

Analysis of disease free survival in cutaneous melanoma patients subject to sentinel lymph node biopsy

Authors' Contribution:

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: Cutaneous melanoma is estimated for 2% of malignant neoplasms occurring in humans. It is characterized by a high level of malignancy and low sensitivity to cytostatic drugs. The incidence of cutaneous melanoma is increasing in Poland. The lymphatic system is the most common route of dissemination of this neoplasm. The appearance of a sentinel node biopsy technique has made it possible to identify patients with a regionally advanced disease. It is a minimally invasive method with a small percentage of complications.

Aim: Analysis of disease free survival (DFS) in cutaneous melanoma patients with sentinel lymph node biopsy.

Material and methods: The analysis included 222 patients with cutaneous melanoma treated in the Department of Oncological Surgery in 2010–2015, who underwent a sentinel node biopsy. The study group consisted of 136 women and 86 men, the average age of patients was 59 years. Patients were qualified for sentinel node biopsy based on clinical evaluation and ultrasound of regional lymph nodes. The average follow-up was 25.1 months. About 2 hours before surgery, patients received a radioisotope, then lymphoscintigraphy SPECT was performed. Additionally, they were administered the Patent Blue dye in the operating room.

Results: The sentinel node was identified in 217 patients (98%), and the average sentinel nodes were 2.25. Twenty-seven patients (12%) had a metastasis in sentinel nodes. In this group, the duration of symptom free survival was significantly shorter. Sentinel node status and age of the patient were independent factors affecting the prognosis of disease free survival.

Conclusions: Sentinel node biopsy is a precise method to identify patients with cutaneous melanoma who have metastasis to regional lymph nodes, as well as the most important prognostic factor.

KEYWORDS:

cutaneous melanoma, disease free survival, lymphadenectomy, sentinel lymph node biopsy, SNB

ABBREVIATIONS

DFS – disease free survival

HR – hazard ratio

SNB – Sentinel Node Biopsy

INTRODUCTION

Cutaneous melanoma is a malignant tumor deriving from melanocytes residing in the basal layer of the epidermis, constituting ca. 2% of all cancers occurring in people. It is the main cause of death due to skin malignancies and has a high grade of malignancy. The condition is characterized by an early occurrence of metastases, a relatively low sensitivity to cytostatic medicines, and hence a high mortality [1, 2]. Annually, there are over 100,000 new cases recorded in the world. In Poland, the incidence of melanoma is about 6 cases per 100,000 population, which means about 3,600 new cases per year. Since over three decades, we have been observing an increased incidence rate in all age groups [3].

Cutaneous melanoma most often spreads via the lymphatic vessels, which is why nodal regions are particularly addressed in the diagnostic and therapeutic processes. Microscopic assessment of the state of regional lymph nodes constitutes a key point in determining the progress of disease in patients with cutaneous melanoma. Historically, elective lymphadenectomy was performed for this purpose; apart from assessing the regional stage of the cancer, it was distinguished

by a dubious therapeutic value, but also a relatively high percentage of early (wound infections, skin flap necrosis) and late complications (lymphoedema of the limbs) [4]. An alternative allowing to withdraw from selective procedures was keeping affected individuals under observation, and performing selective lymphadenectomy upon clinical signs of metastases in regional lymph nodes.

Both strategies were replaced by the sentinel lymph node biopsy technique, or SNB proposed in the early 1990s and developed by the American cancer surgeon Morton. The method permitted a minimally invasive assessment of the regional staging of the disease in the lymph nodes and adjusting the adequate complementary treatment. The sentinel node is the first which could be the potential location of tumor metastases. SNB permits a quick and credible identification of the group of patients who, despite the lack of clinical and radiological premises, have metastases to regional lymph nodes and require lymphadenectomy. Therefore, this method allows to limit the number of patients exposed to the risk of complications after a more invasive surgical procedure, with simultaneous minimization of cases of omission of metastatic lesions. Numerous publications emphasize the prognostic value of SNB, suggesting that it is an effective tool to assess the prognosis in patients with cutaneous melanoma [5–10].

