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SURVIVAL AND PROGNOSIS OF PATIENTS WITH CUTANEOUS MELANOMA ON EXTREMITIES

Noveski Lazo[1], Matveeva N[2], Mirchevska E[1], Dzonov B[1], Zhivadinovik J[2], Ginovski V[1]
[1]University Clinic of Plastic and Reconstructive Surgery, Skopje, R. Macedonia
[2]Institute of Anatomy, Medical Faculty, Skopje, R. Macedonia

Abstract

Advanced melanoma is an aggressive, deadly disease and has a high detrimental impact on patients and society, primarily due to premature death.

The aim of this study was to present the overall survival (OS) in cutaneous melanoma patients with upper and lower extremities primary tumor site, and to obtain as accurate as possible an estimation of survival for these patients.

A total of 100 patients with primary malignant skin melanoma on the extremities, clinically negative and clinically positive regional lymph nodes metastasis with no evidence of distant disease were analyzed. Five and 10-year overall survival were calculated with log rank analysis to determine significant differences. Prognostic factors were evaluated using Cox proportional hazard analysis.

Five-year and 10-year overall survival of all patients included in the study was 72.7% and 45%, respectively. Ten-year OS of patients with clinically unpalpable nodal metastases, but pathologically evident, was 76.9% compared to 20.5% in patients with clinically palpable nodal metastases. In patients with positive regional lymh nodes metastasis, regional lymph nodes tumor burden was dominant predictor of overall survival in a model based on age, gender, localization of the primary tumor, regional lymph nodes tumor burden and N categorization of the patients. Macrometastatic regional lymph nodes tumor burden increased the hazard ratio of death by 4.26 times compared to micrometastatic regional lymph nodes tumor burden.

Our results highlight the importance of nodal status early diagnosis as well as the necessity for individual approach to each patient.

Keywords: melanoma, survival, prognosis

Inroduction

Cutaneous melanoma is by far the most common melanoma subtype, accounting for in excess of 90% of cases of melanoma [1]. Unfortunately the incidence of cutaneous melanoma around the world has been rising annually, at a rate faster than that of any other malignancy [1, 2]. Advanced (stage IIIB/C and IV) melanoma is an aggressive, deadly disease and has a high detrimental impact on patients and society, primarily due to premature death. Understanding the burden of advanced melanoma is therefore important for health policy and allocating appropriate health care resources to treatment.

Several demographic and clinico-pathological characteristics such as age, sex, tumor localization, Breslow thickness, ulceration, mitotic count, vessel invasion, the presence of tumor infiltrating lymphocytes and lymph nodes status are considered as independent prognostic factors for relapse and overall survival of patients with cutaneous melanoma [3, 4, 5, 6, 7, 8]. Tools that allow clinicians to incorporate demographic and clinicopathologic data for a specific patient can ultimately yield personalized and even more accurate estimates of recurrence and survival.

The aim of this study was to present the overall survival in cutaneous melanoma patients with upper and lower extremities primary tumor site, and to obtain as accurate as possible an estimation of survival of these patients.

Material and methods

A total of 100 patients with primary malignant skin melanoma on the extremities were analyzed. The database identified patients with histologically confirmed cutaneus melanoma, clinically negative and clinically positive regional lymph nodes with no evidence of distant disease, who had undergone surgery at the Clinic of Plastic and Reconstructive Surgery, Clinical Center, Skopje in the period from April 2001 until April 2012. An approval to conduct the study was obtained by the Institutional review

board of the University Clinical Center in Skopje. All patients included in the study were informed about the planned surgical procedure and gave their written informed consent.

The database included patients who met the inclusion criteria for the first or for the second group, each one consisting of 50 patients.

Patients in the first group met the following inclusion criteria: primary malignant histologically confirmed skin melanoma on the extremity, without clinically present signs for metastases in the regional lymph nodes or distant metastasis. Exclusion criteria were: presence of any type of metastasis except of SLN, patients after any surgical procedure that could disrupt lymphatic drainage patterns from the primary site and pregnancy.

