

## METASTATIC MELANOMA IN BIOPSY MATERIAL IN THE 1995-2000 PERIOD\*

Božo Krušlin, Danko Müller, Ivana Nola, Majda Vučić, Irena Novosel, Antonija Jakovčević, Jasminka Brozić, Drago DeSyó, Hrvoje Čupić and Mladen Belicza

Ljudevit Jurak University Department of Pathology, and Departments of Dermatology, of Oncology and of Surgery, Sestre milosrdnice University Hospital, Zagreb, Croatia

**SUMMARY** – Although melanoma is less common than other types of malignant skin tumors, including basal and squamous cell cancers, it accounts for about 75% of all skin cancer deaths. Melanoma is much more likely to metastasize to other parts of the body, which is not the case with other types of skin tumors. Metastatic spread is very common, particularly in advanced tumors of higher Clark and Breslow stage. The aim of the study was to analyze the prevalence and distribution of metastatic melanomas among biopsy specimens collected during the 1995-2000 period, and their relationship with primary melanoma, especially regarding Clark and Breslow staging. Metastatic melanomas were found in 210 of 75,390 (0.3%) surgical biopsies. There were 24 patients with 57 metastatic melanoma biopsies related to primary melanoma diagnosed at our hospital during the period of observation. The remaining 153 metastatic melanomas diagnosed at other hospitals or before the period of observation were not included in the study. Metastatic melanomas were more common in male patients (13 male and 11 female), age range 16-91 (mean age 53.0) years. In men, age range was 16-75, and in women 23-91 years. Metastatic melanomas occurred 1 month to 2 years (mean 4.9 months) after the diagnosis. They affected patients with Clark III-V and Breslow III-V. Metastases were not observed in Clark I-II patients, however, two metastases were detected in patients with Breslow thickness II. Also, a statistically significant increase in the prevalence of metastatic and primary melanomas ( $p < 0.01$  both) was recorded during the period of observation.

**Key words:** *Melanoma, diagnosis; Melanoma, pathology*

### Introduction

The incidence of melanoma has risen at least 20-fold in the past century<sup>1</sup>. The rise in melanoma incidence has been observed in whites, particularly in Scandinavia, Australia, North America, Scotland, and Germany. In the United States and Germany, approximately 38,000 and

10,000 new cases, respectively, are diagnosed *per year*<sup>2</sup>. However, according to the last report of the National Registry of Cancer, the incidence of melanoma in Croatia decreased from 6.5/100,000 in 1995 to 5.3/100,000 in 19983. As a result of increased public awareness, melanomas are more commonly diagnosed in earlier stages and most are surgically cured. However, some patients still present with advanced tumors. Metastatic spread to regional lymph nodes and distant sites is very common, particularly in tumors thicker than 2 mm<sup>4-7</sup>. Metastasis usually occurs within few years from the diagnosis. The most important attributes that may help predict the metastasis and prognosis of melanoma are Breslow's thickness and Clark's level of invasion<sup>4-8</sup>. Other major prognostic factors are ulceration, anatomic location, and patient's sex<sup>5,9</sup>.

Correspondence to: *Božo Krušlin, M.D., Ph.D.*, Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia  
E-mail: kruslin@mef.hr

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The aim of the study was to analyze the prevalence and distribution of metastatic melanoma among biopsy specimens in the 1995-2000 period, and their relationship with primary melanoma.

**Patients and Methods**

Computed surgical pathology registry at the Department of Pathology was canvassed for the 1995-2000 period to identify all patients with primary and metastatic melanomas. All relevant data including age and sex of the patients, histologic type, presence of ulceration, level of invasion, and tumor thickness were analyzed. The depth of invasion and tumor thickness were determined according to Clark and Breslow, respectively<sup>10,11</sup>. The patients with metastatic melanoma diagnosed in the period of observation were divided into two subgroups according to the level of invasion and tumor thickness: those with Clark I-II and Breslow I-II primary tumor, and those with Clark III-IV and Breslow III-V primary tumor. Primary ocular melanomas were excluded from the investigation.

