Our Experience of Melanoma Thickness as a Predictor of Outcome of Sentinel Node Biopsy

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A B S T R A C T

All follow up protocols for patients with malignant melanoma (MM) are oriented to early detection of metastases. As most of the relapses happened in regional lymph nodes, special attention is given to this region, using different diagnostic tools. Sentinel lymph node biopsy (SLNB) is generally accepted method in determining status of lymph nodes in MM patients, in their staging. This method provides valuable prognostic information, facilitates early therapeutical lymphadenectomy and so provides good base for identification of those patients who are candidates for different adjuvant modalities of treatment. (In 2001 American Joint Committee on Cancer introduced new staging system for melanoma patients which presents good frame for prognosis and therapeutical approach. Inclusion of new criteria will allow better and more individualized prognosis and treatment.) The most important predictor of SLNB outcome is thickness of tumor according to Breslow, while there is no sufficient data to show correlation with other factors. We retrospectively studded 431 patients, out of which SLNB was performed on 188. Forty patients or 21.3% had positive lymph nodes. Our results showed strong correlation of tumor thickness and Clark level of invasion with SLNB outcome. Metastatic lymph nodes were founded in all acral-lentiginous melanoma patients, followed by nodular melanoma – 55.6% and superficial spreading melanoma – 14.1%. Results showed statistically significant predilection of positive SLNB in male patients and no correlation of positive SLNB with histological type of tumor. On the contrary, it showed significant correlation with development of metastases. Thus our results are similar to other comparable studies.

Key words: malignant melanoma, sentinel lymph node biopsy, melanoma thickness

Introduction

Malignant melanoma (MM) presents one of the most malignant and unpredictable tumor which arises from the melanocytic cells and primarily involves skin, even though can arise in eye (conjunctiva and uvea), meninges and mucosal surfaces. Melanomas take part of 90% of the deaths associated with cutaneous tumors. The incidence of melanoma is increasing worldwide[4,5]. The most important etiological exogenous factor is exposure to ultraviolet irradiation and endogenous is immune system impairment, while role of other factors (toxic substances, medications, hormones) stays controversial. MM is tumor of the middle age. In Croatia this tumor represents serious public and health problem. According to data of National Cancer Registry of Croatia it took 3% of total incidence of all malignant tumors[1] (incidence rate: 12.3 per 100 000 for females and 14.2 per 100,000 for males).

In follow up of these patients, which is based on early detection of recidives, from special interest is early and accurate diagnosis of primary tumor (staging), identification of SLN, and of course separation and more close follow up of those patients who are on a higher risk of developing metastasis. Prognosis given by staging is extremely important, because it gives a good base for further strategy on follow up and choice of different modalities of treatment and of course facilitate early detection of distant metastasis in subclinical phase[6].

Lymph node (LN) status is the most powerful prognostic factor for early stage of MM. Therefore, lymph node assessment is considered today as the main stay of the staging process[7]. Only few years ago only objective method to evaluate tumor involvement of the certain LN

drainage area was elective Radical Lymph Node Dissection (RLND) and the patohistological examination. This method provides high rate of complications and high percentage of patients underwent risk procedures without any benefit.

Sentinel Lymph Node Biopsy (SLNB) is an alternative method which reliably allows detection of LN metastasis in patients with primary MM, while at the same time avoids surgical trauma with high complication rate (20–30%)[8].

But, approximately 80% of melanoma patients undergoing SLNB have negative sentinel lymph nodes (SLNs). Today, we still have no predictor reliable enough to be implemented in the clinical setting in order to reduce the number of SNB procedures[9]. There is a continuous effort to reduce this high portion of an unnecessary SNB, but to keep satisfactory level of accuracy at the same time. Many different clinicopathological variables were considered: the patient's age, gender, the tumor's type, Breslow thickness, Clark level, ulceration, mitotic index, lymphocyte infiltration, regression, angiolymphatic invasion, microsatellitosis, and growth phase or even combination of different variables[8,9]. Some studies showed that thickness could be reliable independent prognostic factors for SLN positivity[10,11–12,13].

The main aim of our study was to examine correlation of tumor thickness and outcome on SNB. On the same group of patients we also tested correlation of gender, type and level of tumor invasion with sentinel node status. We were hoping that all of this will help us to identify group of higher risk patients and to find a way of reducing number of unnecessary procedures at the same time. Moreover, better predictivity in early stage of diseases could significantly influence our interventions and consequently have positive impact on the course of disease.

