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In transit/local recurrences in melanoma patients after sentinel node biopsy and therapeutic lymph node dissection

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ABSTRACT

This study has analyzed the incidence of in transit/local recurrences (IT/LR) in melanoma patients after sentinel node (SLN) biopsy; completion lymph node dissection (CLND) that was performed due to positive node; and therapeutic LND (TLND) due to clinically detected node metastases and factors influencing IT/LR. Between May 1995 and May 2004, 1187 consecutive patients underwent SLN biopsy (median Breslow thickness 2.5 mm) and 224 of them had subsequent CLND. During the same time period, 306 patients had TLND (median Breslow 3.9 mm). The excision margin of primaries was $\geqslant$1 cm. At median follow-up time of 37.5 months, we analyzed the incidence of IT/LR as the first site of relapse and clinicopathological parameters affecting these recurrences. In SLN-negative cases, IT/LR as the site of the first recurrence were rare (46/963; 4.8%) and; in SLN ± CLND IT/LR were detected in 45/224 cases (20.1%). IT/LR in SLNB group correlated with presence of SLN metastases ($P < 0.0001$), higher Breslow thickness ($P < 0.001$) and lower extremity localization ($P = 0.03$). In TLND group, IT/LR were observed in 52/306 patients (17%), which is similar to all CLND patients ($P = 0.3$), but less common when analyzing only patients who relapsed (TLND: 52/209 (24.9%) vs. CLND: 45/121 (37.2%); $P = 0.02$). Estimated 3-year overall survival (from the date of relapse) in IT/LR only patients was better than in other types of relapses after LND (29% vs. 8%; $P < 0.0001$). IT/LR incidence in the entire group of SLN ± CLND patients was similar to that observed in TLND patients and it was affected by presence of nodal metastases, Breslow thickness and lower extremity location.

1. Introduction

Sentinel lymph node biopsy has become a common standard diagnostic procedure used in cutaneous melanoma patients without clinically detectable lymph node metastases (stage I and II) [1–5]. The technique of SLN biopsy was described by Morton et al. [6] to identify subclinical regional lymph node metastases and thus to avoid unnecessary extensive elective dissection of the lymph node basin (ELND) when it is free of tumour involvement. SLN biopsy allows to microstage patients and to distinguish high-risk groups for disease relapse. It has been proven by many authors that SLN biopsy offers several benefits in melanoma patient management including better staging;

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avoiding unnecessary ELND; excellent prognostic information; facilitation of therapeutic lymphadenectomy; homogeneity of patient populations in clinical trials on adjuvant therapy; and, from the patient's point of view, an increased feeling of safety and accuracy of care. However, until phase III trial called Multi-Center Selective Lymphadenectomy Trial I (MSLT) results become fully available [7,8], there is no firm data concerning survival benefits to support the use of sentinel lymph node biopsy in the management of melanoma, despite its widespread acceptance. Furthermore, in the last few years, the debate about the benefit/impact of SLN biopsy on the survival and natural history of melanoma patients, as well as the frequency of in transit metastases/local recurrences (IT/LR) development has been raised [9–13,15–17]. One of the major controversies related to SLNB is the suggestion of a higher incidence of IT/LR after completion lymph node dissection (CLND) performed in consequence of a positive SLN biopsy. In some opinions, the phenomenon is explained by peripheral lymphostasis after wide local excision of primary tumour combined with SLN biopsy and followed by CLND.

The main purpose of the present study was to analyze the incidence of IT/LR as the first site of relapse after negative SLN biopsy; positive SLN biopsy + CLND; and therapeutic LND (TLND) due to clinically detected node metastases. The second aim of the study was to assess factors influencing the IT/LR rate, as well as survival, in these groups of patients.

2. Patients and methods

We analyzed prospectively collected data of 1187 consecutive cutaneous melanoma patients (449 male and 738 female; median age: 51 years; range: 15–84), who underwent SLN biopsies from May 1995 to May 2004 in the Department of Soft Tissue/Bone Sarcoma and Melanoma of the M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology (CCIO) in Warsaw, Poland. All patients undergoing SLN biopsy met the following criteria: (i) primary focus cutaneous melanoma after excisional biopsy with Breslow thickness $\geqslant$0.75 mm or ulcerated or Clark level $\geqslant$IV (all histological diagnoses were confirmed in the Department of Pathology CCIO); (ii) clinically non-palpable regional lymph nodes; (iii) absence of distant metastases (confirmed routinely by physical examination, chest X-ray and ultrasonography of the abdominal cavity); (iv) feasibility for general anaesthesia. Each patient provided written informed consent in accordance with institutional regulatory requirements. The study was approved by the Bio-Ethics Committee of the CCIO.

