

# Multiple Primary Melanoma: Epidemiological and Prognostic Implications; Analysis of 36 Cases

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## ABSTRACT

*Patients who are already diagnosed with cutaneous melanoma are at increased risk of developing another primary melanoma. The occurrence of multiple primary melanoma is a rare phenomenon, varying in frequency, with an estimated incidence ranging from 0.2% to 8.6%. The authors are presenting data on the patients with multiple primary melanoma from the Croatian Referral Melanoma Centre. The clinical, histological and epidemiological characteristics of 36 (3.6%) patients, identified from 991 patients with histologically confirmed melanoma, are analyzed in this study. Twenty-eight of the patients (78%) had two primary melanomas, six had three melanomas (16,7%) and two (5,6%) had four melanomas. Diagnosis was established synchronously in 11 patients (30%) and, in the rest of the patients, time interval between the diagnosis of the first and second melanoma varied from 1 month to the longest interval of 16 years. However, the majority of subsequent melanomas were removed within 2 years of the initial operation. The mean Breslow's thickness of the first melanoma was significantly higher than the mean Breslow's thickness of the second primary melanoma. The proportion of in situ to invasive melanomas was greater for the second melanomas compared with the first melanomas. Therefore, we emphasize the importance of regular follow-up as well as the education in regular self-skin examinations in melanoma patients in order to detect subsequent primary melanomas in the early phase.*

**Key words:** melanoma, multiple primary melanoma, follow up, patient education

## Introduction

Epidemiological data indicate that the incidence of melanoma, one of the most aggressive tumours in humans is in constant rise throughout the world<sup>1</sup>. The incidence of melanoma increases with age, and it mostly occurs between 30–70 years of age. Melanoma is also one of the most common malignant tumours in young adults<sup>2</sup>. The major risk factors for the development of melanoma include excessive sun exposure, number of melanocytic nevi, cutaneous phenotype, and family and personal history of melanoma. UV radiation from sunlight appears to be the principle environmental factor responsible for melanoma development<sup>3–6</sup>. It is well known that patients who have had one cutaneous melanoma are at increased risk of developing a second primary melanoma<sup>7</sup>. However, the appearance of multiple primary melanomas (MPM) in the same patient is not commonly seen in everyday dermatological practice. It has been estimated that the occurrence of MPM ranges from 0.2% to 8.6%<sup>8</sup>.

## Patients and Methods

Data on melanoma patients diagnosed with MPM and registered at the Croatian Referral Melanoma Centre in the period 2002–2008 were retrospectively analyzed according to the patients' medical records. Statistical analysis was conducted using SPSS, version 12. Descriptives and Pearson's correlation coefficient were calculated. Every patient diagnosed with melanoma and registered at the Croatian Referral Melanoma Centre is informed about the disease in details and educated how to perform regular self-examination of the skin. Special attention is given to the recognition of the »A, B, C, D« rules in the assessment of pigment skin lesions.

## Results

During the 7-year period (2002–2008) there were 991 newly registered patients diagnosed with melanoma, including melanoma *in situ*, in the Croatian Referral Mela-

noma Centre. Continuous rise in the number of newly registered melanoma patients was recorded each year, starting with 60 patients in 2002 up to 243 melanoma patients in the year 2008 (Table 1). Out of 991 melanoma patients, 36 patients (3.6%) were diagnosed with MPM; 28 patients (78%) had 2 primary melanomas, six patients (16,7%) had 3 melanomas, and two patients (5,6%) had 4 melanomas. There were 17 female (47%) and 19 male (53%) patients with MPM. The age at the diagnosis of the first melanoma ranged from 19 to 78 years, with the mean value of 53,6 years.

Time interval between the removal of the first and subsequent melanoma ranged from 1 month (more than 30 days) to 16 years, with the average time interval of 41 months. However, most of the subsequent melanomas (N=19; 52%) were diagnosed within 2 years from the diagnosis of the first melanoma. Simultaneous diagnosis of MPM (multiple tumours diagnosed within 30 days of each other) was established in 11 patients (30%).

