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ВІДДАЛЕНІ РЕЗУЛЬТАТИ БІОПСІЇ СТОРОЖОВОГО ЛІМФАТИЧНОГО ВУЗЛА В ПОРІВНЯННІ ЗІ СПОСТЕРЕЖЕННЯМ ЗА ЛІМФАТИЧНИМИ ВУЗЛАМИ У ПАЦІЄНТІВ З МЕЛАНОМОЮ

Мета: оцінка впливу біопсії сторожового лімфатичного вузла без подальшої повної лімфодисекції незалежно від статусу сторожового лімфатичного вузла на результат лікування пацієнтів з меланомою шкіри.
Матеріали та методи. 309 пацієнтів з первинною меланомою шкіри були випадковим чином розподілені в групу широкого висічення первинної пухлини та біопсію сторожового лімфатичного вузла без подальшого повної лімфодисекції, незалежно від статусу сторожового лімфатичного вузла, або в групу широкого висічення меланоми шкіри. В ад'ювантному режимі застосовували інтерферон у низьких дозах .
Результати. 5-річна виживаність без прогресування становила (85,1 ± 3,0) % у групі широкого висічення та біопсії сторожового лімфатичного вузла та (78,4 ± 2,4) % у групі широкого висічення. 5-річна загальна виживаність не відрізнялась в обох групах: (88,6 ± 3,0) % проти (85,1 ± 2,4) % відповідно; відношення ризиків 0,97; $p = 0,42$.
Висновок. Біопсія сторожових лімфатичних вузлів у пацієнтів з меланомою шкіри підвищує показник безрецидивної виживаності, без впливу на загальну, що підтверджує діагностичну цінність цієї процедури.
Ключові слова: меланома, біопсія сторожового лімфатичного вузла, виживаність.
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LONG-TERM OUTCOMES OF SENTINEL LYMPH NODE BIOPSY VERSUS LYMPH NODE OBSERVATION IN MELANOMA PATIENTS

Objective: evaluating the influence of sentinel lymph node biopsy without following completion lymph node dissection independent on sentinel lymph node status on the outcome in patients with skin melanoma.
Materials and methods. Three hundred nine patients with a primary skin melanoma were randomly assigned to wide excision of the primary tumor and sentinel lymph node biopsy without following completion lymph-node dissection independent on sentinel lymph node status or to wide excision of skin melanoma. Low-dose interferon was administrated in the adjuvant setting.
Results. 5-year disease-free survival rate was (85.1 ± 3.0) % in the wide excision and sentinel lymph node biopsy group and (78.4 ± 2.4) % in the wide excision group (hazard ratio, 0.69; $p = 0.006$). 5-year overall survival rates were similar in the two groups: (88.6 ± 3.0) % vs. (85.1 ± 2.4) %, respectively; hazard ratio, 0.97; $p = 0.42$.
Conclusion. Sentinel lymph node biopsy in patients with skin melanoma increases disease-free survival rate without influence on overall survival, confirming the diagnostic, not therapeutical, value of this procedure.
Key words: melanoma, sentinel lymph node biopsy, survival.
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INTRODUCTION

Sentinel lymph node biopsy (SLNB) is a standard diagnostic procedure for accurate staging of skin melanoma. According to current American and European guidelines, SLNB is recommended for staging in melanomas of American Joint Commission on Cancer 8th edition (AJCC8) stage pT2a or higher (> 1.0 mm Breslow thickness) and should be discussed with patients with melanoma of AJCC8 stage pT1b (i.e., with a tumor thickness 0.8–1.0 mm or with a tumor thickness of < 0.8 mm with ulceration) [1, 2].

The prognostic value of SLNB was proved at the end of the last century by the Multicenter Selective Lymphadenectomy Trial – 1 (MSLT-1) study, in which patients with skin melanoma and Breslow thickness more than 1.0 mm or level of Clark invasion IV–V were randomized into two groups. In one of them, patients underwent wide excision of the primary tumor with SLNB followed by completion of regional lymph dissection (CLND) in case micrometastases were found. Another group-wide excision of the primary tumor with the subsequent observation of regional lymph nodes and the implementation of delayed regional lymph nodes in the case of macrometastases were performed [3]. As a result, it was found that the 5-year overall survival in patients with metastases in sentinel lymph nodes (SLN) was (72.3 ± 4.6) %, and without metastases – (90.2 ± 1.3) %. The authors concluded that the presence of metastases in SLN is an important prognostic factor that determines the further course of the disease and affects the survival of patients with skin melanoma. So, since 2002, the presence or absence of metastases in SLN has been included in the AJCC classification [4,5].