MATERIALS AND METHODS

This paper was prepared on the basis of a retrospective analysis of 222 cases of patients affected by cutaneous melanoma treated at the

Surgical Oncology Clinic of the Maria Skłodowska-Curie Institute of Oncology in Krakow in the years 2010–2015, where they were subjected to SNB. The studied group comprised 136 women and 86 men. The average age of these individuals was 59 years (range from 20–87 years). The location of the primary focus in the studied group of patients is the skin of the limbs (126 patients), trunk (88 patients), head and neck (8 patients). The average thickness of infiltration on the Breslow scale in the tested melanomas was 3.51 mm (range from 0.2–44 mm), the median thickness of infiltration was 2.5 mm, and the mitotic rate was 4.96 mitosis/mm² (range from 0–45 mitoses/mm²). The distribution of the pT trait in the examined patients was as follows: pT1a – 5 patients, pT1b – 30, pT2a – 56, pT2b – 11, pT3a – 36, pT3b – 26, pT4a – 20, pT4b – 35, b.d. – 3. The mean time of observation of patients, calculated from the date of excision of the primary change to the time of the last follow-up, was 25.1 months.

Before excision of the sentinel node, all patients underwent diagnostic imaging – chest x-ray, ultrasound of the abdomen and regional lymph nodes. To identify the sentinel node, patients were administered an isotope – Technet 99 about 2 hours before surgery near the primary focus or within the scar after resection of the primary focus of melanoma. This was followed by the performance of SPECT lymphoscintigraphy, the aim of which was to visualize lymph flow from the location of the primary focus. In addition, the Patent Blue dye was administered in the operating room immediately before surgery.

We analyzed disease-free survival. Our retrospective analysis was prepared based on standard statistical methods; the prognostic value of the outcome of SNB was assessed using the Kaplan-Meier survival curves. To determine the parameters of the primary focus which could impact the disease free survival of patients with cutaneous melanoma, we conducted a multifactorial analysis based on the Cox proportional-hazards model.

RESULTS

In the examined group of 222 patients undergoing SNB, sentinel node was correctly identified in 217 cases (98%). Histopathological examination showed an average of 2.25 dissected lymph nodes (range from 1–12). In 27 people this result was positive – we found metastatic lesions within the sentinel node and patients were qualified for lymphadenectomy, of whom 25 individuals underwent the procedure (2 did not agree to the proposed surgical treatment). During the analysis we found that patients in the positive SN group had thicker melanomas (Breslow 4.48 mm vs 3.37 mm), with higher tumor mitotic rate (5.26 mitoses/mm² vs 4.93 mitoses/mm²). The observation of the group of 222 patients revealed a relapse of disease in 31 patients, including: in 10 (37%) with a positive SNB result, in 20 (10.5%) with a negative biopsy result, and in 1 patient in whom we did not manage to identify the sentinel node in the taken specimen. Only 5 (2%) people with negative SN had recurrence in regional lymph nodes. Relapsed patients were older (mean age 63.6 years versus 58.2), had thicker melanomas (Breslow 6.1 mm vs 3.06 mm), with higher mitotic rate (8.3 mitosis)/mm² vs 4.5 mitoses/mm² and they more often ulcerated (55% vs 30%). In most people, recurrence took the form of generalized dissemination – 19 patients (61%).

Differences in asymptomatic experiences between the examined groups of patients are illustrated in Kaplan-Meier survival curves (Fig. 1.).

Analysis using the Cox model shows that SN+ and SN- groups differ by disease free survival. The hazard ratio, or HR for the SN+ group is 3.805, so in this group the probability of relapse at any time is 3.805 times higher than in the SN- group (Tab. I.).

In the analysis of independent prognostic factors of the Cox model, we took into account the following parameters: Breslow thickness of infiltration, presence of an ulcer, mitotic index, age and gender of patients, presence of metastases in sentinel nodes and the number of metastatic lymph nodes (Tab. II.). Sentinel node status (HR – 5.677; p = 0.006) and patient's age (HR – 1.044; p = 0.038) constituted prognostically independent factors influencing symptom-free survival.

In turn, analysis with the use of logistical regression in which we studied the impact of some signs of primary focus on the frequency of spread to the lymph nodes, showed a statistically significant relationship between the location of the primary tumor focus and the probability of nodal dissemination. In this analysis, we considered features such as the age of patients, gender, Breslow thickness of melanoma, tumor location, mitotic activity, ulceration, and the number of sentinel lymph nodes. From the analysis it can be concluded that the location of the primary focus on the upper limb reduces the likelihood of metastases to regional lymph nodes. There was no statistical significance among the study of the remaining features.