Distribution according to tumour localization of the second melanoma on the body was similar to that of the first tumour. Melanomas occurred most commonly on trunk (namely the posterior part), followed by the lower extremities and other sites (Figure 1).

As it is shown in the Figure 2, the level of tumour invasion (Clark level) was significantly decreased in the group of subsequently diagnosed melanomas. Generally, more of the initial primary melanomas were Clark levels III and IV, whereas more of the second melanomas were Clark levels I and II. The proportion of *in situ* (Clark level I) to invasive melanomas was greater for the second melanomas compared with the first melanomas (Figure 2). The mean Breslow thickness of the first melanoma

was 3,1 mm, but the second melanoma was significantly thinner at 1.3 mm.

The most common histological type of melanoma was superficial spreading melanoma. However, in the group of second melanomas, there were less nodular melanomas and more lentigo maligna melanomas diagnosed, compared with the first melanomas (Figure 3).

Six of our patients (17%) with MPM developed metastases, however, there was no statistically significant correlation between the number of primary melanomas and the risk of developing metastatic disease ( $r = -0,091$ ).

Data regarding the occurrence of dysplastic nevi and family history of melanoma was available for 30 out of 36 of our MPM patients. Presence or history of dysplastic nevi was determined in 20 (67%) and family history of melanoma was positive in only 5 (17%) patients. All of

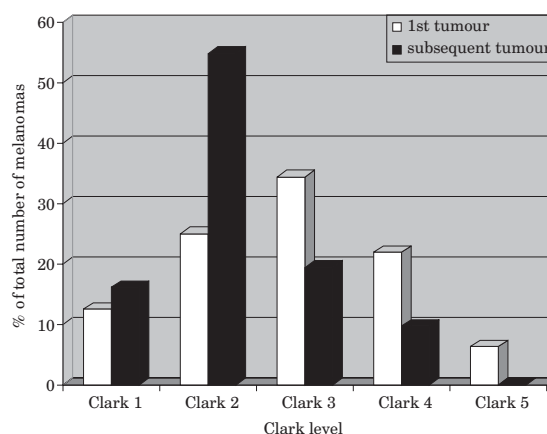


Fig. 2. Distribution of the first and subsequent melanomas by Clark level

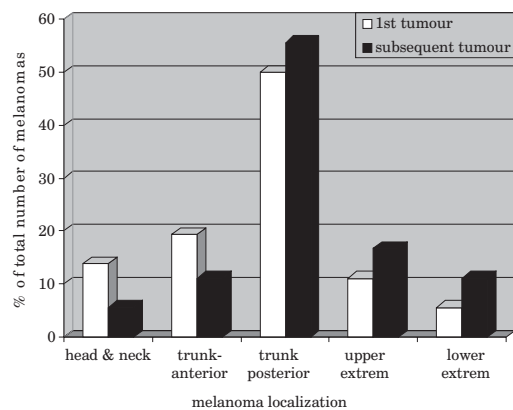


Fig. 1. Distribution of the first and subsequent melanoma by localization

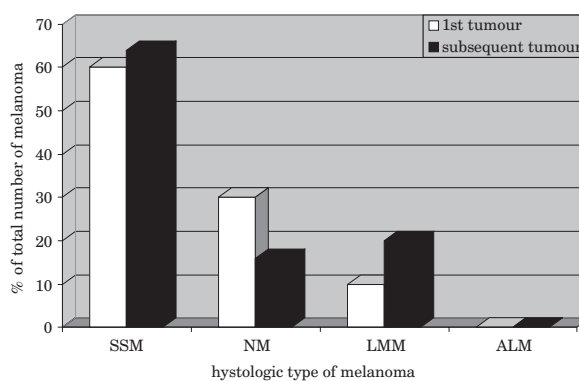


Fig. 3. Distribution of the first and subsequent melanomas by histologic type of tumour

TABLE 1  
NUMBER OF MELANOMA PATIENTS REGISTERED IN THE CROATIAN REFERRAL CENTRE (2002.–2008.)

Year of registration	2002.	2003.	2004.	2005.	2006.	2007.	2008.
N	60	100	121	116	122	191	243

the patients with positive family history of melanoma also had dysplastic nevi.