It was expected that after SLNB patients would have better survival than patients with observation. However, in the same study, it was shown that SLNB affected only on recurrence-free survival (RFS), [(78.3 ± 1.6) % in the SLNB group and (73.1 ± 2.1) % in the observation group ($p = 0.009$] without difference in 5-years overall survival (OS) [(87.1 ± 1.3) % and (86.6 ± 1.6) %, respectively].

The question of immediate or delayed CLND in patients with metastases in SLN has been discussed for a long time. Until recently, in most countries, CLND was performed immediately if micrometastases in SLN were detected, but only 10–15 % of cases metastases were found in non-SLN [6]. The answer to this question was obtained after the results of study MSLT-II, in which patients with micrometastases in SLN were randomized into two groups: in one of them, immediate CLND was performed, and in another, patients underwent observation with delayed CLND if macrometastases developed during the time. It was shown that immediate CLND increased the rate of regional disease control and provided prognostic information but did not increase 3-year melanoma-specific survival among patients with melanoma and sentinel-node metastases [(86 ± 1.3) % in the dissection group and (86 ± 1.2) % in the observation group; $p = 0.42$ by the log-rank test] at a median follow-up of 43 months [7].

Nowadays, the prognostic significance of SLNB is undoubted. However, the question of the therapeutic value of SLNB is still being discussed. Our study aims to evaluate the influence of SLNB without following CLND independently on SLN status on the outcome in patients with skin melanoma.

The primary endpoint of our study is disease-free survival (DFS) (survival without evidence of local recurrence or distant metastasis). Secondary endpoints included OS (survival until death from any reason) and incidence of local and distant metastases in both groups.

MATERIALS AND METHODS

During 2009–2013, 309 patients with primary skin melanoma of the trunk and extremities and tumor thickness ≥ 1.0 mm by Breslow were included in the study. The Ethical Committee of the National Cancer Institute approved the study and Informed concern form.

Diagnosis of melanoma was confirmed by excision biopsy of the skin tumor and pathologic evaluation followed by a standard examination that included chest X-ray and abdominal organs and regional lymph nodes ultrasonography. After signing the Informed concern form, patients were included in the trial and randomized into the main or control group (Fig. 1).

The main group included 151 patients who underwent radionuclide detection of SLN, wide excision (WE) of post-biopsy scar, and SLNB (WE + SLNB).

For identifying SLN, the radionuclide method was used. On the eve of the surgery (24 hours), lymphoscintigraphy was performed to identify SLN in the regional lymph node collector. Colloids «Nanocis» or «Nanocoll» labeled with radioactive ^{99m}Tc activity of 75– 100 MBq were used as lymphotropic radiopharmaceuticals with a total volume of 1.0 ml, which were injected around the postoperative scar intradermally. Lymphoscintigraphy was performed immediately after ^{99m}Tc administration and after 2 hours on a digital gamma camera («Spirit DH Mediso») or a single-photon emission computed tomography. Based on the data of lymphoscintigraphy, preliminary detection of SLN was performed using a portable