Patients in the second group met the following inclusion criteria: primary malignant histologically confirmed skin melanoma on the extremity, with clinically present metastases in the regional lymph nodes, without signs for distant metastases. Exclusion criteria were presence of distant metastasis. All patients underwent routine preoperative examinations.

Inguinal and popliteal lymph nodes were considered to be regional metastases for lower extremity primaries; axillary nodes, for upper extremity primaries. Other patterns of lymph node metastasis were considered to be distant and were excluded.

Patients from the first group underwent radical skin excision of the primary malignant lesion and SLN mapping. After the identification, the lymph nodes were carefully removed and histologically examined. The radical lymphadenectomy was performed as a separate procedure in patients with SLN positive for metastasis (SLN+).

All patients from the second group underwent radical skin excision of the primary malignant lesion and radical lymphadenectomy of the regional lymph nodes with clinically present metastasis.

Pathohistological analysis was made on primary melanoma lesion and on lymph nodes sectioned at 2 mm intervals. Sections were evaluated after hematoxylin-eosin staining. Features routinely examined were used for pTNM classification and tumor stage determination. Patients were followed up for evidence of recurrence (local and regional) using physical examination, laboratory analysis and appropriate radiologic investigations.

Data obtained for each patient were gender, age, localization, clinical and pathologic stage of the primary tumor according to AJCC Melanoma Staging System (7^{th} edition).

Follow-up time was defined from the date of diagnosis to the date of the last follow up or death. Estimates of cumulative survival probabilities according to Kaplan-Meier were described together with 95% confidence intervals (CIs) and compared using two sided log-rank test statistics. Median survival times are presented (MST). For the analysis of overall survival (OS) patients who were alive at the last follow up or died without evidence of metastatic melanoma were considered to be censored cases, while patients who had died due to melanoma were considered an ñeventò. Multivariable Cox proportional hazard models were used to determine independent prognostic factors. All the data obtained were included in the Cox regression models. Forward and backward stepwise procedures of multivariate modelling process were conducted. Results of Cox model were described by means of hazard ratios together with 95% CIs and p value based on the Wald test. Throughout the analysis p value less than .05 was considered statistically significant. All statistical analysis were made by using SPSS, version 20 (IBMSPSS, Chicago, Illinois, USA).

Results

A total of 50 patients in the first group underwent SLN mapping with 1% solution of methylen blue and SLNs were identified, removed and histologically examined. Of these, 14 (28%) were positive for metastases in sentinel lymph nodes (SLN+) and 36 (72%) were negative for metastases in sentinel lymph nodes (SLN-). The median age of these patients was 52.5 years. Nineteen (38%) of them were males and 31 (62%) were females. There were no significant differences in age or sex between SLN + and SLN - patients. The median age of patients in the second group was 56.5 years. Twenty-six (62%) of them were males and 24 (48%) were females. After sentinel lymph node lymphadenectomy, 14 patients previously staged ñnode negativeò migrated in the second group of patients, hence they had clinically undetected nodal metastases.

Survival analysis

Five-year and 10-year OS of all patients included in the study was 72.7% and 45%, respectively (MST 76 months). A significant decrease in 5-year and 10-year OS was notified in the second group of patients, clinically positive for metastases in regional lymph nodes (45.6% and 20.5%, respectively; MST 54 months CI=41.058-66.942), compared to the first group of patients, clinically negative for metastases in regional lymph nodes (88.6% and 75.7%%, respectively), log rank p=.000.

Analysis of all 64 patients with pathological evidence of metastases in regional lymh nodes, after sentinel or therapeutic lymphadenectomy, showed significant survival advantage for 14 patients with clinically unpalpable nodal metastases compared to 50 patients with clinically palpable nodal metastases, log rank p=.002. The 10-year OS of patients with clinically unpalpable nodal metastases, but pathologically evident, was 76.9% compared to 20.5% in patients with clinically palpable nodal metastases.