Statistical analysis was performed by Statistica software on an IBM PC/AT compatible computer. The observed frequencies were tested by  $\chi^2$ -test.

**Results**

During the above mentioned period, there were 75,390 surgical biopsies, and 347 (0.46%) were skin melanoma related biopsies. Primary skin melanoma was found in 137 (0.18%) biopsies. Analyzing the prevalence of skin melanoma, we found 13 primary melanomas in 1995 ver-

sus 37 in 2000 (Fig. 1). Primary melanomas were more common in females (78 cases in females and 59 in males), with a female to male ratio of 1.3:1 (Fig. 2). In the period of observation, the mean age of patients with primary melanoma was 59.0 years, however, younger and older patients were recorded towards the end of the period, especially among women. A majority of primary tumors were diagnosed at an advanced stage (Clark III-V, Breslow III-V). The distribution of primary melanomas according to Clark and Breslow staging is shown in Table 1.

Another 210 (0.3%) biopsies were metastatic melanomas related either to primary melanomas diagnosed in the period from January 1, 1995 till December 31, 2000 (24 patients with 57 biopsies), and at another hospital or be-

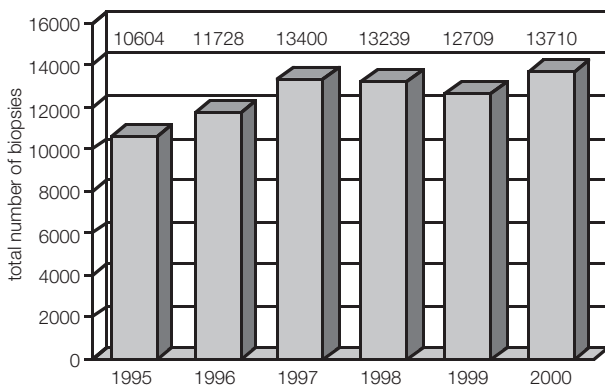


Fig. 1. Total number of biopsies at the Department of Pathology during the 1995 – 2000 period

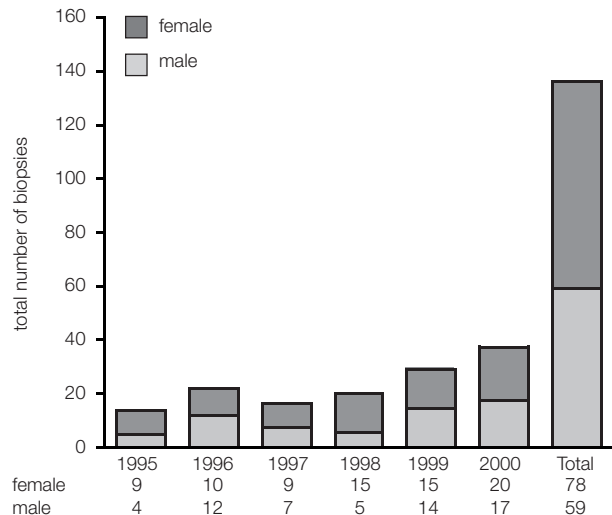


Fig. 2. Prevalence and sex distribution of primary melanoma in biopsy material during the 1995–2000 period

Table 1. Distribution of primary melanomas during the 1995 – 2000 period according to Clark and Breslow classification

Stage	Clark	Breslow
n	n	
I	3	8
II	12	17
III	40	21
IV	53	20
V	20	66
Unkown	9	5
Total	137	137

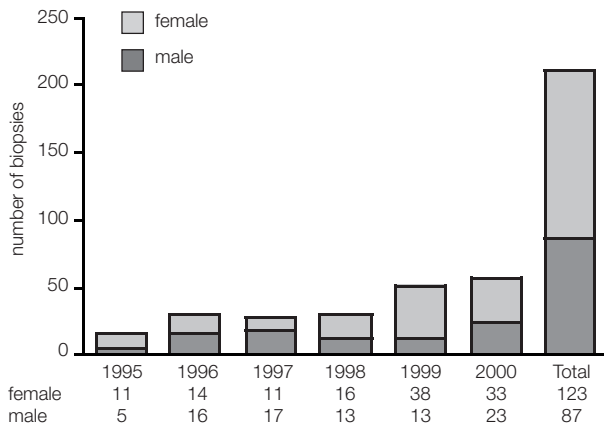


Fig. 3. Prevalence and sex distribution of metastatic melanoma in biopsy material during the 1995-2000 period

fore the observed period (153 biopsies) (Fig. 3). In this study, the group of 24 patients with primary melanoma who had presented during the 1995-2000 period were further analyzed.

