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Sentinel node biopsy for skin melanoma

Biopsija čvora stražara kod melanoma kože

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Abstract

Background/Aim. Skin melanoma is one of the most malignant diseases with increasing incidence rate. Sentinel node biopsy (SNB) is very important for early detection of metastatic spread. The aim of the study was to analyze the first 40 patients with skin melanoma of 1 to 4 mm Breslow thickness when SNB was indicated. **Methods.** The patient characteristics, localization of the primary melanoma as well as histology grade were analyzed. SNB with intraoperative radiocolloid and methylene blue dye detection was performed. **Results.** Complication rate after SNB was analyzed and seroma was found in 5% of the patients. The therapeutic node dissection was performed in 10 patients with positive sentinel biopsy. The follow-up lasted two years. In five patients the false negative SNB was defined after the mean time of 11 months and the therapeutic dissection was performed. **Conclusion.** SNB in melanoma patients is a useful diagnostic procedure. It is advised for melanoma of 1 to 4 mm Breslow thickness.

Key words:
melanoma; skin neoplasms; sentinel lymph node biopsy; organotechnetium compounds; methylene blue; dissection.

Apstrakt

Uvod/Cilj. Melanomi kože su jedan od najmalignijih neoplazmi sa sve većom stopom incidencije. Biopsija limfnog čvora stražara (sentinel biopsija) veoma je važna za rano otkrivanje metastaza. Cilj istraživanja bio je da se analizira prvih 40 bolesnika sa melanomom kože debljine 1–4 mm kod kojih je bila indikovana biopsija čvora stražara (BČS). **Metode.** Analizirane su demografske karakteristike bolesnika, lokalizacija primarnog melanoma kao i histološki gradus melanoma kože. Vršena je BČS uz primenu intraoperativne detekcije radiokoloidima i boje metilen plavo. **Rezultati.** Analizirane su komplikacije BČS i utvrđena je pojava seroma kod 5% bolesnika. Terapijska disekcija limfnih čvorova (LČ) urađena je kod 10 bolesnika kod kojih je bila pozitivna BČS. Bolesnici su praćeni dve godine. Kod pet bolesnika utvrđeno je da je BČS bila lažno negativna. Kod te grupe bolesnika urađena je terapijska disekcija LČ posle prosečno 11 meseci od biosije. **Zaključak.** Primena BČS kod bolesnika sa melanomom korisna je dijagnostička procedura. Može se preporučiti kao standardna procedura za bolesnike sa primarnim melanomom debljine 1–4 mm.

Ključne reči:
melanom; koža, neoplazme; limfni čvorovi, stražarski, biopsija; organotehnecijumska jedinjenja; metilensko plavilo; disekcija.

Indtroduction

Skin melanoma is one of the most malignant diseases with increasing incidence rate in the last few decades. Melanoma accounts for 1–4.6% of all skin malignancies, but it involves 70% of mortalities related to cutaneous malignant tumors. The incidence rate is 10.6–45 per 100 000 [1]. These facts imply high importance of sentinel node biopsy (SNB) which enables an early detection of metastatic spread.

The biological growth pattern of melanoma is defined in two phases: radial growth and vertical growth. The distant spread of the disease can be defined as lymphatic or hematogenous. Lymphatic metastases can arise in the regional lymph nodes (LN). Melanoma metastases of the extremity spread to the adjacent axillary of inguinal nodes. The metastatic spread into the trunk or head and neck is not that simple. As for melanoma of the head, lymphatic metastases can be detected on both sides of the neck. The biggest problem is to define metastatic pathways in the trunk melanomas. The

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lymphatic spread can go forward to both axillary, and inguinal nodes or through umbilical ligament straight into the liver or in the LN adjacent to the internal mammary artery. The current investigations are related to the induction of lymphangiogenesis caused by stroma of the melanoma [2]. These facts indicate that there is no strict metastatic patterns for trunk melanoma. The aim of an early detection of metastases is to determine the possible metastatic pathways and check if the first LN along the pathway involve micrometastases. Sentinel node biopsy meets these criteria.

