

Multiple primary melanomas: Our experience

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Abstract. Patients with melanoma have an increased risk of having other neoplasms, and particularly other melanomas and non-melanoma skin cancers. The study aimed to describe multiple primary melanomas in a large medical university centre from Romania (Cluj-Napoca) from 2004 to 2020. Out of 699 patients with melanoma included in the study, 26 (3.71%) developed multiple tumours. The 26 patients developed a total of 59 melanomas, corresponding to a mean of 2.3 melanomas per patient. The site and histological subtype of the first and second melanomas were not consistent. The proportion of subsequent melanomas that were *in situ* (51.5%) or thin melanomas (<1 mm, 24.2%) was higher compared with first melanomas (7.7%, respectively 11.5%). The median and mean time to diagnosis was 2.75 months, respectively, 28.09 months. In total, 76.92% of second melanomas were detected within three years, but we were able to document a subsequent melanoma more than ten years after the first diagnosis. The study highlights the importance of follow-up in patients diagnosed with melanoma, not only in the first years after the primary diagnoses but for the entire life.

Introduction

Although cutaneous melanoma represents only 10% of the total cutaneous malignant tumours, it is responsible for over 90% of the deaths caused by these tumours (1). Incidence rates of cutaneous melanoma are increasing worldwide in the

fair-skinned population (2). However, early detection and the development of new drugs for metastatic melanoma lead to an increased survival rate and, therefore, an increasing population at risk of developing other neoplasms, especially cutaneous malignant tumours (3-5). It is well known that patients with melanoma have an increased risk of having other neoplasms, and particularly other melanomas and non-melanoma skin cancers (6-16). A personal history of melanoma proved to be a potent risk factor for the development of a subsequent primary melanoma (6-16). Multiple lesions can be detected as synchronous or asynchronous lesions. Synchronous lesions are defined as subsequent primary melanomas diagnosed within three months of the incident primary melanoma (7). Studies show that the percentage of patients who develop multiple primaries ranges from 0.2 to 8.6%, out of which 26-40% develop as synchronous lesions (7,8). The risk of a subsequent primary melanoma seems to be higher in the first year following the first diagnosis, but it remains increased for at least 20 years (7,8).

The present study aimed to describe multiple primary melanomas in a large medical university centre from Romania (Cluj-Napoca) from 2004 to 2020, focusing on the number of lesions detected, tumour and patient characteristics, as well as time to subsequent diagnosis.

Materials and methods

Setting. This observational, retrospective, cohort study was carried out in Cluj County, in the North-Western Region of Romania. The present study was approved by the Ethics Committee of 'Iuliu Hațieganu' University of Medicine and Pharmacy (Cluj-Napoca, Romania).

Participants. All patients diagnosed with melanoma and followed-up in the Dermatology Department of the Cluj-Napoca Emergency County Hospital were eligible for analysis. Patients identified as having more than one invasive or *in situ* melanoma, followed up for at least one year, were included in the study. Data on patient characteristics included age, sex, family history of melanoma, presence of atypical nevi. The tumour was characterised according to the site (head and neck, trunk, upper limbs and lower limbs), histological subtype [superficial spreading melanoma (SSM), lentigo

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maligna melanoma (LMM), nodular melanoma (NM) and acral lentiginous melanoma (ALM) other], other histological characteristics (Breslow index, presence of mitosis, ulceration, vascular and neural invasion) and melanoma stage. The time to diagnosis was defined as the time from the first melanoma diagnosis to subsequent melanoma diagnosis. Subsequent melanomas were divided into synchronous and asynchronous melanomas. Synchronous melanomas were defined as those diagnosed simultaneously or within the first three months after the diagnosis of the first melanoma.

Statistical analysis was carried out using the MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd.; <https://www.medcalc.org>; 2020). Quantitative variables were expressed as mean and standard deviation, or median and 25-75 percentiles, depending on the normality of distribution. Qualitative data were characterised as frequency and percentage. Comparisons between groups were performed with Man-Whitney or chi-square test. The agreement between several variables (location and histology of melanoma) was established with Cohen's kappa coefficient. A P-value <0.05 was considered statistically significant.