Median Breslow thickness of primary tumours was 2.50 mm (range: 0.75–35 mm), median Clark level of invasion was III and 45% primaries were ulcerated. The minimal margin of excision/re-excision of primaries was 1 cm in all cases. The primary melanoma was localized to the head and neck (12 cases, 1%); the trunk (502, 42%); the upper extremity (208, 18%); and the lower extremity (465, 39%) patients.

In the first 167 analyzed patients (14.1%) we performed preoperative lymphoscintigraphy combined with intraoperative vital blue-dye lymphatic mapping only [Patent Blau V®], while in other 1020 analyzed patients (85.9%) the procedure was a three-part technique of preoperative lymphoscintigraphy with a combination of dye injection and intraoperative lymphoscintigraphy with hand-held γ-detecting probe (Neoprobe 1000®, Neoprobe Corp., Dublin, OH, USA or Navigator®, RMD Watertown, MA, USA) according to previously described techniques [5]. During routine pathologic examination, SLNs were cut serially along the major axis and stained with Hematoxylin and Eosin. Paraffin embedded specimens were examined in light microscopy (40×; 200×). In doubtful cases additional immunohistochemical staining (S 100, HMB 45) was performed.

In all 224 SLN-positive cases (18.9%) completion regional lymphatic basin dissection (CLND) was performed three to six weeks after SLN biopsy. During the same period, 306 stage III (according to American Joint Committee for Cancer [AJCC] 2002 system) patients had radical therapeutic lymph node dissection due to clinically detected (palpable) regional lymph node metastases, confirmed pathologically by fine needle aspiration biopsy. In the TLND group 27 patients demonstrated an occult primary site. Patients' characteristics for CLND and TLND groups are summarized in Table 1.

The initial clinicopathological stage of melanoma patients at the time of admission was determined by pathological evaluation of the primary lesion and dissected lymph nodes as well as by physical examination and routine imaging examinations (chest X-ray, ultrasonography of the abdominal cavity). All patients were followed carefully with median follow-up time of 37.5 months for survivors. Postoperative follow-up consisted of physical examination and routine imaging investigations (chest X-ray, ultrasonography of the abdominal cavity). Routinely the surveillance was recommended every 3 months for the first 2.5 years, every 6 months for years 2.5–5, and thereafter annually.

During follow-up time we analyzed the incidence of IT/LR as the site of the first recurrence after SLN biopsy, CLND or TLND. In the TLND group, we excluded patients who had already developed local/in transit lesions before TLND. In transit/local recurrences were defined as any cutaneous or subcutaneous metastases localized between a primary melanoma and the regional lymph nodes or situated in the vicinity of the scar after wide excision of primary tumour. Recurrences within the scar after a radical regional lymphadenectomy were defined as nodal, not IT/LR, relapse. In case of concurrent different recurrence sites, if one of them was IT/LR, we also counted it as the first site of recurrence.

The majority of IT/LR were treated surgically whenever possible; some patients received palliative cytostatic limb infusion/perfusion or radiotherapy or celecoxib.

For prospective data collection we used the hospital system "Oncosys" and the "Sarcoma" database. All statistical analyses were performed using Statistica software [Statsoft®]. Contingency tables were analyzed by the χ^2 test. Intergroup statistical comparisons used χ^2 and logistic regression tests. For the survival analysis, the Kaplan–Meier method, in combination with the log-rank, test was used for univariate analysis. Differences were considered statistically significant if P-values were <0.05.

