3 with 5 (3.2%), and 1 with 8 primary melanomas (1.1%).

Among the second melanomas, 65 (68.4%) were diagnosed during the first 5 years following diagnosis of the first melanoma, and 30 (32.6%) were diagnosed after more than 5 years. Figure 1 shows the number of cases per year diagnosed after the first diagnosis. Moreover, four patients had synchronous tumors, defined as less than 30 days between excision of first and second lesions. Regarding tumor localization on the body, the most common location was the lower extremities, followed by the trunk, then other sites.

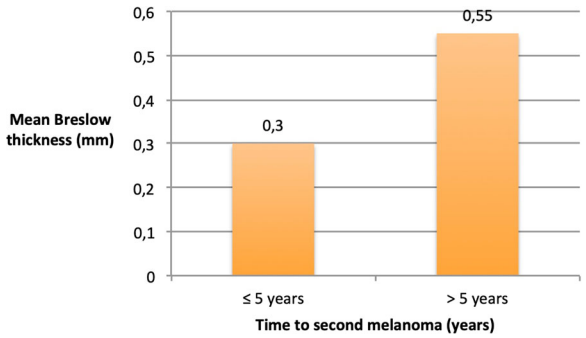

Fig. 2 Mean Breslow thickness of the second melanomas diagnosed during or after the first 5 years

Histology

Among the 95 MPM patients, 29 (30.5%) presented an in situ melanoma as their first melanoma. Among the second melanomas, 38 (40%) were in situ melanomas. Out of the 29 first in situ melanomas, 14 (48%) developed a second invasive melanoma. Moreover, there were significantly more in situ second melanomas in the first 5 years ($n = 31$) than > 5 years ($n = 7$).

The mean Breslow thickness of the first melanomas (0.84 mm; min: 0; max 16 mm; SD

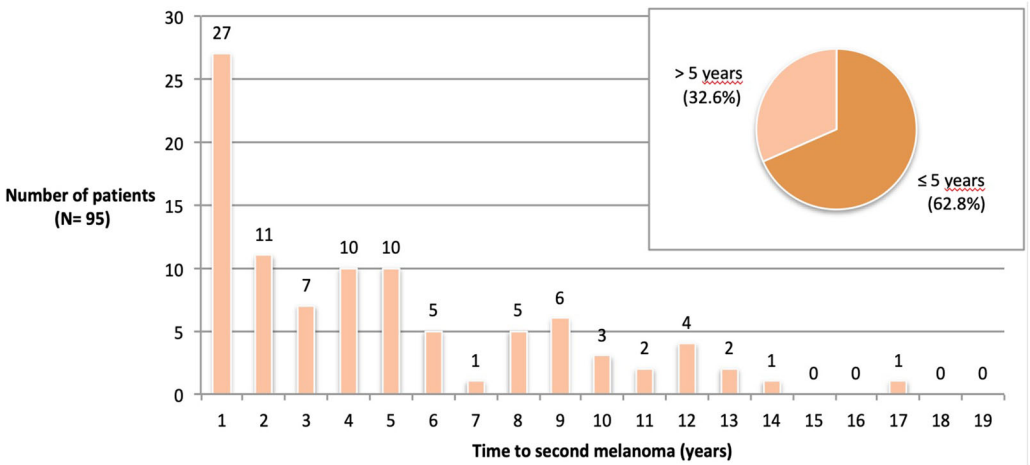

Fig. 1 Number of cases per year diagnosed after the first diagnosis

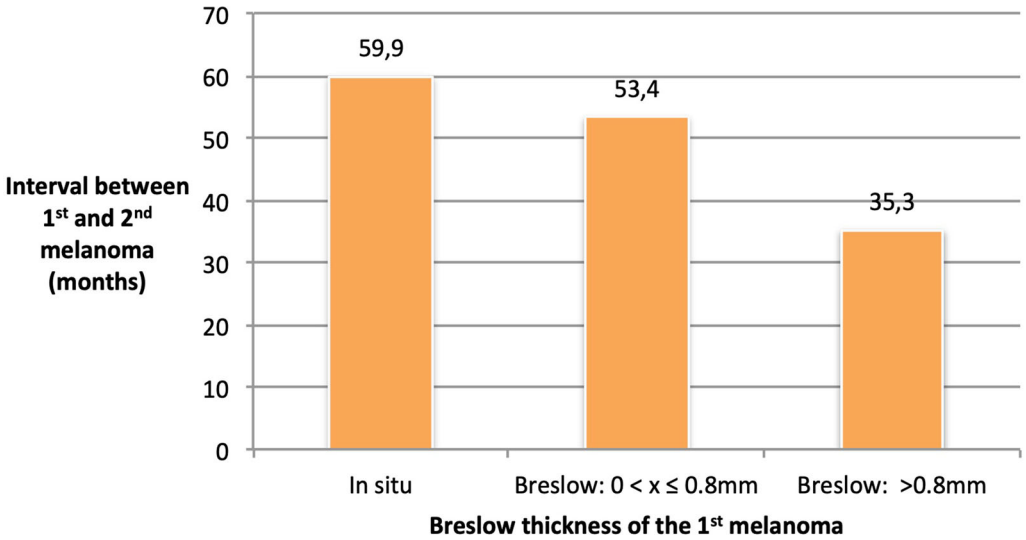

Fig. 3 Mean time interval between first and second melanoma according to the Breslow thickness of the first melanoma

1.77) was greater than that of the second (0.38 mm) and third (0.33) invasive melanomas.