DISCUSSION

The treatment of cutaneous melanoma has been evolving for years. Nevertheless, surgery still remains the fundamental method of choice. The results of treatment depend on the early diagnosis of the tumor which, due to the fact that it occurs on the skin, is relatively easily detectable. Hence, the awareness of the patient and doctors has the most significant impact on early diagnosis, and therefore the results of treatment. Local treatment consisting of excision of the primary tumor with an appropriate margin determined by the Breslow thickness of infiltrate has been a recognized standard for years. According to current therapeutic guidelines, SNB is a standard procedure in patients with cutaneous melanoma after excisional biopsy (not after a broad primary tumor excision), in cases of cancer diagnosis ≥ T1b, i.e. with Breslow thickness of infiltration ≥ 0.8mm or with (micro-)ulceration on the surface of melanoma regardless of the thickness of infiltrate, without clinical metastases in regional lymph nodes and distant organs [11–13].

Until recently, the diagnosis of SN metastases was an indication for a complementary lymphadenectomy. The results of the MSLT-I study indicated that the SNB result is one of the key prognostic factors. In patients with intermediate cutaneous melanomas (1,2–3.5 mm) and thick melanomas, SNB improved tumor free survival (in the group of patients with regional lymph node metastases confirmed in SNB). Complementary lymphadenectomy dramatically improves regional disease control, but is associated with a significant percentage of both early complications – those associated with wound healing – and distant ones, i.e. the occurrence of lymphoedema [14–15].

Recent DeCOG-SLT and MSLT-II studies indicate no benefit in survival resulting from adjuvant lymphadenectomy. This caused a change in the algorithms of conduct. The currently recommended follow-up after a positive SNB is observation with some exceptions

(size of metastasis in the node, number of changed metastatic nodes, or crossing the nodular capsule) [16, 17]. The introduction of new medicines to the therapy of cutaneous melanomas can cause further changes in conduct in algorithms.

The analysis of Melanoma Institute Australia published in 2014 on a group of 5,840 patients with cutaneous melanoma presented the benefits of SNB. The authors confirm that in the group of patients whose sentinel node was excised and examined, there was better control in the regional lymph nodes, which translated into a prolonged time of disease free survival compared to the control group. Although the percentage of local recurrences and distant metastases is similar in the whole study group, a significant decrease in the incidence of distant metastases was observed in the subgroup with infiltration thickness between 1 and 4 mm [18].

Similar conclusions are drawn by American authors of a study conducted on a group of over 4,500 patients with cutaneous melanoma. They emphasize the role of SNB in assessing the stage of disease, although they do not demonstrate the effect of the procedure on the symptom-free survival rate in high-grade cases (Breslow > 4 mm). According to the authors, SNB as a prognostic factor is used in patients with melanoma of infiltrative thickness 1.2–3.5 mm [19]. Other insights have been made by Italian authors. They show that in a group of 250 people with locally advanced melanoma (Breslow > 4 mm, mean 7 mm), patients undergoing SNB have a significantly lower percentage of cases of progression, which translates into the duration of disease free survival [20].

The research shows a significantly statistical difference in the percentage of relapses of the disease in patients who were found with the presence of metastases of cutaneous melanoma in the sentinel node. In a multifactorial analysis, we showed an almost 6-fold increased risk of relapse in patients after a positive biopsy compared to patients with a negative result. This is reflected in the length of asymptomatic experiences which speaks in favor of the use of SNB as a prognostic tool in assessing the prognosis in patients, as well as a method to improve symptom free survival results.

The authors of a paper published in 2015 at the Oncology Center in Warsaw also investigated the usefulness of SNB in the treatment and prognosis of patients with melanoma. In a group of 1,764 people undergoing the procedure, the presence of melanoma cells was found in 19.9% of sentinel nodes. Among patients with dissemination to the nodes we observed almost double the percentage of overall survivals over a period of 8 years after resection of the primary lesion [21]. However, in a 2016 publication based on an analysis of almost 2,000 cases of patients with cutaneous melanoma, it was estimated that in individuals with no signs of dissemination, SNB will reveal metastases of melanoma in 15–22% cases. These patients qualify for complete lymphadenectomy and possible complementary systemic treatment, which increases the percentage of disease free survival [22]. Lymphadenectomy after positive SNB reduces the percentage of regional relapses [23, 24]. Our analysis is consistent with the 2014 report showing the relationship between disease free survival time and depth of primary infiltration [23]. According to Morton (the creator of the concept of SNB in the treatment of cutaneous melanoma), abandoning this procedure increases the percentage and number of subsequent node metastases, and thus worsens the prognosis of patients [25].