Table 1 – Patient characteristic in CLND and TLND groups

	CLND group	TLND group	P-value
Number of patients	224	306	
Male/female	124/120	158/148	NS
Age mean/median	51.0/50.0	53.0/54.0	NS
Primary site			
Lower extremity	77 (34.4%)	116 (38%)	<0.0001
Upper extremity	32 (14.3%)	45 (14.7%)	
Trunk	113 (50.4%)	106 (34.6%)	
Head/neck	2 (0.1%)	12 (3.9%)	
Unknown	0	27 (8.8%)	
Thickness of melanoma			
Mean/median	6.2/3.8	5.8/3.9	
T1 (⩽1.00 mm)	14 (6.3%)	13 (4.2%)	NS
T2 (1.01–2.00)	29 (12.9%)	41 (13.4%)	
T3 (2.01–4.00)	69 (30.8%)	78 (25.5%)	
T4 (>4.00 mm)	106 (47.3%)	118 (38.6%)	
Data not available	6 (2.7%)	56 (18.3%)	NS
Clark – median	IV	IV	
Clark II	15 (%)	31 (%)	NS
Clark III	73 (%)	84 (%)	
Clark IV	90 (%)	82 (%)	
Clark V	41 (%)	46 (%)	
Data not available	5	60	
Ulceration of the melanoma			
Yes	156 (69.6%)	168 (54.9%)	NS
No	50 (22.3%)	53 (17.3%)	
Data not available	18 (12.4%)	85 (27.8%)	
Pathological type			
NM	137 (%)	139 (45.4%)	NS
SSM	48 (%)	60 (19.6%)	
ALM	9 (%)	15 (4.9%)	
LLM	8 (%)	14 (4.5%)	
	22	78 (25.5%)	
Regional basins site			
Axillar	124 (55.4%)	145 (47.4%)	NS
Inguinal	99 (44.2%)	147 (48.0%)	
Cervical/other	1 (0.4%)	14 (4.6%)	
Number of lymph node(s) with metastases: mean/median	2.0/1	4.5/3	
1	121 (54.0%)	92 (30.1%)	
2–3	71 (31.7%)	100 (32.7%)	<0.0001
⩾4	32 (14.3%)	114 (37.2%)	
Extracapsular extension of lymph nodes metastases			
Yes	66 (29.5%)	143 (46.7%)	NS
No	158 (70.5%)	163 (53.3%)	

CLND group – patients with regional lymph nodes metastases detected by sentinel lymph node biopsy followed by completion lymph node dissection; TLND group – patients with clinically detected regional lymph node metastases confirmed by fine needle aspiration biopsy followed by lymph node dissection; NS – statistically not significant; NM – nodular melanoma; SSM – superficial spreading melanoma; ALM – acral lentiginous melanoma; LLM – lentigo malignant melanoma.

3. Results

In the entire group of patients undergoing SLN biopsy the in transit/local recurrences occurred in 7.7% of cases (91/1187). In SLN-negative cases IT/LR as the site of the first recurrence were rather rare (46/963; 4.8%), but in SLN-positive cases followed by CLND, IT/LR were detected in 45/224 cases (20.1%). The false negative rate, calculated as the percentage of nodal recurrences in the same biopsied basin, was 4.9% (47 nodal recurrences in relation to 963 basins with negative SLN biopsy). The factors which influenced the IT/LR occurrence in the entire SLN biopsy group were: presence of SLN metastases ($P < 0.0001$; hazard ratio (HR) 1.9); higher Breslow thickness $\geqslant 4$ mm ($P < 0.001$; HR 1.6); higher Clark level of primary tumour ($P < 0.01$; HR 1.4); and lower extremity localization ($P = 0.038$; HR 1.2).

In transit/local recurrences were observed as the first relapse site in 17.0% of cases (52/306) in TLND patients, which

is not significantly less frequent than the IT/LR rate in CLND group. However, IT/LR were slightly less common in TLND, as compared with CLND, taking into account only patients who relapsed: 24.9% (52/209) vs. 37.2% (45/121) ($P = 0.02$), respectively. In some cases the IT/LR occurred as the first site of relapse simultaneously with other metastases in 20.0% in CLND group (9/45); and 19.3% in TLND group (10/52) (difference not significant). The median time to the occurrence of IT/LR was 236 days from the date of lymphadenectomy in the CLND group (231 days) and in the TLND group (240 days) (difference not significant, $P = 0.4$), but it was 351 days, if calculated from the date of primary tumour excision (300 days in CLND group and 410 days in TLND group, $P = 0.05$). Estimated 3-year overall survival (from the date of relapse) in patients with IT/LR as the first site of relapse was significantly better as compared with the other types of relapses after LND (29% vs. 8%; $P < 0.0001$) (Fig. 1). A similar trend was observed in TLND and CLND groups of patients: 28% vs. 8% and 30% vs. 7%, respectively. The survival curves (from the date of relapse) for patients who developed IT/LR as the first site of recurrence are shown in Fig. 2. The median overall survival time from the date of relapse was 460 days for patients with IT/LR as the first site of relapse vs. 140 days with other types of relapses.