The mean Breslow thickness of the second melanomas diagnosed in the first 5 years after the first one was 0.30 mm, compared with 0.55 mm after the first 5 years (Fig. 2). Concerning the other histological features, including melanoma subtype, Clark level, mitotic activity, tumor-infiltration lymphocytes (TIL), presence of microscopic satellites, lympho-vascular embolization, neurotropism, presence of ulceration, melanomas developing on previous existing melanocytic lesions, and signs of regression, no differences were found between the first and subsequent melanomas.

MPM patients with a greater Breslow thickness for the first melanoma had a significantly decreased mean interval between first and second tumor (Fig. 3).

Histologically, most first tumors were superficial spreading melanomas (64.2%), followed by in situ melanomas (28.4%), nodular melanomas (6.3%), and lentigo maligna melanomas (1.1%). The distribution for the second melanomas was similar, except for lentigo maligna melanomas being as frequent as nodular melanomas.

In MPM patients, the percentages of the first and second melanoma developing on preexisting naevi were 13% and 12%, respectively.

Survival

The overall 5-year survival rates of the total cohort of MM patients (n = 3853) was 91.5%. The overall survival rate of the SPM group (n = 3758) and the MPM group (n = 95) were 91.4% and 96.8%, respectively (Fig. 4).

The univariate and multivariate (adjusted for sex and age) Cox regressions revealed no statistically significant differences between death risk for SPM and MPM patients, respectively (p = 0.26, p = 0.99).

Taking account of the phenomenon of immortal time, the univariate Cox regression did not reveal a statistical difference (HR 1.219, p = 0.52), whereas the multivariate Cox regression, adjusted for age and sex, revealed a tendency towards a worse prognosis with a HR of 1.683 (p = 0.09).

DISCUSSION

The incidence of MPM is in our population was 2.5%, similar to the 0.2–12.7% reported in other series [5–24].

Contradictory results regarding the sex ratio in MPM patients were described, but our population presented a significant preponderance of female patients [5–7, 9, 11–15, 17, 19–22, 24, 29]. In fact, the sex ratio seems to correlate with that of the

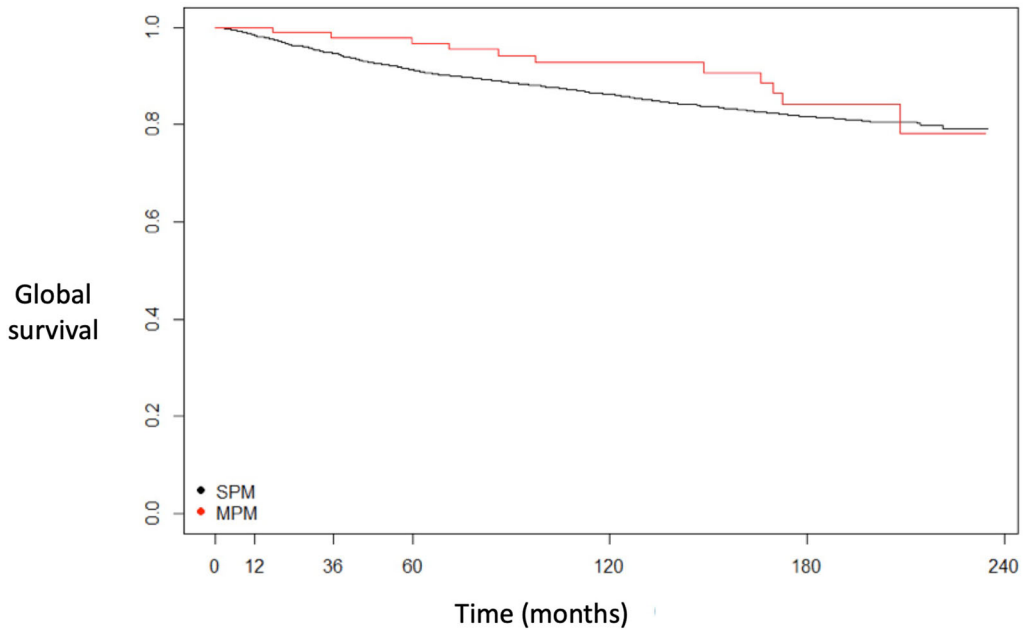

Fig. 4 Global 5-year survival rates of SPM and MPM patients

SPM population, as published in previous studies [6, 11, 14, 15, 22]. Moreover, 10 out of the 14 (71%) patients with three or more melanomas were females, contrasting with previous observations stating that male patients tended to have a greater number of primary melanomas [7, 13].