## Discussion

The first description of the patient with multiple MPM was reported in 1952, by Pack et al.<sup>9</sup>. The occurrence of MPM is a well-known, but uncommon phenomenon, with an estimated incidence ranging from 0.2% to 8.6%<sup>8</sup>. The incidence of MPM in our study, which was 3.6%, correlates with the incidence reported in previous series<sup>10</sup>. Studies report different data of the sex ratio in MPM patients<sup>10–12</sup>, however in our population there was a slight female preponderance noted. Most of the patients (63–88%) with MPM have two primary tumours<sup>8,9,11,13,14</sup>, as it was the case in our study. Interestingly, a patient with as many as 48 primary melanomas has been described in the literature<sup>15</sup>.

Risk of the second primary melanoma in a patient with a prior melanoma is significantly higher than the risk of an initial melanoma in an individual from the general population. Moreover, patients with a prior melanoma have 10–25-fold higher incidence rate of developing second melanoma compared with the general population<sup>16,17</sup>.

Besides the personal history of prior melanoma, risk factors for the development of MPM include positive family history of melanoma (family melanoma meaning first-degree relative diagnosed with melanoma) and the presence of dysplastic nevi<sup>7</sup>. In a study conducted by Titus-Ernstoff et al.<sup>18</sup> the presence of 3 or more dysplastic nevi compared with none was associated with more than a 4-fold risk of MPM. In a prospective study conducted by Ferrone et al.<sup>8</sup>, in which 4484 melanoma patients were analyzed, the estimated cumulative 5-year risk of the second primary melanoma for the entire cohort was 11.4%, whereas this risk was much higher (at 19.1% and 23.7% respectively) for the patients with a positive family history or dysplastic nevi<sup>8</sup>. Among patients with MPM, 38–46% are reported to have a presence or a history of dysplastic nevi<sup>16,19</sup>, and 18–38% of MPM patients are reported to have a positive family history of melanoma<sup>12,19</sup>. Generally, 6–12% melanomas are family cases, and approximately 12% of melanoma patients with family history of melanoma are diagnosed with MPM<sup>20</sup>. Patients with numerous dysplastic nevi and positive family history of melanoma are at the highest risk of melanoma. In these patients, melanoma is usually diagnosed 10 years earlier than in general population and are at higher risk of developing MPM<sup>20</sup>. However, it is important to emphasize that to date, the clinical phenotypes of increased number of atypical nevi and nevi body distribution are considered to be independent risk factors for melanoma risk, regardless of family history<sup>21</sup>. The familial melanoma syndromes are associated with germline mutations in three highly penetrant gene products: p16, alternate reading frame, and cyclin-dependent kinase 4 (CDK-4)<sup>21</sup>. Certain variants in a low-penetrance gene, MC1R, the melanocortin 1 receptor gene, increase melanoma risk to

a lesser extent and act as a genetic modifier when cosegregating with a deleterious p16 gene. The penetrance of these melanoma-predisposing genes is largely influenced by ultraviolet exposure across geographic latitude<sup>21,22</sup>.

Most second melanomas in this study were detected within two years of the first, and in one third of cases multiple melanomas were diagnosed simultaneously. In various studies, synchronous lesions were found in 20–40% of MPM patients<sup>8,10</sup>. It has also been reported that synchronous lesions appear more often in older patients<sup>10</sup>. The longest interval between the diagnoses of the first and subsequent melanoma in our study was 16 years. These data are in concordance with the those from the literature where in several series the highest risk for a second melanoma was reported during the first 5 years, but a much longer time interval of 31 years is possible<sup>10,11,14</sup>. Therefore, continued medical follow-up with complete skin examinations seems prudent, but it is very important to promote self-skin evaluation in patients to detect not only metastases but also subsequent primary melanomas in their earliest phase<sup>10</sup>.

The melanoma thickness is considered to be one of the most important independent melanoma prognostic factors. Therefore, it is important to emphasize that, like in the majority of other studies<sup>7,8,10</sup>, our data also confirmed that second primary melanoma is significantly thinner than the first one. Also, in our MPM patients the proportion of *in situ* (Clark level I) to invasive melanomas was greater for the second melanomas compared with the first melanomas, confirming the trend toward thinner subsequent melanomas. Most probably, this is due to patients' education and regular and thorough clinical follow up.