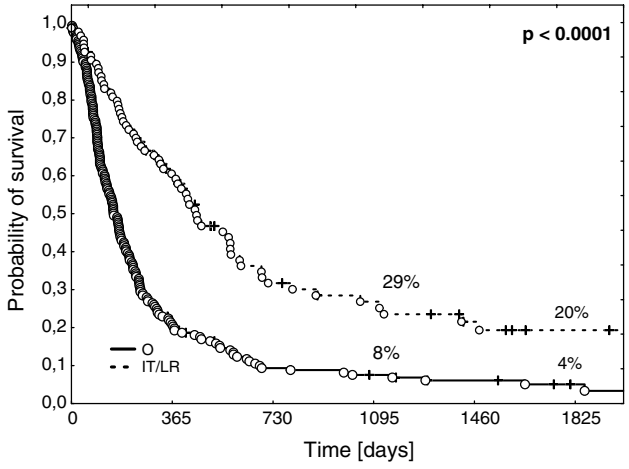

Fig. 1 – Estimated overall survival (from the date of relapse) in patients with in transit/local recurrences (IT/LR) as the first site of relapse and other types (O) of recurrences after lymph node dissection.

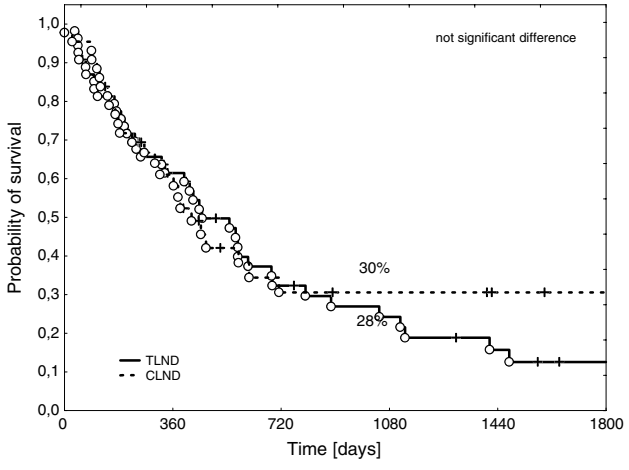

Fig. 2 – Estimated overall survival (from the date of relapse) in patients with in transit/local recurrences (IT/LR) as the first site of relapse in CLND and TLND groups.

4. Discussion

Sentinel node biopsy is currently a valuable and reliable diagnostic procedure for precise staging of patients with clinically N0 cutaneous melanoma [1–4,18]. The WHO in 1999 has declared in the consensus statement that SLN biopsy is the new standard in the care of melanoma patients [1]. In 2002, the new AJCC melanoma staging system formally incorporated sentinel node biopsy as a staging tool in clinically stage I/II primary melanoma with likely regional nodal metastases not detectable by clinical examination [19,20]. Although the implementation of a new staging system of melanoma forced the necessity of sentinel node biopsy as a staging tool, we have yet to receive firm proof of a survival benefit for this procedure [21]. Moreover, there are some questions about the influence of SLN biopsy on the natural history of melanoma and development of in transit/local recurrences in the biopsied nodal basin by the disturbances in the lymphatic flow following early regional node dissection, which is a treatment challenge for the patient and the surgeon [22–24].

In our retrospective analysis of a large database of melanoma patients we have shown that IT/LR as the first site of relapse are rather common in SLN-positive patients after completion lymphadenectomy. However, with long follow-up it does not differ significantly from patients after therapeutic LND. In transit/satellite and local recurrences were analyzed together, because in many series these subgroups of patients had shown similar prognosis. Regrowth of melanoma cells in these patients, accounted as local recurrences, is related to the spread of primary tumour cells into surrounding lymphatic channels, such that microsatellites becomes macrosatellites and local recurrence manifests as satellite/in transit metastases [20].