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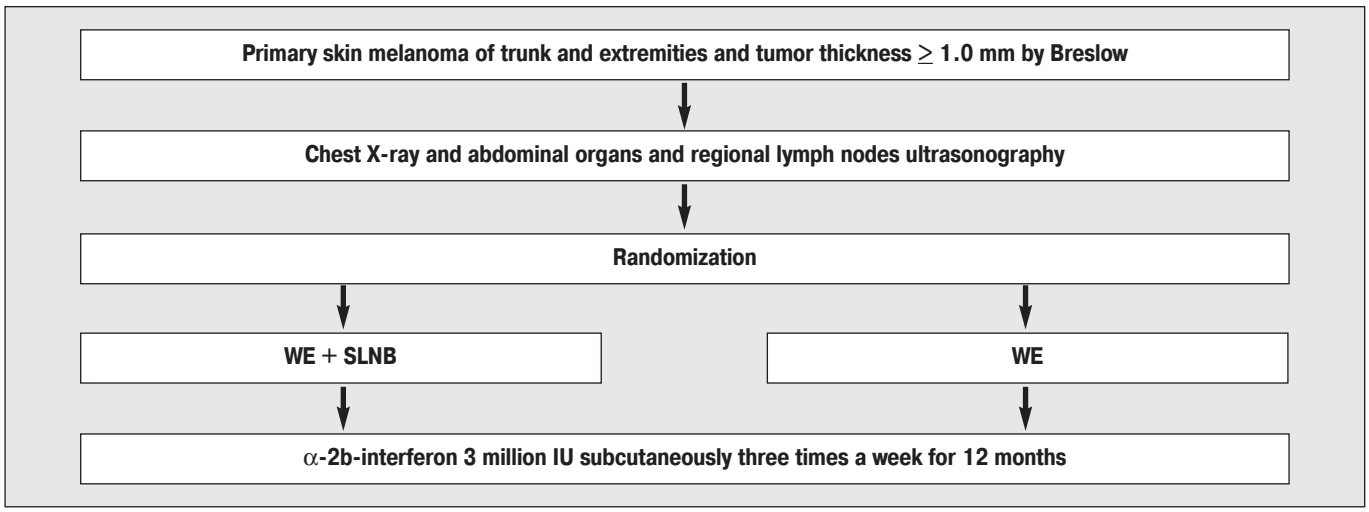

Figure 1. Study design

gamma counter Eurorobe («Canberra Packard»), marking the location of SLN on the patient's skin.

Twenty-four hours after the ^{99m}Tc injection WE of post-biopsy scar and SLN performed. Margins for WE were 1–2 cm depending on tumor thickness; if necessary, skin flaps or grafts were used to close the wound defect. Immediately before SLNB, the localization of SLN was again clarified to prevent mismatch with the label due to the patient's relaxation during surgery. The skin incision was done above the point with the highest level of radioactivity. Lymph nodes with high radioactivity were identified in the wound using a portable gamma probe and removed.

The diagnosis of melanoma was confirmed by pathology examination of the primary tumor, skin scar, and lymph nodes, which were fixed in a buffered 10 % formalin solution (pH 7.4) and sealed in paraplast using a histoprocessor «Histos-5» («Milestone», Italy). Histological sections five μm thick were made from paraffin blocks using a Microm HM325 microtome (Thermo Scientific, Germany) stained with hematoxylin and eosin.

After surgery, low-dose recombinant α-2b interferon was administrated regardless of the presence or absence of micrometastases subcutaneously 3 million IU three times a week for 12 months.

The control group included 158 patients whose surgery was limited by WE of post-biopsy scar, followed by subsequent low-dose recombinant α-2b interferon administration.

After treatment, patients were followed up for five years with chest X-ray and abdominal and regional lymph node ultrasonography.

The comparative characteristics of patients in Table 1 show that the main prognostic features in groups were comparable. Moreover, it can be noted that the control group had a favorable prognosis regarding the thickness and ulceration of the primary tumor.

Table 1

Demographic and clinical characteristic patients in study groups

Characteristic		Main group n = 151		Control group n = 158	
		n	%	n	%
Gender	Male	63	41.7	66	41.8
	Female	88	58.3	92	58.2
Age, years	< 30	16	10.6	15	9.5
	30–50	53	35.1	55	34.8
	> 50	82	54.3	88	55.7
Localization of primary tumor	Trunk	84	55.7	86	54.4
	Upper extremities	23	15.2	20	12.7
	Lower extremities	44	29.1	52	22.9
Tumor thickness by Breslow, mm	1.0–2.0	50	33.1	62	39.3
	2.01–4.0	66	43.7	59	37.3
	> 4.0	35	23.2	37	23.4
Ulceration of primary tumor	Yes	65	43.0	48	30.4
	No	86	57.0	110	69.6

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The statistical analysis was performed using Microsoft Excel 2010 and Stat Plus. Data were summarized with means and standard deviations, medians, and ranges. Survival curves were computed with the use of the Kaplan–Meier method. For the primary and secondary endpoints, RFS and OS, we used the log-rank test to compare the rates among patients in the WE and SLNB group and the SLNB group. Comparisons of categorical variables were performed using Chi-square. The differences were estimated as statistically significant at $p < 0.05$.

RESULTS

From March 2009 through April 2014, 309 patients were enrolled in the study and underwent randomization. In the group of WE and SLNB, micrometastasis in SLN was detected in 35/151 patients (23,2 %).