Patients and Methods

This retrospective study was performed based on data from Croatian State Referral Centre for Malignant Melanoma, at University Hospital »Sestre milosrdnice«. For analysis we used clinical records of 431 patients: 228 female and 197 male patients. They were all diagnosed and followed from 2005 to 2007 (121 patients in 2005, 125 in 2006 and 185 in 2007). Out of this group 188 patients underwent SNB at our institution.

There was only one inclusion criterion: equal or more than 1.00 mm of Breslow thickness. From all of patients included in analysis, who underwent SLNB in our institution 15 patients did not meet mentioned criteria (12 of them with Breslow thickness from 0.75 to 1 mm). From 188 patients on whom SLNB was performed, 40 patients (21.3%) had positive sentinel nodes. The four tables represent distribution of the main clinicopatological parameters: tumor's histological subtype (Table 1), localization of tumor (Table 2), tumor invasion by Clark level (Table 3) and Breslow thickness (Table 4).

Diagnosis of MM (histological subtype, Clarck and Breslow level) was done based on the histopathological examination of the surgically removed lesions. Tumor thickness was determined according to criteria of Breslow into four groups: (I: 0–0.75 mm; II: 0.76–1.5 mm; III: 1.5–4.00 mm and IV: >4.00 mm). Invasion of tumor is determined by Clark criteria into five groups: (I: tumor cells in epidermis only (melanoma in situ); II: tumor cells extend from epidermis into (but do not fill) papillary dermis; III: tumor cells extend from epidermis into and fill papillary dermis; IV: tumor cells extend into reticular dermis; V: tumor cells extend through the dermis into

TABLE 1
TUMOR'S HISTOLOGICAL SUBTYPE

Histological subtype	Number of patients	Valid percent
Superficial spreading melanoma	127	61.4
Nodular melanoma	51	24.6
Lentigo maligna melanoma	19	9.2
Acral-lentiginous melanoma	5	2.4
Others	5	2.5
Total	207	100.0
Missing System	224	
Total	431	

TABLE 2
TUMOR LOCALIZATION

Localization	Number of patients	Valid Percent
Head and neck	36	8.5
Trunk front side	58	13.6
Trunk back side	166	39.1
Head and shoulder	57	13.4
Leg and hip	88	20.7
Acral localization	11	2.6
Eye	2	0.5
Unknown localization	7	1.6
Total	425	100.0
Missing System	6	
Total	431	

TABLE 3
TUMOR INVASION BY CLARK LEVEL

Clark level	Number of patients	Valid Percent
I	10	2.8
II	108	29.9
III	115	31.9
IV	112	31.0
V	16	4.4
Total	361	100.0
Missing System	70	
Total	431	

TABLE 4
TUMOR BRESLOW THICKNESS

Breslow thickness	Number of patients	Valid Percent
I	97	27.5
II	98	27.8
III	102	28.9
IV	56	15.9
Total	353	100.0
Missing System	78	
Total	431	

underlying subcutaneous fat. SN was identified by the standard procedure of preoperative lymphoscintigraphy with radioactive nanocolloid and intraoperative use of a hand – held gamma probe. SNs were pathologically analyzed according to EORTC Melanoma Group protocol (staining was standard: H&E, S100 and HMB-45). Correlation of SLNB results and traditional melanoma prognostic indicators were analyzed by SPSS 12.0, standard statistical analytical program.

Results

Mean age of our patients was 53.55 yrs (SD=14.85), ranging from 7 to 90 yrs of age. Mean Breslow thickness was 2.15 mm (SD=2.15) in range between 0.11 to 14.00 mm. Our results showed slightly higher incidence of positive sentinel lymph nodes in male patients with statistically proven correlation of gender and SLNB outcome (p<0.05). Rate of positive sentinel nodes increased with higher tumor thickness, higher Breslow and Clark level. As assumed, we also founded strong correlation of tumor thickness and appearance of metastases. All correlations were with p<0.05. Histological subtype of melanoma was unable to predict SLNB outcome, but as a contrary in correlation analysis we founded different malignant potential of developing metastases by different type of tumor (p<0.05). According to type of melanoma: all of our patients with Acral Lentiginous Melanoma (ALM) developed metastases (valid 2; missing system 3; 100 valid percent); in the group of patients with Nodular Melanoma Malignum (NMM) 55.6% of patients developed metastases (valid 27; missing system 24; 55.6 valid percent). In Superficial Spreading Melanoma (SSM) group, 14.1% developed metastases (valid 64; missing system 63; 14.1 valid percent). Nobody from Lentigo Maligna Melanoma (LMM) group didn't develop metastases (valid 4; missing system 15; 100.0 valid percent). In the group of patients with Breslow thickness I, there were no positive sentinel nodes, and no detected metastases. In Breslow thickness II group were 10.3% (valid percent) of positive lymph nodes, and 21.6% (valid percent) of metastases. Breslow thickness III group of our patients had positive nodes in 19.1% (valid percent), and 40.4% of metastatic development. In Breslow thickness IV group 40.5% (valid percent) had positive sentinel nodes and 69.0% (valid percent) of them developed metastases. In separate analyzes of the group of 34 patients with MM thickness equal or less than 1 mm (partly met inclusion criteria), 4 patients had positive sentinel lymph nodes.