Among 66 patients with primary melanomas who were regularly followed at the Department of Oncology of the Sestre milosrdnice University Hospital from Zagreb, metastases were observed in 24 (36.4%) patients (13 male and 11 female), age range 16-91 (mean age 53.0) years. Metastatic melanoma occurred between 1 month and 2 years (mean 4.9 months) from the diagnosis. There was a statistically significant difference in the prevalence of primary ( $\chi^2=16.96$ , d.f.=5,  $p<0.01$ ) and metastatic ( $\chi^2=33.36$ , d.f.=5,  $p<0.01$ ) melanomas in the examined period. Among 24 patients with primary melanoma, there were 12 nodular melanomas, 7 superficially spreading melanomas, and two cases with acral type of melanoma. In three patients, the histologic type could not have been determined. Ulceration was present in 9 of 24 melanomas (6 nodular, 2 superficially spreading, and one acral melanoma). Metastatic melanoma was found in 20 patients with Clark III-V. In four patients, Clark level was not determined because the tumor extended to the specimen margin. Concerning Breslow's thickness, metastases occurred in two patients with Breslow I-II and 19 patients with Breslow III-V. In three patients, Breslow thickness could not be determined because the tumor was not completely excised. Skin was most commonly involved by metastases (n=18), followed by lymph nodes in 14 and other sites in 25 cases. Numerous metastases were observed in one patient with acral melanoma, three patients with melanoma of the nasal cavity, and one patient with melanoma of the anal region.

## Discussion

Major factors associated with the incidence of melanoma include race and ethnicity, sunlight exposure, and genetic and familial predisposition<sup>9</sup>. Major factors associated with melanoma prognosis include tumor thickness, ulceration, anatomic localization, and patient's sex<sup>5,9,12,13</sup>. Other less important factors are mitotic count, cellular polymorphism, vascular invasion, and regression. Evaluation of large databases showed that tumor thickness was the most important prognostic variable studied<sup>5</sup>. In our study, metastases were significantly more common in patients with Clark and Breslow stages III-V. We found metastatic melanoma to predominantly affect the skin and regional lymph nodes, as also reported by others<sup>2,14-16</sup>. This could in part be due to sentinel lymph node biopsies that have relatively recently been introduced in clinical practice, as also noted elsewhere<sup>5,8,14-16</sup>. In a study reported by Jansen *et al.*<sup>15</sup>, sentinel lymph nodes were identified in 27 out of 30 patients with melanoma of the head and neck region. The sentinel node was positive in eight patients<sup>15</sup>. In a study by Averbook *et al.*<sup>16</sup> including 133 patients who underwent lymph node dissection, 28 (21.1%) patients had nodal metastases. Patients with a primary melanoma thicker than 4 mm had 50% metastatic involvement of their lymph nodes<sup>16</sup>. It is obvious that sentinel lymph node biopsy will increase the number of identified positive lymph nodes. However, as summarized by Balch<sup>17</sup>, sentinel lymph node lymphadenectomy has multiple advantages in the care of melanoma patients with clinically normal nodes, who may have occult metastases. Several studies have demonstrated that the sentinel lymph node evaluation for the underlying metastatic disease reflects the status of the entire lymph node region, and is therefore a useful prognostic factor<sup>2,14,15,17</sup>. A multi-institutional study has stressed the sentinel lymph node status as the most significant prognostic factor superior to the measurement of tumor thickness in primary melanoma<sup>2,14,15,17</sup>.