The primary therapy of melanoma is surgery. If the first operative treatment fails, or if the primary treatment does not fulfill the guideline, the chances for cure are minimal or absolutely lost.

The excision biopsy is crucial and must include 3 to 5 mm healthy margin. After histological confirmation of melanoma, a complete clinical and radiological staging is mandatory including chest radiography and ultrasound of regional LN [3].

If enlarged LN are found in clinical or ultrasound investigation, a radical therapeutic dissection must be done. Radical excision with safe margins of 2 cm must be used at the primary site of melanoma. An operative wound should be primarily closed by local flaps or skin grafting.

If clinical and ultrasound examinations do not present enlarged LN, there are two treatment options. The first option is, elective lymphonodectomy (in hospitals without technical possibilities for SNB) classified as T2, T3 or T4 and N0M0 [4, 5]. This protocol can be used only for melanoma of the extremities, but not for trunk, head and neck melanoma. Primary site is treated by excision of 2 cm safe margins. Hafner et al. [1] suggest radical excision surgery four weeks after melanoma biopsy. The suggested clear margins are 2 cm for melanoma thinner than 4 mm but thicker than 4.1 mm; for recurrent disease the suggested margins are 3 cm. The second option is SNB. The metastases in LN were referred as most important prognostic factor for melanoma. The benefits of SNB have been documented in some studies [6]. Removal of micrometastases in LN interrupts the lymphatic spread of the tumor and the survival rate is statistically significantly improved. The SNB for melanoma was suggested by the World Health Organization in 1999, but the American Joint Committee on Cancer introduced this method in diagnostic protocol in 2002 [7]. Nowecki et al. [7] and other autors suggest the SNB for melanoma thicker than 1 mm and thinner than 4 mm (T2 and T3) [8, 9].

A positive finding of SNB can be defined as single tumor cells (this is not an indication for therapeutic dissection); micrometastases (less than 2 mm in diameter) – therapeutic dissection is indicated; metastases (diameter more than 2 mm) – therapeutic dissection is indicated [1].

The literature data refer to complication rate after SNB. These complications are managed by conservative treatment and are not permanent or life-threatening. The described complications include allergic reaction on methyilene blue, seroma or hemathoma formation and transient paresthesias [8].

The aim of this study was to analyze the first 40 patients with skin melanoma of 1 to 4 mm Breslow when SNB was indicated.

Methods

The retrospective consecutive case study model was used for analysis of 40 patients with skin melanoma and clinicaly negative LN. All the patients underwent excisional biopsy with magrins of 0.5 cm. Male predominance was found (62.5%), with an average age of 52 years and the lower extremity mostly involved (32.5%). After histological confirmation of melanoma the SNB starts with lymphoscintigraphy. Radiocolloide Technetium-99 (^{99}Tc) in the amount of 0.3 mL (65.5 MBq or 1.8 mCi) was injected adjacent to biopsy scar one day before the surgery. Dynamic and static scintygraphy were performed using a Siemens lymphoscintigram. Dynamic scintygraphy was performed during radiocolloide injection and 30 minutes after the injection detecting the lymphatic route. Static scintygraphies both early (after 60 minutes) and late (12–16 hours after the injection) are performed. The results were properely documented with lymphoscintigraphies. The projection of a detected node was marked on the skin. On the day of surgery, an hour before the procedure, methylene blue in the concentration of 1% and the amount of 1 mL was injected around the biopsy scar. During the surgery, a gamma probe detector was used for localization of SN. After SN removal, radioactivity of the lymph basin should be 10 times less than the radioactivity of the SN. If the radioactivity is still high after the removal of the first node, the detection should be continued and other SN removed until the rate of radioactivity of SN and lymph basin reaches 10 : 1.