Results

During the 16 years of the study period, 699 patients developed 732 melanomas. Out of the study population, 318 (45.4%) were men, and 381 (54.5%) were women. Of all patients, 673 (96.28%) developed only one primary melanoma, whereas 26 (3.71%), 11 men and 15 women, developed multiple tumours. The median age of the patients having multiple primaries at the diagnosis of the first melanoma was 55.34 (25-75th percentile: 40.37-64.29) and the mean 52.47 years (SD 14.129). There were no statistically significant differences regarding gender and age between patients with one or multiple primary melanomas.

The 26 patients with multiple primaries developed a total of 59 melanomas (26 for men and 33 for women), corresponding to a mean of 2.3 melanomas per patient. Most patients (n=21, 80.76%) developed only 2 melanomas; 3 patients (11.53%) developed 3 melanomas and 2 patients (7.69%) developed 4 melanomas.

Table I describes the tumour characteristics of the first melanoma, compared with the characteristics of subsequent melanomas.

We studied the concordance between the site of the first and second melanoma, and we found a fair concordance ($P=0.007$) (Table II). In 14 of the second melanomas (53.84%) the site coincided with the first melanoma, a fact that occurred more frequently on melanomas occurring on the head and neck (80%), followed by those on the trunk (61.5%).

Regarding the histological subtype, the superficial spreading melanoma was the most frequent type in both first and subsequent melanomas, but nodular melanoma was more frequently seen as the first primary. We studied the concordance between the histological subtype of the first and second melanoma, but we found no concordance ($P=0.087$) (Table III).

Analysis of the distribution of multiple primary melanomas with respect to their Breslow index, showed that a higher proportion of subsequent melanomas were *in situ* (51.5%)

or thin melanomas (<1 mm, 24.2%) compared with first melanomas (7.7%, respectively 11.5%), the difference being statistically significant ($P<0.05$). Except for two patients, in whom the Breslow index for the first tumour was not specified, all the others had proper registration of the tumour thickness both for the first and subsequent melanomas. Twelve out of the last patients had invasive melanoma in both the first and second melanoma; ten (83.33%) patients developed thinner second melanoma, while thicker second melanoma was documented in two (16.66%) patients. One of the patients, who had *in situ* melanoma as the first primary, developed an invasive second melanoma. All the patients with more than two melanomas developed thinner subsequent melanomas.

Ulceration and lymph node involvement were more common in the first primary tumour. Regarding stage at diagnosis, most of the subsequent melanomas were *in situ* or stage I, while first primary melanomas had a higher probability of being stage II or more advanced.

The median time to diagnosis was 2.75 months (25-75th percentile: 0-30.99), while the mean was 28.09 months (SD 58.511). From the subsequent melanomas, 13 (45.45%) developed as synchronous tumours. Out of the 15 (57.69%) patients with multiple lesions, four (15.38%) had a subsequent melanoma within the first and second year. Still, five patients (19.23%) were diagnosed with a subsequent melanoma after >5 years of follow-up (Fig. 1).

Discussion

The present study was conducted to document multiple primary melanomas in a large medical university centre from Romania (Cluj-Napoca), in the period from 2004 to 2020. The study focused on the number of lesions detected, tumour and patient characteristics, as well as time to subsequent diagnosis, being the first study performed in this country.

In our study comprising a series of 699 patients with melanoma, 3.71% developed a second melanoma during the follow-up, an incidence in the range reported in previous studies and similar with the one reported by Pastor-Tomás *et al* in Valencia, Spain (6). However, the literature presents an incidence which varies from 0.2 to 8%, variability caused by the lack of homogeneity in the studies, but also by differences in ultraviolet radiation across geographical regions (6-16). Moreover, the above-reported incidence may underestimate the lifetime incidence due to limited data capture and follow-up periods (7).

Most patients in our study developed only two primary melanomas, but two patients developed four primary melanomas during follow-up. In the literature, we found a reported case of as many as 48 melanomas in one patient (17).