The peak hazard rate for death from metastatic melanoma was recorded in the 48 months of follow-up<sup>2</sup>. After 120-month survival, the risk of dying from metastatic melanoma is very low, approaching zero<sup>2</sup>. In our study, metastases occurred 1 month to 2 years from the diagnosis. Vollmer reviewed 11 large studies and observed ulceration to be an additional significant prognostic factor in 7 of them<sup>18</sup>. In our study, distant metastases were more

frequently diagnosed in patients with large, ulcerated tumors. Primary tumors were more common in females, while metastatic melanomas were more common in males. It has been suggested that women with metastatic melanoma have better prognosis than males<sup>19</sup>, however, we could not confirm this observation. In up to 4% of patients presenting initially with metastatic melanoma, no primary tumor can be found<sup>20</sup>. In our series, primary melanoma was identified in all 24 cases.

There was a statistically significant increase in metastatic and primary melanomas diagnosed at our Hospital in the 1995-2000 period. However, official data from the National Cancer Registry showed a decreasing incidence during the 1995-1998 period<sup>3</sup>. This discordance could probably be due to the larger number of patients treated at our Hospital, or to some failure in the registration of melanoma patients. It seems that this topic should be further evaluated.

We also observed an increasing number of primary melanoma in younger and older patients with a small gap in middle ages. There was a wider range in the pathohistologic stages among primary melanomas, however, the reason for this phenomenon is uncertain. Should it be attributed to better diagnosis, or it simply reflected a recent increase in the number of melanoma patients, or both?

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## Sažetak

## METASTATSKI MELANOM U BIOPSIJSKOM MATERIJALU U RAZDOBLJU OD 1995. DO 2000. GODINE

*B. Krušlin, D. Müller, I. Nola, M. Vučić, I. Novosel, A. Jakovčević, J. Brozić, D. DeSyo, H. Čupić i M. Belicza*

Melanom je rjeđi od ostalih vrsta malignih tumora kože, uključuje bazocelularni i planocelularni rak, ali uzrokuje oko 75% svih smrti od raka kože. Melanom ima veću vjerojatnost metastaziranja u druge dijelove tijela, što nije slučaj s drugim vrstama kožnih tumora. Metastatsko širenje je vrlo često, poglavito kod uznapredovalih tumora višega stadija po Clarku i Breslowu. Cilj ovoga ispitivanja bio je analizirati učestalost i raspodjelu metastatskih melanoma među biopsijskim uzorcima u razdoblju od 1995. do 2000. godine, te njihov odnos s primarnim melanomom, poglavito u smislu Clarkove i Breslowljeve klasifikacije prema stadijima bolesti. Metastatski melanomi nađeni su u 210 od 75.390 (0,3%) kirurških biopsija. U razdoblju od 1995. do 2000. godine u našoj su Bolnici dijagnosticirana 24 bolesnika s 57 biopsija metastatskih melanoma povezanih s primarnim melanomom. Preostala 153 metastatska melanoma koji su dijagnosticirani u drugim bolnicama ili prije razdoblja promatranja nisu uključeni u ovo ispitivanje. Metastatski melanomi bili su češći u muških negoli u ženskih bolesnika (13 muških i 11 ženskih) u dobi od 16 do 91 godine (srednja dob 53,0 godine). U muških se bolesnika dobni raspon kretao od 16 do 75 godina, a u ženskih od 23 do 91 godine. Metastatski melanomi su se pojavili 1 mjesec do 2 godine nakon dijagnoze (srednja vrijednost 4,9 mjeseci). Metastatski melanom zahvatio je bolesnike sa stadijem III. – V. prema Clarku te III. – V. prema Breslowu. Metastaze nisu zabilježene u bolesnika sa stadijem I. – II. prema Clarku, međutim, dvije su metastaze nastale u bolesnika s debljinom II. stupnja prema Breslowu. U ispitivanom razdoblju opažen je i statistički značajan porast učestalosti metastatskih i primarnih melanoma ( $p < 0,01$  oboje).

Ključne riječi: *Melanom, dijagnostika; Melanom, patologija*