The treatment of primary site of melanoma was performed under general anesthesia obtaining 2 cm clear margins and primary reconstruction.

The follow-up took two years. The primary site of melanoma, clinical and hystology grade were analyzed as well as SN positivity and false negativity. Statistical analysis was performed. All the patients were treated during a 16-month period.

Results

Melanoma staging and grouping are presented in Tables 1 and 2.

The structure according to sex, age and localization of primary melanoma is presented in Table 3. Analysis of melanoma clinical stage according to TNM staging system in the group of 40 patients is presented in Table 4.

Sentinel node biopsy was performed in 24 (60%) axillary, in 15 (37.5%) inguinally and in one (2.5%) node in the neck region. In three patients, bilateral axillary node biopsy was performed according to the lymphoscintigraphy. In 95% of the patients, LN was marked with radioisotope and dye, and in 5% only with radioisotope.

In 14 (35%) patients we found one SN, in 18 (45%) two nodes and in 8 cases we detected three SN. An average number of nodes was 1.85. In 10 cases we found micrometastases (25%), while in 30 patients (75%) they were negative, histologically. In a group of patients with positive histology in

Table 1

TNM classification of melanoma [3]

Primary tumor (T)	Thickness (mm)	Ulceration	
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Melanoma *in situ*		
T1	≤ 1.0	a: no ulceration and Klarc level II or III b: ulcerated and Klarc level IV/V	
T2	1.01–2.0	a: no ulceration b: ulcerated	
T3	2.01–4.0	a: no ulceration b: ulcerated	
T4	> 4.0	a: no ulceration b: ulcerated	
Regional lymph nodes (N)	**Number of nodes**	**Metastatic tumor mass**	
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	1 node	a: occult (microscopic)* b: clinically apparent (macroscopic)†	
N2	2–3 nodes	a: occult (microscopic)* b: clinically apparent (macroscopic)† c: in- transit metastases or satellite without nodal metastases	
N3	4 or more nodes, or matted nodes or intransit metastases or satellite with nodal metastases		
Distant metastases (M)	**Site**	**Serum Lactic Dehydrogenase**	
Mx	Distant metastases cannot be assessed		
M0	No distant metastases		
M1	Distant metastases		
M1a	Skin, subcutaneous tissue, distant lymph nodes	Normal	
M1b	Lung	Normal	
M1c	All other visceral sites	Normal	
	Any visceral site	Elevated	

*Occult metastases (micrometastases) are diagnosed by sentinel node biopsy (SNB) or elective lymphonodectomy;
†Clinicaly apparent metastases are diagnosed by clinical and radiological evaluation and prooved by therapeutic lymphonodectomy

Table 2

Melanoma grouping 3

Neoplasm staging	Clinical grouping			Pathological grouping		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2a	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III	Any T	N1 N2 N3	M0			
IIIA				T1-4a	N1a	M0
				T1-4a	N2a	M0
				T1-4b	N1a	M0
				T1-4b	N2a	M0
IIIB				T1-4a	N1b	M0
				T1-4a	N2b	M0
				T1-4a/b	N2c	M0
				T1-4b	N1b	M0
IIIC				T1-4b	N2b	M0
				Any T	N3	M0
IV	any T	any N	any M	any T	any N	any M

Clinical staging includes microstaging of primary melanoma and clinical and radiological evaluation of melanoma.

Pathologic staging includes microstaging for primary melanoma and pathologic information about regional LN after SNB or complete lymphonodectomy. The exceptions are patients staged as 0 or 1A where pathological evaluation of LN is not necessary.
T – tumor; N – nodes; M – matastasis

LN, an average number of nodes was 1.9. That was not statistically significant difference regarding the whole series (1.85). After histology of LN, the patients were reevaluated and the grades are presented in Table 5.

The micrometastases were found in SN in one patient from the group IB, five patients in the group IIA and four patients in the group IIB and they were defined as group III. The pathology restaging is presented in Table 5.

