

# Management of metastases in regional lymph nodes in melanoma patients in 2019

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For several years, the standard of management in case of melanoma metastases in regional lymph nodes was to remove an adequate node group. In 2016 and 2017, the results of two large, well-designed clinical trials with randomization and a control group were published, which changed the current management. The authors of DeCOG-STL study came to the conclusion that withdrawal from completion lymph node dissection in the case of a small melanoma metastasis in a sentinel lymph node (metastasis diameter  $\leq 1$  mm) is not associated with a worsening of the 3-years' survival chance (both in terms of overall survival and survival time to the occurrence of distant metastases). The results of MSTL-II study were similar. Based on the results of both studies presented above, in 2018 the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO) presented joint recommendations concerning, among others, current indications for completion lymph node dissection in SNB positive melanoma patients.

NOWOTWORY J Oncol 2019; 69, 3–4: 108–110

**Key words:** melanoma, SNB, completion lymphadenectomy

## Introduction

For several years, the standard of management in case of melanoma metastases in regional lymph nodes (both clinically/cytologically confirmed and by means of sentinel lymph node biopsy) was to remove an adequate node group. For example, the recommendations of Sociedad Española de Oncología Médica (SEOM) formulate this principle as follows: "lymph nodes must be completely removed when there is a metastasis in a sentinel lymph node or when there is a clinical finding of metastasis (i.e. degree IIIB or IIIC) [1]." SEOM described the strength of this recommendation as A (strong) and the evidence base as 2A. Therefore, the scientific premises for such a procedure at the time of publication of the recommendation did not raise any doubts. This strategy was unanimously confirmed by the recommendations of other organizations, including the national recommendations of the Polish Society of Clinical Oncology [2].

In 2016 and 2017, the results of two large, well-designed clinical trials with randomization and a control group were published, which changed the current management and resulted in the content modification of clinical recommendations, both global and national [3, 4]. The above mentioned studies were based on data available in the medical literature suggesting that completion lymph node dissection (CLND) – i.e. lymphadenectomy following the confirmation of metastasis in a sentinel lymph node – in a certain group of patients does not bring any additional benefit in terms of total survival time compared to therapeutic lymph node dissection (TLND) [5]. Moreover, it has been observed in both small and large groups of patients that clinical practice differs significantly from the academic canon in the case of e.g. metastases in the sentinel lymph node [6, 7]. For example, in a group of approximately 125 000 melanoma patients undergoing a sentinel lymph node biopsy in the USA (2002–2012), metastasis in this node was

found in approximately 25 000 patients. However, completion lymph node dissection was performed only in about 13 000 patients, which accounted for slightly more than half (56%) of all patients in whom the procedure should be performed according to the commonly accepted indications [7].

### DeCOG-SLT study

The first study, which changed clinical practice, was designed in Germany and conducted at 41 skin cancer treatment centers there, between 2006 and 2014 [3]. The study included 483 patients with melanoma of the trunk or a limb with a metastasis in the sentinel lymph node (selection criteria are presented in table I).

The study participants were randomly assigned to two compared groups: 242 patients were qualified for completion lymph node dissection and 241 for follow-up with strict ultrasound control of the relevant nodal group. It should be emphasized that about 2/3 of the participants had a small metastasis in the sentinel lymph node – a diameter  $\leq 1$  mm. The median of the follow-up period was 35 months. The percentage of patients surviving 3 years without distant metastases was 77.0% (90% confidence interval – CI: 71.9–82.1) in the group of patients under follow-up and 74.9% (95% CI: 69.5–80.3) in the group of patients undergoing completion lymph node dissection. The total percentage of patients surviving 3 years was 81.7% (90% CI: 76.8–86.6) in the observation group and 81.2% (95% CI: 76.1–86.3) in the completion lymph node dissection group. The small percentage differences between the two endpoints were not significant. The authors of the study – noting its weakness resulting from insufficient number of participants in relation to the intended number (underpowered) – came to the conclusion that withdrawal from completion lymph node dissection in the case of a small lesions

of melanoma metastasis in a sentinel lymph node (metastasis diameter  $\leq 1$  mm) is not associated with a worsening of the 3-years' survival chance (both in terms of overall survival and survival time to the occurrence of distant metastases). In a non-inferiority study, this conclusion seems to be justified [3].

### MSLT-II study

The second of studies mentioned above, MSLT-II, was conducted mainly in the USA between 2004 and 2014 with a similar patient group as in the German study. A significant difference between the two studies was the fact that MSLT-II also included patients with scalp and neck melanoma [4]. The study was multi-center in nature, it was conducted with randomization and a control group. The objective of the study was to compare the results of completion lymph node dissection after excision of sentinel node containing melanoma metastasis with exclusive follow-up (without completion lymph node dissection). It is worth noting that the median size of the metastatic lesion in the sentinel lymph node was about 0.65 mm in study participants and in over 2/3 of patients the size of the metastatic lesion did not exceed 1 mm. After 3 years there were no significant differences between the compared groups in terms of survival time, including melanoma specific survival (86.13% vs. 86.12%;  $p = 0.43$ ). The authors of this study observed a borderline significance ( $p = 0.05$ ) in terms of the percentage of patients surviving 3 years without symptoms of the disease in favor of the group undergoing completion lymph node dissection (68% vs. 63%), which resulted from better local control after that time in the group of patients undergoing lymphadenectomy (92% vs. 77%;  $p < 0.001$ ). At the same time, the authors demonstrated several times higher