Discussion and Conclusion

Our research showed similar results as other comparable studies. As expected we founded correlation between thickness and invasion of tumor with incidence of positive SLNs, as well as higher predilection of positive sentinel nodes with male gender. Last we can explain with worse prognosis of male melanoma patients[14]. It seems from our and many other studies that thickness by itself can be independent selector of those patients who will undergo SLNB. We, as most of other melanoma centers are performing SLNB on all of the patients with thickness of more than 1 mm. But, do we take too wide safety margin? Or, do we risk too much? Most of the controversies arise within the group of thin (less than 1 mm), thick melanomas (more than 4 mm), and from the group of locally recurrent melanomas[15]. We also had few exemptions from the „rule« not to do SLNB for MM of thickness less than 1 mm. Most of them were very close to 1 mm, or dissection was based on some other clinical facts. The youngest patient on whom SLNB was performed, although he did not meet criteria, was 10 yrs old with 0.85 mm of tumor thickness. We learned that from that group 4 of our patients had positive sentinel nodes (all of them between 0.75 and 1 mm). We didn't have any positive sentinel nodes in Breslow I stage within our patients. Knowing that course of disease is worse with a younger age, we could ask ourselves: do we need to exclude some of our younger patients from the general rule, especially if we face with aggressive type of tumor, and tumor thickness is over 0.75 mm. On the other hand from literature and our experience we know that there is a huge number of „unnecessary« performed SLNB – negative results. We are aware of that, but there is still no alternative. Finding a better way to reduce some of unnecessary performed SLNB, will lead us to obvious advantage in terms of patient's quality of life and financial savings. Further studies will give the answer. We hope that implementation of non-invasive and cheaper methods for preoperative staging and follow up will improve sensitivity and specificity of current diagnostic tools. In this respect we are planning to prospectively study possibilities and limits of ultra sound (US) and US guided biopsy[16] alone or in combination with other methods.

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NAŠA ISKUSTVA O DEBLJINI MELANOMA KAO PREDIKTORU ISHODA SENTINEL BIOPSIJE

SAŽETAK

Svi protokoli praćenja bolesnika oboljelih od malignog melanoma, orijentirani su ka ranoj detekciji metastaza. Obzirom da se većina relapsa zbiva u regionalnim limfnim čvorovima, posebna pažnja posvećena je toj regiji, koristeći različite dijagnostičke alate. Sentinel biopsija limfnog čvora (SLNB) je općenito prihvaćena metoda u određivanju statusa limfnih čvorova bolesnika, odnosno u postupku stupnjevanja bolesti. Ova metoda omogućuje vrijednu prognostičku informaciju, doprinoseći ranoj terapeutskoj limfadenektomiji i ujedno pruža dobru osnovu za identifikciju onih bolesnika koji su kandidati za različite adjuvantne modalitete liječenja. 2001. *American Joint Committee on Cancer* uveo je novo stupnjevanje melanoma, koje predstavlja dobar okvir za prognozu i terapeutski pristup. Daljnje uključivanje novih kriterija omogućit će bolji i individualizirani tretman. Najvažniji prognostički čimbenik ishoda SLNB je debljina tumora, prema Breslow-u. Retrospektivno smo proučavali 431 bolesnika, od kojih je SLNB izvršena na 188. 40 bolesnika ili 21,3% imalo je pozitivne limfne čvorove. Naši rezultati pokazali su čvrstu korelaciju debljine tumora i stupnja invazije po Clarku sa ishodom SLNB. Metastatski limfni čvorovi pronađeni su kod svih bolesnika sa akro-lentiginoznim melanomom, slijedi nodularni melanom sa 55,6% bolesnika kod kojih su pronađeni metastatski limfni čvorovi, te površinsko-šireći tip melanoma sa 14,1%. Rezultati su pokazali statistički značajnu predilekciju pozitivnih limfnih čvorova kod muških bolesnika. Povezanost pozitivnih čvorova i histološkog tipa tumora nije dokazana, iako je tip tumora pokazao korelaciju sa razvojem metastaza. Naši rezultati, tako su slični onima u drugim komparativnim studijama.