No significant differences in 5- and 10-year OS according to demographic data and anatomic localization of the primary tumor was observed in both groups of patients, positive and negative for metastases in regional lymh nodes. Survival advantage was evaluated in males, younger patients and in patients with upper extremities primary tumor localization without regional lymh nodes metastasis (Table 1).

Table 1. Five and ten-year OS in patients negative and positive for metastases in regional lymph nodes according to gender, age and primary tumor location.

	Patients negative for metastasis in regional lymph nodes			**Patients positive for metastasis in regional lymph nodes**		
	N	**5-year OS**	**10-year OS**	**N**	**5-year OS**	**10-year OS**
Gender						
Females	24	93.3%	59.6%	31	51.8%	31%%
Males	12	100%	100%	33	53.9%	36%
Age						
<50	16	100%	85.7%	24	50.4%	41.3%
50-70	16	100%	100%	20	55.7%	39%
Ó70	4	66.7%	33.3%	20	52.9%	17.6%
Location						
Upper extremities	11	100%	100%	35	47%	34.5%
Lower extremities	25	94.7%	55.%	29	56%	32%

OS ï overall survival

Further analysis was made according to pathologic staging of patients that provided information on both microstaging of primary melanoma and pathological evaluation of nodal status after complete lymphadenectomy. A significant difference in 5- and 10-year OS according to the pathologic stage was notified only between patients positive for metastases in regional lymh nodes, log rank p=.033 (Table 2).

Table 2. Five and ten-year OS in patients negative and positive for metastases in regional lymph nodes according to the stage of the primary tumor

Patients negative for metastasis in regional lymph nodes				**Patients positive for metastasis in regional lymph nodes**			
Pathologic stage	**N**	**5-year OS**	**10-year OS**	**Pathologic stage**	**N**	**5-year OS**	**10-year OS**
IA	4	100%	100%	IIIA	4	75%	75%
IB	8	85.7%	85.7%	IIIB	9	75%	75%
IIA	8	100%	100%	IIIC	51	46.8%	22.3%
IIB	8	83.3%	62.5%				
IIC	8	100%	66.7%				

OS ï overall survival

The range of survival rates among various subgroups of pathological stage III patients was large, from 22.3 to 75% in 10-year survival. Since these patients represent a heterogeneous group with regard to staging and prognosis, we made further analysis in order to determine independent predictors of survival in this cohort. We included tumor thickness and ulceration (accepted as dominant independent predictors for overall survival). Patients with unulcerated melanoma presented survival advantage compared to patients with ulcerated primary lesion of equivalent T category. As primary tumor thickness increased, long term survival decreased (Table 3).

Table 3. Five and ten-year OS in patients positive for metastases in regional lymph nodes stratified by tumor thickness and tumor ulceration.

Patients without primary tumor ulceration (N=20)				**Patients with primary tumor ulceration (N=44)**			
Tumor thickness (mm)	**5-year OS**	**10-year OS**	**MST**	**Tumor thickness (mm)**	**5-year OS**	**10-year OS**	**MST**
T2a (1.01-2)	60%	60%		T2b (1.01-2)	50%	50%	
T3a (2.01-4)	40%	30%	64 months	T3b (2.01-4)	58.3%	41.7%	62 months
T4a (>4)	75%	25%	CI (45.52-82.48)	T4b (>4)	50%	25%	CI (50.00-74.01)

MST ï median survival CI ï confidence interval

The overall survival according to the number of regional lymh nodes harboring metastatic desease was analyzed in patients without clinical evidence of lymph node meatastases, in patients with pathologic evident nodal metastasis defined by convention as microscopic tumor burden and in patients with clinical and pathological evidence of lymph node meatastases defined as macroscopic tumor burden (Table 4).