Table 3
The structure of patients by sex, age and localization of melanoma

Patients	n	%
Sex		
M	25	62.5
F	15	37.5
Age (years)		
< 40	6	15
41–50	12	30
51–60	12	30
> 61	10	25
Site		
Upper extremity	6	15
Lower extremity	13	32.5
Trunk anterior	11	27.5
Back	9	22.5
Head and neck	1	2.5
Total	40	100,0

Table 4
Clinical grouping of melanoma patients

Clinical grade	Patients	
	n	%
0	0	0
IA	2	5
IB	10	25
IIA	19	47.5
IIB	9	22.5
IIC	0	0
III	0	0
IV	0	0
Total	40	100,0

Table 5
Pathological grouping in the study group after sentinel node biopsy (SNB)

Pathological stage	Patients	
	n	%
0	0	0
IA	2	5
IB	9	22,5
IIA	14	35
IIB	5	12,5
IIC	0	0
IIIA	6	15
IIIB	4	10
IIIC	0	0
IV	0	0
Total	40	100,0

We found two cases with seroma formation in postoperative course after sentinel biopsy.

Analysis of nonsentinel LN in a subgroup of patients with positive SN who underwent therapeutic dissection revealed the positive nonsentinel LN in one patient. In nine patients, the SN were the only positive nodes. The details during the surgery are presented in Figures 1–3.

The follow-up lasted from six months to two years. The mean follow-up was 18.7 months. During the follow-up, five patients were operated on with therapeutic dissection of the lymph basin previously sentinel biopsied. The disease-free period was 11 months (6 to 23 months) after the sentinel biopsy. Those were the patients with false negative sentinel biopsy.

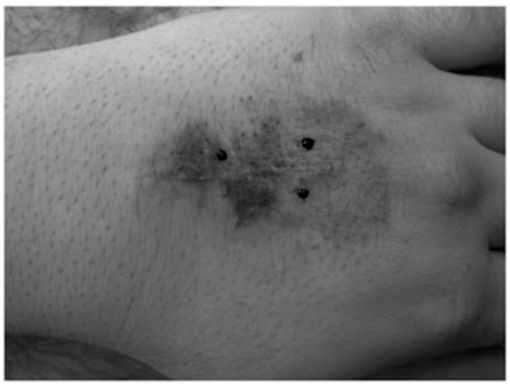

Fig. 1 – Intraoperative view after limphoscintigraphy and methylene blue injection around the biopsy scar in dorsal aspect of the hand

Fig. 2 – View on screen of gama detector during the surgery

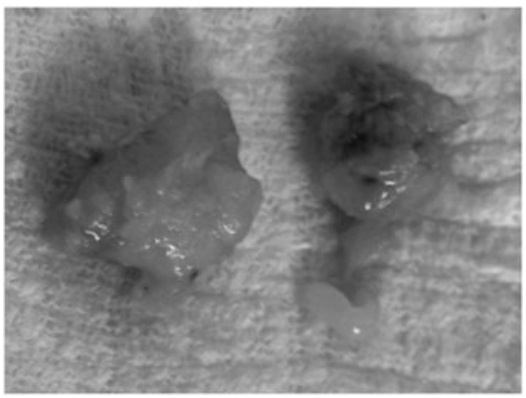

Fig. 3 – Two sentinel nodes (SN) from the left axillary region removed

Discussion

The SNB is a diagnostic method introduced in 1992 [6, 7, 10]. This method is not only advised for melanoma but also for breast cancer, penile cancer, head and neck malignancies as well as non-melanoma skin cancers [11]. The importance of early diagnostics of melanoma metastases is enhanced by the