**Table I.** Selection criteria for the DeCOG-SLT study

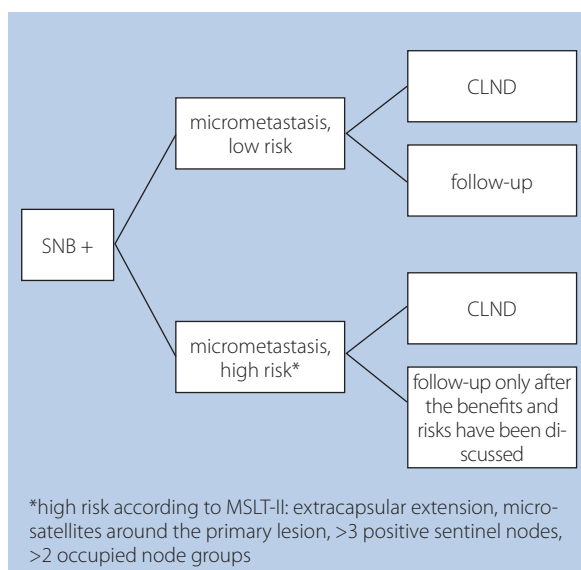
Inclusion criteria	Exclusion criteria
Primary skin melanoma of the trunk or limb	Melanoma located within the head and neck
Patient age: 18–75 years	Satellite tumors/ <i>in transit</i>
Melanoma thickness according to Breslow $\geq 1$ mm	M1
SLB + (micrometastasis and isolated neoplastic cells)	Macrometastasis

SLB + – positive result of sentinel node biopsy; M1 – current distant metastases (M parameter according to TNM)

**Table II.** Results of DeCOG-SLT and MSLT-II studies, in which the CLND was compared with exclusive follow-up after a sentinel node biopsy and metastasis confirmation

Study	Number of patients	Median time of observation	Results (follow-up vs. CLND)
Leiter et al. DeCOG-SLT [3]	483	34 months	OS HR 1.02, $p = 0.95$ 10-year OS 62.6% vs. 61.9% RFS HR 0.959 DMFS HR 1.19 10-year DMFS 55.8% vs. 55.5%
Faries et al. MSLT-II [4]	1755	43 months	MSS HR 1.08, $p = 0.42$ DMFS HR 1.1 follow up 63% vs. DFS CLND 68%

CLND – completion lymph node dissection; DFS – disease-free survival; DMFS – distance metastases-free survival; HR – hazard ratio; OS – overall survival; RFS – relapse-free survival; MSS – microsatellite stability



**Figure 1.** Management in case of positive results of sentinel node biopsy in melanoma patients (based on ASCO and SSO 2018 common recommendations [8])

risk of lymphedema in the group undergoing lymphadenectomy compared to the group undergoing only sentinel node biopsy and follow-up (24.1% vs. 6.3%;  $p < 0.001$ ). The authors of the MSLT-II study concluded that completion lymph node dissection increases the percentage of local control, but does not improve survival by taking into account the cause of death. However, it contributes to a significant increase in the incidence of a serious complication, which the limb's lymphoedema. Therefore, they recommended limiting the indications to completion lymph node dissection in patients with clinical characteristics that corresponded to the characteristics of the study participants (mainly low metastatic mass in the sentinel lymph node) [4].

Table II presents a summary of the results of both studies – DeCOG-SLT and MSLT-II. Both cited studies confirmed the basic prognostic role of sentinel node biopsy.

## Summary

Based on the results of both studies presented above, in 2018 the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO) presented joint recommendations concerning, among others, current indications for completion lymph node dissection [8]. The course of action suggested in these recommendations is presented in figure 1.

However, clinical follow-up as a management option may be used only in patients with a small metastatic lesion in a sentinel lymph node (metastasis diameter does not exceed 1 mm), not burdened with other prognostic factors that may increase the risk of melanoma metastases in non-sentinel lymph nodes (metastatic lesion diameter in a sentinel lymph node, number of occupied sentinel lymph nodes, thickness/presence of ulceration in the primary lesion) [9].

Also in the Polish recommendations on melanoma published in 2017 and 2019, the follow-up with a strict ultrasound monitoring of the lymphatic flow area after a sentinel lymph node biopsy, which confirmed the presence of a small melanoma metastasis, was presented as an acceptable course of action [10, 11]. The authors of joint ASCO and SSO recommendations emphasize that in the case of follow-up, strict ultrasound supervision over regional lymph nodes is necessary every 4–6 months (strength of recommendation according to ASCO – strong) [8].

In clinical practice, the role of completion lymph node dissection is gradually reduced and individualized, however, each patient who has not undergone this procedure must be subject to strict supervision, including ultrasound evaluation of regional lymphatic flow every 3–4 months. Moreover, patients should be consulted with regard to the possibility of implementing systemic complementary treatment [11]. This issue is described in another article in this issue of *Nowotwory*.

**Conflict of interest:** none declared

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Received and accepted: 23 Jul 2019

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