Table 4. Five and ten-year OS in patients with microscopic and macroscopic regional tumor burden stratified by number of lymph nodes harboring metastatic disease.

Patients with microscopic regional tumor burden(N=14)				**Patients with macroscopic regional tumor burden (N=50)**			
N category	**5-year OS**	**10-year OS**	**MST**	**N category**	**5-year OS**	**10-year OS**	**MST**
N1a	100%	100%		N1b	66.7%	16.7%	
N2a	75%	75%	>120 months	N2b	56.3%	45%	54 months
N3a	50%	50%		N3b	37.9%	13.8%	CI 41.06-66.94

MST ï median survival CI ï confidence interval

Our analysis showed that 5- and 10-year survival rates for the same N category of patients with macroscopic vs patients with microscopic regional tumor burden decreased significantly. Patients with macroscopic tumor burden had an absolute 10-year survival rates 30-83% lower compared to patients with microscopic tumor burden of equivalent N category. Patients with both clinical evidence of nodal metastasis and pathologic examination documenting lymh nodes melanoma metastasis defined as having macroscopic or clinical apparent nodal metastasis had significantly decreased survival rates compared to patients with microscopic or clinically occult lymph node metastases, log rank p= .002. In all patients with regional lymph nodes metastases as the number of lymph nodes harboring metastatic increased, 5-year and 10-year OS decreased, but did not reach statistical significance.

Multivariate analysis of prognostic factors in patients positive for regional lymph nodes metastasis

Our analysis demonstrated that in patients positive for regional lymh nodes metastasis, the regional lymph nodes tumor burden was a dominant predictor of overall survival in a model based on age, gender, localization of the primary tumor, regional lymph nodes tumor burden and N categorization of the patients. Our model was statistically significant, χ^2 (7 N 64) =17.342, p=0.015. Macrometastatic regional lymph nodes tumor burden increased the hazard ratio of death by 4.257 times compared to micrometastatic regional lymph nodes tumor burden (Table 5, Figure1).

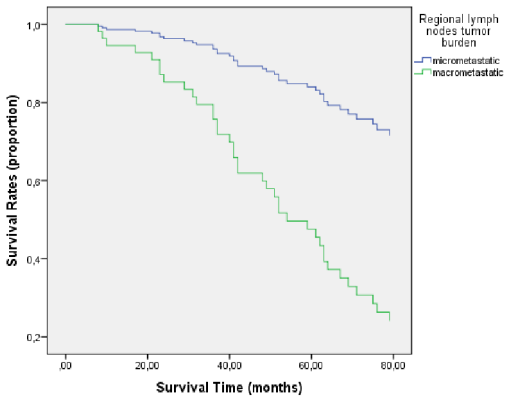

Figure 1. Survival rates in patients with macroscopic and microscopic regional lymph nodes tumor burden

Table 5. Multivariate Cox regression analysis of Factors Predictive of Overall Survival (OS) in patients positive for metastasis in regional lymph nodes

Variable	Chi square value (Wald)	P value	Risk ratio	95% CI
Age	.360	.835		
<50 years			1	
50-69 years	.204	.652	1.224	.509-2.940
Ó70 years	.331	.565	1.272	.561-2.88
N classification	4.022	.134		
N1	-	-	1	
N2	.033	.855	.890	.255-3.111
N3	1.828	.176	1.991	.734-5.400
Reg. nodes tumor burden				
Micromet. reg. lymph nodes	-	-	1	
Macromet. reg. lymph nodes	5.232	.022	4.257	1.23-14.732
Gender				
Males	-	-	1	
Females	.366	.545	1.257	.599-2.634
Localization				
Upper extremities	-	-	1	
Lower extremities	.621	.431	.755	.376-1.518