It must be noted that the results presented here may be influenced by bias related to the comparison of the SLN-positive group with completion lymphadenectomy and patients who develop overt nodal metastases after wide local excision and undergo therapeutic lymph node dissection. This most straightforward comparison assumes prognostical equivalence of these two groups, which is probably not true, because the earlier excision of regional nodes in the CLND group may prevent this type of disease recurrence. The TLND group excludes by definition the portion of patients who had developed other recurrences (IT or distant) within an interval after wide local excision of primary tumour and before nodal metastases and TLND. This may explain a slightly different distribution of the first recurrence sites among CLND and TLND groups of patients. The higher rate of IT/LR in CLND patients, taking into account only patients with recurrences,

shows that the earlier excision of the likeliest site of first recurrence-regional lymph nodes-changes only the pattern of recurrences. The median time of development of IT/LR after completion lymphadenectomy in SLN-positive patients is shorter than that in patients after therapeutic node dissection for overt metastases, if calculated from the date of primary tumour excision and not lymph node dissection. However, due to long follow-up (in our group median follow-up time was more than 3 years) these differences in the total rate of IT/LR as the first recurrence site in both groups disappear and finally the overall absolute probability of IT/LR is not increased by the type of lymph node dissection. We have to remember that median interval between primary tumour excision and lymph node dissection is 1 month in the CLND group and 12 months in the TLND group [11,25]. Earlier regional lymph node dissection could cause earlier lymphostasis and may influence the occurrence of IT/LR, but it does not generally change the biology of the disease [26,27]. We have demonstrated the same (better) prognosis in patients with IT/LR as the first site of relapse in comparison to the other types of relapses after lymph node dissection in both the CLND and the TLND group. Kretschmer et al. [11] have stressed the point that the early removal of lymphatic metastases by CLND prevents overt recurrences in the regional nodal basin, therefore prolongs the recurrence-free interval and increases the chance of manifestation of IT/LR as the first site of recurrence.

The percentage of IT/LR as the first site of relapse varies in the literature reports (both in pre-SLB biopsy era and currently after SLN biopsy) and ranges from 4% to 31% [17,18,28–31]. The IT/LR rates of 17% and 20.1% after lymph node dissection are higher than reported by some authors [13,28], although comparable or even lower than other data [14,17]. One of the explanations is the relatively high median Breslow thickness and Clark level in our group of patients (comparable in the CLND and TLND groups), as factors which increase the risk of developing IT/LR [15,30]. In our inclusion criteria for SLN biopsy, we did not exclude patients with primary melanoma thickness over 4.0 mm, because the prognostic relevance of the SLN biopsy remains very strong in this patient cohort [32]. The second explanation for the differences in the IT/LR rate is the various duration of follow-up time between the studies [11,17,18,27–29,31,31], where 80% IT/LR become apparent within 3 years after initial diagnosis of melanoma [22]. The third point is the percentage of primary site melanoma on the lower extremity in the analyzed subgroups (in our data the percentage of localization of primary tumour on lower extremity in CLND and TLND groups is similar), which can significantly influence the IT/LR rate.

A higher IT/LR rate might suggest a different prognosis for patients after CLND and TLND, but as there is no difference in the prognosis for both patient groups with IT/LR (Fig. 2), it supports the option of not interfering with the biological course of the disease with SLN biopsy in clinically node-negative melanoma patients. Of course our data also indicates that SLN biopsy is an excellent, low invasive staging and diagnostic procedure, not harmful in terms of development of loco-regional recurrences, but it should currently be considered as an experimental procedure until the favorable results of interim analysis of MSLT I presented by Morton et al. [8] are proven. We have to mention that the main difference of cohort of patients presented by Morton et al. [8] as compared to our group is a nearly two times thinner median Breslow thickness of primary melanomas.

In conclusion, our data suggest that IT/LR incidence in the entire group of SLN-positive/CLND patients is similar to that observed in TLND melanoma patients; however it is a more frequent type of relapse in CLND considering only patients with recurrences. The relative increase of IT/LR after CLND may be, mainly, the result of changes in the pattern of relapse due to a decrease of regional nodes recurrences. The risk of IT/LR is solely a function of melanoma biology, not the type of operative intervention. IT/LR have more favorable outcomes in comparison with other recurrences. The most important factors affecting IT/LR incidence are the presence of nodal metastases; higher Breslow thickness; and lower extremity location.

Conflict of interest statement

All authors declare that they have not to disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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