well-known high malignant potential of melanoma and the resistance of melanoma to additional therapy. The technetium lymphoscintigraphy and methylene blue were routinely advised. Some studies confirm the use of methylene blue with stressed advantage over the lymphazurin blue [18]. In 95% of the patients, SN was mapped both with radioisotope and dye, and in 5% only with radioisotope. Estorugie et al. [14] found that SN was double marked in 86%, in 13% with radioisotope and in 1% with dye [12–18]. Some authors refer that micrometastases are present in 90% of the patients and can be proved by SNB [1]. Some studies present that SNB are positive in 15.8% [12], 17.6% [4], 20% [5], 20.7% [13] and 24% [14]. In our study, 25% of melanoma patients had positive SNB. In two patients, metastases were confirmed by imunohistochemistry. The similar findings have been referred elsewhere [4, 15]. According to the Tumor Nodes Metastasis (TNM) classification, the patients in our study were classified in the stage IB and IIA (10 and 19 patients, respectively). In the studies of other authors the corresponding data were published [10, 16]. In 48% of all cases with positive SN the inguinal nodes were involved [4]. In our series, the most predominant SN were in the axillary region (60%). The majority of patients had primary melanoma in the lower extremities (32.5%), followed by the sites in the back region (27.5%). The average number of SN described in the literature varies from 1.2, to 2.3 [4, 14, 16]. In our study, the average number of SN was 1.85. The SNB was mostly performed in male patients; the mean age was 52 years. Similar demographic data have been presented by other authors, as well [10, 16, 17]. All patients were treated according to the two-day protocol introduced by Estorugie [14], but in the literature the one-day protocol is also advised [4]. Additional analysis of nonsentinel nodes in specimens of therapeutic dissections after positive SNB showed that SN was the only involved node in 82% of cases [13]. In our study, SN was the only affected node in 90% of the patients. In one patient, we found metastases in nonsentinel nodes after therapeutic dissection. This patient had micrometastases in two of three SN detected. The literature data confirm the possibility of metastases in nonsentinel nodes in patients with micrometastases in two or three SN [19]. For critical approach to SNB we have to bear in mind the possibility of false positive findings, including the subcapsular benign melanocyte in LN [1]. Clinical follow-up lasted two years. In this group of patients, neither lymphatic nor hematogenous spread was detected. However, some literature data describe regional recurrences in 14.7% after 36 months of follow-up [10]. The 5-year survival rate is higher in melanoma cases after SNB and therapeutic dissection, because metastases are recognized in preclinical phase and dissection was performed in the earliest stage [1]. A 3-year disease-free interval was reported in 85% for SN negative and in 62% for SN positive patients. A 5-year disease-free interval was documented in 80% for SN and 53% for SN positive cases [14]. During a 2-year follow-up of patients with negative SNB, the lymphatic metastases in regional nodes were detected in five patients. The mean disease-free period was 11 months. Those patients were defined in protocols as false negative SNB [13, 14]. In three of five cases, the therapeutic dissection was performed during the first six months, and two patients during the further course of the follow-up. The false negative SNB results can be obtained due to inexperience of a surgeon, nuclear medicine specialist or pathologist. This occurs in studies including a large number of patients [13, 14, 19, 20]. The other reason for false negativity in SN can be the tumor embolisation of the lymph vessels with melanoma cells and no evidence of metastases in LN during the SNB. In our study, seroma formation is the only described complication documented in two cases. In the literature data, the complication rate is low and the complications are not life-treating and can be managed conservatively. The referred complications are allergic reaction on metilen blue, seroma formation, hemathoma formation, transient paresthesias etc [4, 14]. The suggested number of biopsies for single center is 30 [8]. In our series, a complication rate was 5%.

Conclusion

The SNB in patients with melanoma provides an early diagnosis of micrometastases in the regional nodes before their clinically detectable presentation. This enables a therapeutic dissection in the earliest stage. The protocol of double-mapping of sentinel LN offers the relevant data for LN localization with shorter operative time. Complication rate after SNB is low and significantly lower than the elective dissection.

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