Discussion

The prognosis in patients with localized melanoma (Stage I and II) is generally favorable. In the 7th edition of AJCC melanoma staging system, tumor thickness, mitotic rate, and the presence of ulceration are used to define T categories [9, 10]. Patients with regional metastasis (Stage III) (ie, regional lymph node, satellite, and/or in-transit metastasis) represent a heterogeneous group with regard to staging and prognosis. These patients are sometimes incorrectly assumed to be at uniformly high risk of distant metastases and therefore may be offered very intensive forms of systemic therapy. It is well established that regional lymph nodes are the most common first site of metastasis in melanoma patients. The regional nodal basin is the first site of recurrence in 60% to 70% of melanoma patients with clinically localized disease who develope metastases [11, 12]. Retrospective studies, however, suggest a survival benefit for patients undergoing elective lymph node dissection (ELND) compared to those undergoing wide excision alone [13, 14]. Once regional nodal metastases are palpable, a patientôs opportunity for long-term survival is reduced by 20% to 50% over those found to have microscopically positive lymph nodes at ELND.

Our study demonstrate significant decrease in 5- and 10-year OS in patients clinically positive for metastases in regional lymph nodes (45.6% and 20.5%, respectively), compared to patients clinically negative for metastases in regional lymph nodes (88.6% and 75.7%%, respectively) similar to the results presented by Weide et al, and Balch et al. Previously understaged clinical stage III melanoma patients who migrated in the second group after sentinel node lymphadenectomy, contributed to heterogenity of the range of survival rates. Our results demonstrate significantly increased 10-year OS in patients with clinically unpalpable nodal metastases, but pathologically evident nodal metastases after sentinel lymphadenectomy, 76.9% compared to 20.5 % patients with clinically palpable nodal metastases.

Recent analyses of patients from the AJCC melanoma staging database confirmed the number of metastatic regional lymph nodes, presence of micrometastasis and macrometastasis and ulceration of the primary lesion as independent predictors of survival [15, 16]. Many authors have reported the number of metastatic nodes as the most important predictor of survival in patients with regional metastasis [8, 15]. The current AJCC N-category stratifies patients according to number of nodes involved: 1 node (N1) /2ï 3 nodes (N2)/ 4 or more (N3) metastatic nodes. Regional node tumor burden

(defined in the AJCC melanoma staging system as microscopic or macroscopic metastasis) was the second most important prognostic factor in patients with stage III disease [8, 10, 15]. Regional node tumour burden is used to subcategorize N category in the AJCC staging system. Microscopic disease refers to metastatic deposits detected on histologic analysis following elective or sentinel lymph node biopsy dissection (N1aï N3a). Macroscopic disease refers to nodal metastases that are clinically or radiographically apparent and pathologically confirmed (N1b-N3b). Remarkable heterogeneity in survival rates among N subcategories was reported [8, 15].

In addition, older age is found to be an independent adverse prognostic factor, regardless of nodal tumor burden. However, in patients with nodal micrometastases, features of the primary tumor including thickness, mitotic rate, ulceration, and anatomic location are found to significantly impact survival. In contrast, these primary tumor features were not independent predictors in patients with nodal macrometastases [16].

In our study lower values of tumor thickness and absence of ulceration of the primary tumour slightly improved the survival rates, thus we have made further analysis in order to determine dominant independent predictors of survival in patients positive for regional lymh nodes metastasis. The regional lymph node tumor burden was the most dominant predictor for overall survival in our model based on age, gender, localization, regional node tumor burden and N categorization of these patients. Macroscopic regional lymph node tumor burden increased the hazard ratio of death by 4.26 times compared to microscopic regional lymph node tumor burden.

Our results highlight the importance of early diagnosis of the nodal status using lymphatic mapping and sentinel lymphadenectomy, before the appearance of clinically evident lymph node metastasis, as well as the necessity for individual approach to each patient. Patients with positive sentinel node biopsies who (immediately) underwent lymphadenectomy had the most significant survival benefit as opposed to those who waited for clinical evidence of lymph node metastases.

The limitation of this study was the small number of patients, which corresponds to the population in our country.

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