During the subsequent follow-up, metastases in the WE and SLNB group were identified in 36 (23.8 %) patients, while in the WE group – in 43 (27.2 %) patients ($p = 0.496$).

The DFS rate was significantly higher in the WE and SLNB group than in the WE group at five years: (85.1 ± 3.0) % vs. (78.4 ± 2.4) %; hazard ratio, 0.69; 95 % confidence interval [CI], 0.13 to 0.63; $p = 0.006$ by the log-rank test, (Fig. 2).

At five years of follow-up, there was no significant difference in the OS between the WE+SLNB group and the WE group: (88.6 ± 3.0) % vs. (85.1 ± 2.4) %; hazard ratio, 0.97; 95 % confidence interval [CI], 0.63 to 1.21; $p = 0.42$ by the log-rank test, (Fig. 3).

The localization of the first metastases detected in study groups is presented in Table 2. The most frequent first metastases in both groups were regional lymph nodes: 50.0 % in WE and SLNB vs. 60.5 % in the WE group — simultaneous regional lymph nodes and distant metastases were observed in 8.3 % and 11.6 %, respectively. The difference in the incidence of metastases in regional lymph nodes and both regional lymph nodes and distant metastases was insignificant. At the same time, the difference in the incidence of distant metastases was statistically significant: 50 % in the WE and SLNB group vs. 27.9 % in the WE group; $p = 0.043$.

CONCLUSIONS

Our randomized prospective study comparing SLNB with nodal observation in patients with skin melanoma found a survival benefit for the primary endpoint of disease-free survival of nearly 6.7 %. At the same time, SLNB did not increase overall survival. Comparing observation versus SLNB in patients with melanoma, the group with SLNB showed better disease control in the regional lymph node basin: incidence rate of macrometastases in regional lymph nodes developed during follow-up was slightly higher in the group of WE compared with WE and SLNB, but this difference (10,5 %) was not significant. The incidence rate of dis-