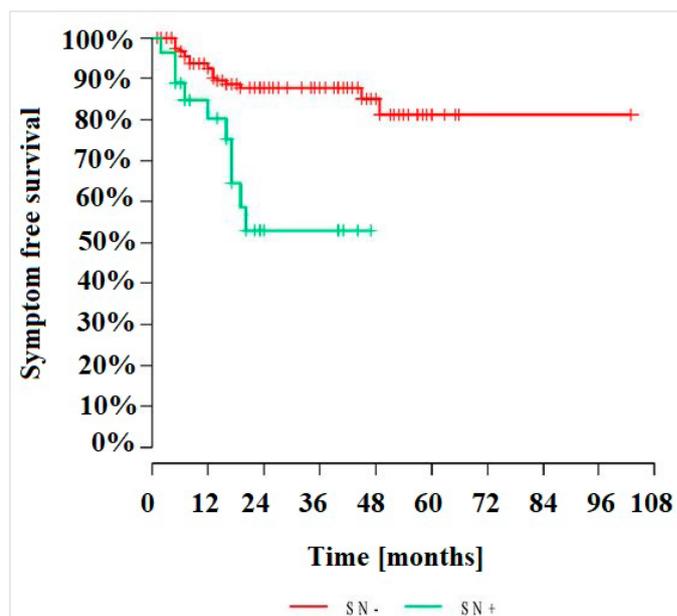


Fig. 1. Survival curves of disease free negative and positive SNB groups ($p = 0.001$).

Whilst there is some controversy as to whether SNB improves overall and cancer-dependent survival, most authors agree that it is an effective tool to assess prognosis [26].

Australian authors found a significant improvement in distant metastasis free survival in patients who were diagnosed with metastatic lesions in the sentinel node and had an adjuvant lymphadenectomy performed immediately. A significant advantage of immediate lymphadenectomy over distant metastasis free survival in SNB (+) patients has been proven in comparison with the group of patients who underwent only observations in whom lymphadenectomy was performed only after the dissemination of the disease to the nodes [18].

The subject of discussion is also the prognostic value of SNB depending on the location of the primary change. A 2014 publication showed that the procedure for head and neck melanomas is characterized by a higher percentage of false negative results [26]. In our analysis it is difficult to refer to this, because patients with this location of the primary focus accounted for less than 4%. The low percentage of people with melanoma in the head and neck in our analysis stems from the fact that lymphatic drainage in this area of the body is quite complicated and such patients were qualified for SNB less often. The paper from 2000 demonstrates the benefit in the use of SNB over selective lymphadenectomy in patients with the primary lesion located within the skin of the limbs [27].

In our study, people with a positive SNB had a PET-CT scan to exclude distant metastases before deciding on complementary lymphadenectomy. Unfortunately, there is a lack of prospective studies assessing the usefulness of modern imaging techniques, such as CT, MRI or PET-CT in determining the presence of metastases to regional lymph nodes and distant organs. The percentage of distant metastases reaches 50% in patients with a deeply infiltrative, ulcerative primary site with a positive sentinel node biopsy. Although PET-CT is performed in such people, it should be noted that the percentage of false negative results is close to 20% [28].

The outcome of histopathological examination and microscopic assessment of the stage of melanoma remains a subjective matter,

Tab. I. Disease free survival analysis according to the Cox model in both groups of patients, the median survival in both groups is greater than the time of the longest follow-up. This means that after the observation was completed, in both groups more than half of the patients lived without symptoms of recurrence.

GROUP	NUMBER OF PATIENTS	NUMBER OF EVENTS	SURVIVAL			SURVIVAL MEDIAN [MONTHS]	HR	95% CONFIDENCE INTERVAL FOR HR			P
			YEARLY	3-YEAR	5-YEAR						
SN-	195	21	92.41%	87.70%	81.26%	> najdł. obs.	ref.				
SN+	27	10	80.38%	52.85%	52.85%	> najdł. obs.	3.805	1.778	8.143		p = 0.001

Tab. II. Multivariate analysis of disease free survival according to the Cox model.

VARIABLE	HR	95% CONFIDENCE INTERVAL FOR HR	SIGNIFICANCE		
Age [years]	1.044	1.002	1.087	p = 0.038	
Gender					
	F – ref.				
	M	1.235	0.469	3.252	p = 0.669
T Breslow [mm]	1.041	0.968	1.119	p = 0.278	
Mitotic activity	1.018	0.961	1.078	p = 0.541	
Ulceration					
	No – ref.				
	Yes	1.899	0.651	5.54	p = 0.24
SN					
	SN – ref.				
	SN+	5.677	1.645	19.598	p = 0.006
Number of involved lymph nodes	1.232	0.792	1.914	p = 0.355	

Tab. III. Risk of SN metastasis depending on tumor location.