Superficial spreading melanoma (SSM) is the most common type of melanoma which represents 60–70% of all melanomas<sup>23</sup>. Nodular melanoma is the second most common form of melanoma and often has bad prognosis because it is frequently diagnosed at a thicker stage, while lentigo maligna melanoma usually has better prognosis because of its very long radial growth phase. Among our MPM patients, the most common histological type of melanoma was SSM. However, there were less nodular melanomas and more lentigo maligna melanomas diagnosed in the group of second melanomas, compared with the group of first melanomas (Figure 3).

Burden et al.<sup>7</sup> carried out a case comparison study of mortality from melanoma in which each patient with multiple melanoma was randomly matched with a patient with a single melanoma in terms of age, sex, Breslow thickness, and body site. The apparent survival advantage in those with multiple melanoma was not significant when the two groups were analysed as two independent samples<sup>7</sup>. On the other hand, Ferrone et al.<sup>8</sup> reported 5.6% of patients with MPM who died from melanoma, compared with 15.8% of patients who had a single melanoma diagnosed and died from it. They speculate that, besides the trend towards the thinner subsequent melanomas, less aggressive disease biology in the MPM patients may play a role<sup>8</sup>. In our study, higher

number of primary tumours in patients with MPM did not indicate greater risk of developing metastases.

## Conclusion

The occurrence of MPM is a rare, but well known phenomenon in the field of dermatooncology. Until today, various studies have shown that patients with a prior melanoma are at significantly higher risk of developing

second melanoma compared with the general population. Among other things, our study confirmed that second melanoma is usually thinner than the first one. Therefore, it emphasizes the importance of a life-long follow-up as well as the education in regular self-skin examinations for all melanoma patients, and especially for those with dysplastic nevi and/or positive family history of melanoma, in order to detect subsequent primary melanomas in the earliest phase.

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## VIŠESTRUKI PRIMARNI MELANOMI; EPIDEMIOLOŠKI I PROGNOŠTIČKI POKAZATELJI; ANALIZA 36 SLUČAJEVA

## SAŽETAK

Bolesnici kojima je dijagnosticiran melanom kože pripadaju u skupinu s povećanim rizikom za razvoj slijedećeg primarnog melanoma. Višestruki primarni melanomi su rijetka pojava, a učestalost varira od 0,2 do 8,6%. Autori iznose podatke o bolesnicima s višestrukim primarnim melanomima iz Hrvatskog Referentnog centra za melanom. Opisani su klinički, patohistološki i epidemiološki pokazatelji 36 bolesnika s višestrukim primarnim melanomima, a koji su registrirani iz skupine od ukupno 991 bolesnika s dijagnosticiranim melanomom kože. U 32 bolesnika dijagnosticirana su 2 primarna melanoma, u 2 bolesnika dijagnosticirana su 3 primarna melanoma, dok su u 2 bolesnika dijagnosticirana 4 primarna melanoma. Višestruki primarni melanomi u 11 bolesnika dijagnosticirani su istovremeno, dok je u ostalih bolesnika dijagnoza slijedećeg primarnog melanoma postavljena u razdoblju od 1 mjesec do 16 godina nakon dijagnoze prvog primarnog melanoma. Većina kasnije otkrivenih primarnih melanoma prepoznata je unutar 5 godina od odstranjenja prvog primarnog melanoma. Srednja vrijednost debljine melanoma po Breslowu bila je značajno viša kod prvih primarnih u odnosu na slijedeće primarne melanome. Udio melanoma in situ u ukupnom zbroju dijagnosticiranih tumora bio je značajno veći u skupini drugih primarnih melanoma. Stoga je iznimno važno naglasiti potrebu za doživotnim redovitim kontrolnim dermatološki pregledima, kao i važnost edukacije bolesnika u redovitim samopregledima kako bi se što veći broj novonastalih melanoma dijagnosticirao u najranijoj fazi.