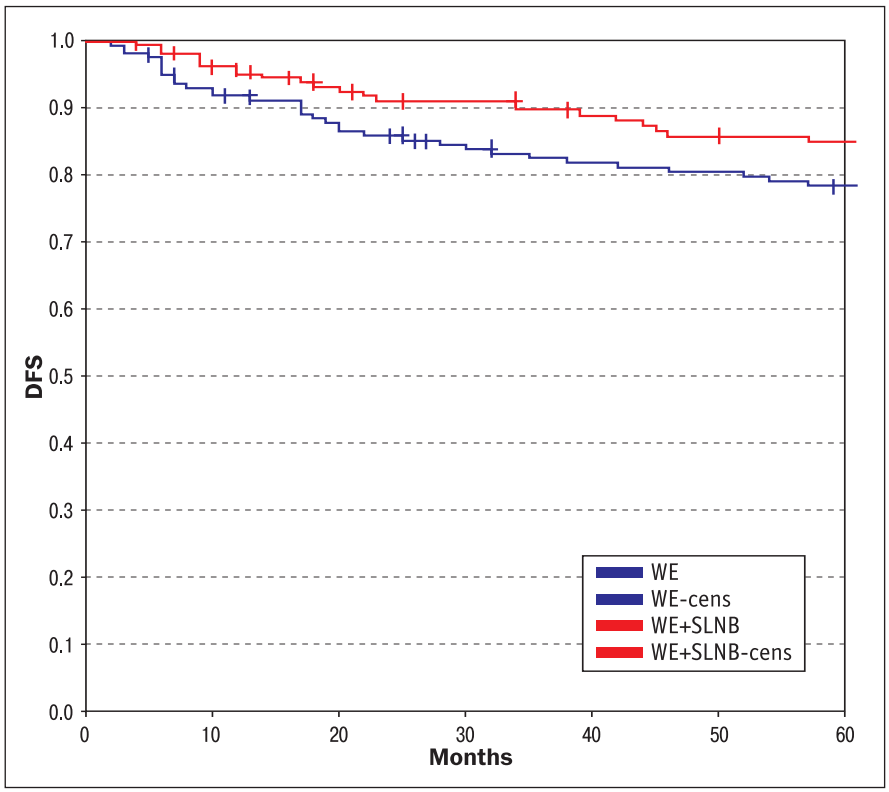

Figure 2. 5-year disease-free survival

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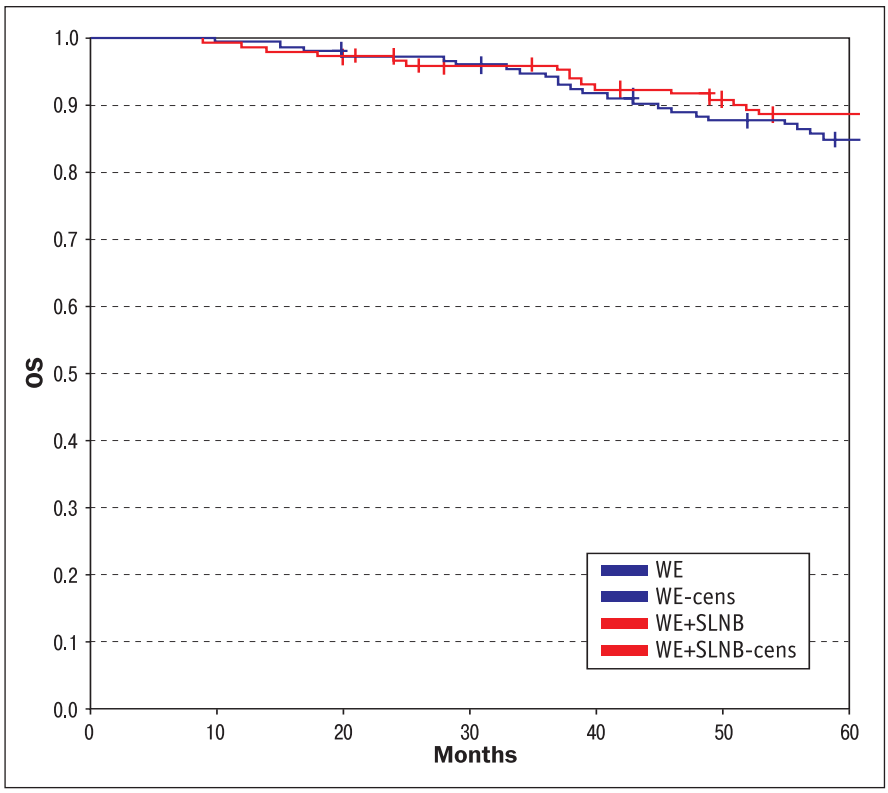

Figure 3. 5-year overall survival

Table 2
Localization of first metastases

Localization of first metastases	WE+SLNB n (%)	WE n (%)	Chi-square	P-value
Regional lymph nodes	15 (41.7)	26 (60.5)	2.77	0.095
Distant metastases	18 (50.0)	12 (27.9)	4.06	0.043
Both regional and distant metastases	3 (8.3)	5 (11.6)	0.23	0.628
All	36 (100)	43 (100)	–	–

tant metastases as first relapse was higher in group WE and SLNB. Based on our findings, SLNB, preserving its value as a diagnostic procedure, does not influence the overall survival of patients with skin melanoma.

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REFERENCES

1. Coit D, Thompson J, Albertini M, Barker C, Carson WE, Contreras C, et al. Cutaneous melanoma, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2019;17(4):367-402. doi: 10.6004/jnccn.2019.0018.
2. Michielin O, van Akkooi A, Ascierto P, Dummer R, Keilholz U; ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019;30(12):1884-1901. doi: 10.1093/annonc/mdz411.
3. Morton D, Thompson J, Cochran A, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370(7):599-609. doi: 10.1056/NEJMoa1310460.
4. Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, et al. In: Amin MB, Edge SB, Greene FL, editors. *AJCC cancer staging manual.* New York: Springer; 2017. Vol. 1024.
5. Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. *Expert review of anticancer therapy.* 2018;18(8):775-784. doi: 10.1080/14737140.2018.1489246.
6. Namikawa K, Aung PP, Milton DR, Tetzlaff MT, Torres-Cabala CA, Curry JL, et al. Correlation of tumor burden in sentinel lymph nodes with tumor burden in non-sentinel lymph nodes and survival in cutaneous melanoma. *Clin Cancer Res.* 2019;25.24:7585-7593. doi: 10.1158/1078-0432.CCR-19-1194.
7. Faries M, Thompson J, Cochran A, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med.* 2017;376(23):2211-2222. doi: 10.1056/NEJMoa1613210.

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