TUMOR LOCATION	N	PATIENTS WITH METASTASES	%	OR	95%CI	P*	
Lower limb	66	11	16.67%	1	poz. ref.		
Upper limb	60	2	3.33%	0.172	0.037	0.813	0.026
Trunk	88	13	14.77%	0.867	0.361	2.079	0.749
Head/neck	8	1	12.50%	0.714	0.08	6.402	0.764

* Univariate logistic regression

with significant differences depending on the experience of the medical examiner assessing the preparation. In a paper published in 2014 by Australian researchers, it is recommended that the assessment and treatment of all patients with malignant melanoma take place in specialized centers. Re-evaluation of microscopic preparations by specialists in the assessment of cutaneous melanoma showed that a change in the classification of the T characteristic occurred in 22% of people [29]. The results of the pT assessment in our work relate primarily to patients originally operated outside our clinic. On the one hand, this is a factor that could be a weak point of the paper, while on the other it presents a real clinical picture of treated patients.

A cohort analysis report by Canadian authors on a group of over 1,000 patients highlights the correlation between infiltration depth and the probability of nodal dissemination. The presence of melanoma cells in regional lymph nodes was found in 21% of people undergoing SNB. Higher mitotic rate of tumor cells was also observed in patients with a more locally advanced lesion [30]. Similar results were obtained in the aforementioned study of Polish authors. Here too, a positive correlation between Breslow thickness of infiltration and mitotic rate of tumor cells was observed. Among the statistically significant factors associated with positive SNB, the authors of the analysis mention: male sex, presence of ulceration and infiltration on the Breslow scale > 2 mm [21].

Numerous studies stress the impact of age on prognosis in patients with cutaneous melanoma. In our analysis, age also presents itself

as an adverse prognostic factor. Furthermore, we demonstrated that with each year of life, the rise of recurrence increases by 4.4%. Elderly people have a slightly different natural course of disease and survival rates. Primary foci usually infiltrate to a greater depth, have a higher mitotic index and are more often covered with ulceration. These features have an adverse impact on the prognosis of disease in older patients. Paradoxically, a smaller percentage of metastatic sentinel nodes was found in elderly patients. Given the greater likelihood of distant metastases, some authors suggest a tendency to disseminate via blood vessels in older patients. It should be mentioned, however, as shown by American researchers based on a database from 2008–2009, that patients after 75 years of age were less frequently subjected to SNB. Furthermore, in the case of a positive histopathological examination, only 50% of people underwent complementary lymphadenectomy. The justification of such conduct was to be the worse general condition of the patients and the presence of concomitant diseases. It is also believed that older people have a weaker immune response to the presence of cancer cells, which affects life expectancy [31]. SNB is the key independent prognostic factor in assessing disease free and tumor-dependent survival, allowing for satisfactory assessment and control within the regional lymphatic system. Age alone should not be an indication for abandoning this procedure [32].

CONCLUSIONS

SNB constitutes a precise tool for the identification of patients with cutaneous melanoma in whom there was dissemination

Tab. IV. Factors affecting metastases in sentinel nodes.

VARIABLE	OR	95% CI		P*			
Breslow thickness of melanoma [mm]	1.045	0.971	1.123	0.241			
Age [years]	1.001	0.975	1.027	0.969			
Mitotic activity	1.006	0.944	1.073	0.845			
Number of excised sentinel nodes	0.797	0.581	1.093	0.16			
GENDER	N	PATIENTS WITH METASTASES	%	OR	95%CI	P*	
Women	136	13	9.56%	1	poz. ref.		
Men	86	14	16.28%	1.84	0.819	4.131	0.14
PRESENCE OF ULCERATION							
no ulceration	131	14	10.69%	1	poz. ref.		
Ulceration	76	9	11.84%	1.123	0.461	2.733	0.799
TUMOR LOCATION							
lower limb	66	11	16.67%	1	poz. ref.		
upper limb	60	2	3.33%	0.172	0.037	0.813	0.026
Trunk	88	13	14.77%	0.867	0.361	2.079	0.749
head/neck	8	1	12.50%	0.714	0.08	6.402	0.764
TYPE OF MELANOMA							
Nodular	107	19	17.76%	1	poz. ref.		
superficial	56	4	7.14%	0.356	0.115	1.104	0.074
Other	20	1	5.00%	0.244	0.031	1.934	0.182

of the carcinoma to regional lymph nodes. The method allows for assessment of patient prognosis, since a positive result correlated with a greater risk of disease recurrence. The group of individuals who have relapsed can be characterized by greater local

advancement of the primary focus – greater depth of infiltration of the primary focus on the Breslow scale and the presence of adverse biological features of the tumor. Patient age and location of the primary focus are major factors for disease free survival.

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