In 53.84% of the cases, the site of the first and second melanoma was the same, the correlation being fair. The head/neck, followed by the trunk, was the site with the highest correlation. In contrast, other studies failed to show a correlation between the first and second site (6,18-21). These findings emphasise the importance of full skin examination in melanoma patients, not only at the first visit but also at follow-ups. However, close surveillance of the same body region as the initial primary melanoma in the follow-up is equally important (6-8).

Table I. Tumour characteristics of the first and subsequent melanomas.

Characteristics	First melanoma n (%)	Subsequent melanoma n (%)	P-value
Histological subtype			0.025
SSM	16 (61.5)	26 (78.8)	
NM	8 (30.8)	1 (3.0)	
LMM	-	3 (9.1)	
ALM	-	1 (3.0)	
Not specified	2 (7.7)	2 (6.1)	
Breslow index			0.001
<i>In situ</i>	2 (7.7)	17 (51.5)	
<1 mm	3 (11.5)	8 (24.2)	
1-2 mm	6 (23.1)	4 (12.1)	
2-4 mm	10 (38.5)	3 (9.1)	
>4 mm	3 (11.5)	1 (3.0)	
Not specified	2 (7.7)	-	
Ulceration			0.012
No	14 (53.8)	27 (81.81)	
Yes	9 (34.6)	3 (9.09)	
Not specified	3 (11.5)	3 (9.09)	
Lymph node involvement			0.008
No	19 (73.1)	31 (93.93)	
Yes	5 (19.2)	-	
Not specified	2 (7.7)	2 (6.07)	
Stage			0.001
MIS	2 (7.7)	17 (51.5)	
IA	3 (11.5)	10 (30.3)	
IB	4 (15.4)	4 (12.1)	
IIA	3 (11.5)	-	
IIB	5 (19.2)	2 (6.1)	
IIC	1 (3.8)	-	
IIIA	1 (3.8)	-	
IIIB	-	-	
IIIC	3 (11.5)	-	
IV	2 (7.7)	-	
Not specified	2 (7.7)	-	
Total	26 (100)	33 (100)	

SSM, superficial spreading melanoma; NM nodular melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma.

Table II. Concordance between the site of the first and second melanoma.

First melanoma	Second melanoma				Total (%)
	Head/neck (%)	Trunk (%)	Upper limbs (%)	Lower limbs (%)	
Head/neck	4 (80)	1 (7.7)	0 (0)	0 (0)	5 (19.2)
Trunk	1 (20)	8 (61.5)	1 (25)	2 (50)	12 (46.2)
Upper limbs	0 (0)	2 (15.4)	1 (25)	1 (25)	4 (15.4)
Lower limbs	0 (0)	2 (15.4)	2 (50)	1 (25)	5 (19.2)
Total	5 (100)	13 (100)	4 (100)	4 (100)	26 (100)

Table III. Concordance between the histological subtype of the first and second melanoma.

First melanoma	Second melanoma					Total (%)
	SSM (%)	NM (%)	LMM (%)	ALM (%)	Not specified (%)	
SSM	15 (68.2)	1 (100)	0 (0)	0 (0)	0 (0)	16 (61.5)
NM	6 (27.3)	0 (0)	1 (100)	1 (100)	0 (0)	8 (30.8)
LMM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not specified	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (100)	2 (7.7)
Total	22 (100)	1 (100)	1 (100)	1 (100)	1 (100)	26 (100)

SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma.

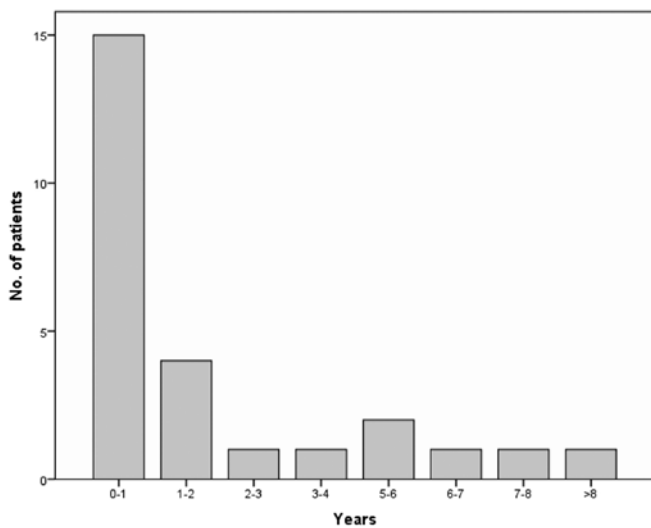


Figure 1. Time from diagnosis of the first melanoma to the diagnosis of the subsequent melanoma.