Regarding the age at first diagnosis of MPM patients, our results indicated a younger age (male = 54.6 years, female = 44.8 years) compared with the age at first diagnosis in SPM patients (male = 63.3 years, female = 58.2 years) [6, 12]. However, other authors described the opposite trend [13, 19, 21, 22, 24, 29]. This may be explained by the higher number of patients included with a stronger statistical significance.

In accordance with previous reports, the majority of MPM patients developed two primary tumors [6–14, 17, 19, 20, 22–24].

Again, as mentioned in previous studies, the subsequent melanomas were more likely to be in situ or thinner than the first one. [6–12, 14–19, 22–24] This phenomenon has been linked to closer follow-up visits and self-surveillance [11, 12, 16, 22]. In addition, one study failed to prove that MPM patients have a less aggressive tumor biology [22]. Furthermore, 22 patients (23%) had a second melanoma with a higher Breslow thickness than the first melanoma, consistent with previous results [6, 14, 15]. This may be related to the fact that some patients evade medical surveillance by noncompliance or relocation.

Of the second subsequent melanomas, 28.4% of the total number of MPM detected were surgically excised during the first year, rising to 38.9% in the first 2 years, and to 68.4% within 5 years. The remaining 31.6% were excised after 5 years. This is in line with previous studies reporting that the majority of second subsequent tumors were detected within the first 2 years. [6, 8, 14, 15, 17, 18, 20] Only four patients (4.2%) had synchronous lesions, defined as multiple melanomas excised within 3 months, contrasting with previous findings, ranging from 13% to 45%. [6–8, 10–15, 17, 20, 23]

Regarding the anatomical region, the lower extremities were the most common site in women for SPM and MPM, while the posterior trunk was the most frequent in men. Only one article revealed the head and neck area as the most commonly involved site [19]. The anatomical site of the first and second subsequent melanomas was the same in 44% patients, similar to previous results. [7, 10, 11, 14, 15, 22]

Our study revealed that the Breslow's thickness of second subsequent melanomas

diagnosed during the first 5 years was lower (0.3 mm) than those diagnosed after 5 years (0.55 mm). Furthermore, there were more in situ melanomas identified during the closer follow-up schedule (< 5 years) (31/65; 47.7%) than afterwards (7/30; 23.3%). Again, these demonstrate the benefit of a closer follow-up system.

Another interesting finding was that the thicker the primary melanoma was, the sooner the subsequent was identified (Fig. 3). This could be linked to a better compliance to the follow-up by the patient, as an initial prognosis of a thicker lesion probably renders the patient and the dermatologist more observant.

Concerning the overall survival of MPM patients, two major hypotheses are given: first, survival could be better for SPM patients as follow-up is usually closer and there might be an immunological surveillance, as has been described for patients with three or more primary melanomas [13]. On the contrary, survival could be worse as there could be an increased risk for metastasis. [29] Our results evidenced only a slight difference in overall survival (91.4% versus 96.8%) at 5 years. Avoiding the methodological bias of the "survival bias" or "immortal time," the statistical analysis also showed a tendency of worse survival for MPM patients (HR 1.683, $p = 0.09$), in accordance with previous publications [24, 30]. Another study used delayed-entry methods and also found a worse survival for MPM patients [29]. Finally, it has also been suggested that including in situ melanomas in the survival studies does not influence the survival of MPM patients, and that it might dilute the opportunity to detect a real effect [31].

One limitation of these results could be that some subsequent melanomas could have been excised in other centers, underestimating the number of MPMs.

Another limitation is that data relating to familiarity, the presence of predisposing mutations, *BRAF* mutational status, and general endogenous and exogenous risk factors in both groups of patients were not available in our study cohort.

A final limitation is that only the overall survival was studied and not the melanoma-related death rate. Having MPMs could decrease the overall 5-year survival not only due to melanoma, but also to other medical origins or a genetic predisposition for other cancer types; data that were not available in our database.

CONCLUSIONS

In our cohort, a younger age at first diagnosis was identified as a risk factor for developing subsequent melanomas. Furthermore, our results sustain the hypothesis that MPM patients might have a worse overall survival compared with SPM patients, and that an increased follow-up is recommended.

Guidelines should take this phenomenon into consideration, and patients with cutaneous melanoma regardless of the tumor thickness should be followed-up for life. Precise follow-up regimens are still to be determined. In the future, genetics may be added as an additional tool to identify patients at risk of MPM.

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Author contributions. G. Absil, P. Collins, L. Seidel, T.Damsin and AF Nikkels contributed to the study conception and design. Material preparation, data collection and analysis were performed by G. Absil and AF Nikkels. Statistical analysis was performed by L. Seidel. Histopathological reviews were performed by P. Collins. The first draft of the manuscript was written by Gilles Absil and all authors commented on previous versions of the manuscript.

Disclosures. Gilles Absil, Patrick Collins, Laurence Seidel, Thomas Damsin and Arjen F. Nikkels declare that they have no competing interests.

Ethics. The institutional ethics committee (« Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège») approved the research (Ref 2017/334).

Data availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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