In our study, SSM and NM were, in decreasing order, the most common histopathological subtypes, in line with the results of other studies (8). While SSM was the most frequent type both in first and subsequent melanomas, NM was predominantly seen as the first melanoma. We did not find a correlation between the histological subtype of the first and second melanoma, SSM being the variant with the highest agreement.

A significant finding, reported in most previous studies, is the reduction in tumour thickness for subsequent melanomas (6-8,21-23). In our study, we observed a proportion of thin melanomas (<1 mm) of 19.2, 69.3, 100 and 100% for the first, second, third and fourth subsequent melanomas, respectively. This situation may be explained by early detection due to medical surveillance and self-examination. The early detection hypothesis is supported by studies that demonstrated that patients undergoing rigorous controls and adherent to regular follow-up had significantly thinner subsequent primary melanomas than those who did not (6,7,24). Another possible explanation for the reduction of tumour thickness would be the potential biological difference between the first and second melanoma (6). Multiple

studies have suggested that melanoma is in fact, not a single entity but a group of different neoplasms with variable etio-pathogenesis, biologic behaviour and prognosis (25-30). This hypothesis needs to be tested in further studies in patients with multiple melanomas.

Among patients with multiple primary melanomas, synchronous lesions were reported in 26-40% of the cases, while the remainder develops as asynchronous tumours (7). In our study, 45.45% of the lesions presented as synchronous lesions, underscored the importance of total body examination during the first visit in melanoma patients. Previous studies have shown that the risk of a subsequent primary melanoma is highest in the first year of the incident primary melanoma and remains higher in the first five years (6-8). However, cases reported up to 2 to 3 decades after the first melanoma and some studies indicate that the risk remains stable in time (6). In our study, almost 20% of the patients developed a second melanoma after more than five years of follow-up. Moreover, a patient who presented with a very thin first melanoma (BI=0.25 mm), developed two synchronous *in situ* melanomas after seven years of follow-up. All these data reveal the importance of lifetime clinical follow-up in melanoma patients, although some guidelines support a limited follow-up of one year for stage IA melanoma (31).

The main strength of our study is the homogeneous information collection in a single institution for a long period. The main limitation consists in the relatively low number of cases, but this can be explained by the fact that data was collected in a single centre.

In conclusion, almost 4% of melanoma patients in our centre developed subsequent melanomas during 2004 and 2020. Most patients developed only two primary melanomas, and we could not find a strong correlation between the sites and the histopathological subtypes of the first and subsequent melanoma. The most important findings of our study are the reduction in tumour thickness in subsequent melanomas as well as the possibility of diagnosing a subsequent melanoma more than five years after the first diagnosis. However, the risk is highest in the first year. Our findings highlight the need for lifetime clinical follow-up and self-examination in melanoma patients regardless of the first melanoma stage.

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Availability of data and materials

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

Authors' contributions

LU and SS contributed to the research-creation and design of the study, data acquisition, analysis and interpretation of data, statistical analysis, manuscript drafting, and critical revision of the manuscript for valuable intellectual content. IZ contributed to the data acquisition, analysis and interpretation of data, statistical analysis, manuscript drafting, and critical review of the manuscript for valuable intellectual content. IC and AV contributed to the research-creation and design of the study, data acquisition, and critical revision of the manuscript for valuable intellectual content. SV performed the analysis and interpretation of data, and the critical review of the manuscript for valuable intellectual content. RC contributed to the research-creation and design, and critical revision of the manuscript for valuable intellectual content. All authors read and approved the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the 'Iuliu Hatieganu' University of Medicine and Pharmacy (Cluj-Napoca, Romania). All the participants gave their consent to be included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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