ELSEVIER

European Journal of Cancer 41 (2005) 531–538

European Journal of Cancer

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Sentinel lymphonodectomy does not increase the risk of loco-regional cutaneous metastases of malignant melanomas

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Received 9 September 2004; received in revised form 29 October 2004; accepted 30 November 2004
Available online 7 January 2005

Abstract

With regard to malignant melanoma, the impact of lymph node surgery on the development of loco-regional cutaneous metastases (LCM) has not yet been adequately addressed. However, this aspect is of interest, since sentinel lymphonodectomy (SLNE) has been suspected of causing LCM by inducing entrapment of melanoma cells. We analysed 244 patients with SLNE and compared the data with 199 patients treated with delayed lymph node dissection (DLND) for clinically palpable metastases. Analysis of both groups commenced at the time of excision of the primary tumour, using the Kaplan–Meier method. LCM that appeared as a first recurrence, as well as the overall probability of developing LCM, were recorded. For sentinel-negative patients with a primary melanoma >1 mm thick, the 5-year probability of developing LCM as a first recurrence was 6.9 ± 0.02% (±standard error of the mean (SEM)). The probability was 17.6 ± 0.03% in the DLND group. Comparing the two node-positive subgroups, the probability of developing LCM as a first recurrence was significantly higher in patients with positive SLNE (27.3 ± 0.05%, $P = 0.03$). However, the 5-year overall probability of developing LCM did not differ significantly in the node-positive groups (33.3% in the DLND group *vs.* 33.7% in patients with positive sentinel lymph nodes (SLNs)). Since early excision of lymphatic metastases by SLNE avoids nodal recurrences, thereby prolonging the recurrence-free interval, the chance of LCM to manifest as a first recurrence should inevitably increase. However, the overall in-transit probability is not increased after SLNE.

Keywords: Cutaneous melanoma; Sentinel lymphonodectomy; In-transit metastases; Lymph node excision; Prognostic factors

1. Introduction

Sentinel lymphonodectomy (SLNE) is the most precise staging technique currently available for use with patients with primary malignant melanoma. Although not undisputed [1], two large retrospective studies [2,3] have recently suggested that overall survival after positive SLNE may be superior to that of stage III patients who received a delayed lymph node dissection (DLND) only after the development of clinically enlarged node metastases.

Unfortunately, an effective adjuvant immunotherapy and chemotherapy which might be offered to node-positive patients, is currently not available. Moreover, the impact of completion node dissection after positive SLNE has not yet been clarified. Thus, an unequivocally proven therapeutic outcome of a histologically positive sentinel lymph node (SLN) is presently lacking and one could argue that the routine use of SLNE should be restricted to controlled trials. As an additional argument against the sentinel-node procedure,

Abbreviations: ELND, elective lymph node dissection; DLND, delayed lymph node dissection; SLN, sentinel lymph node; SLNE, sentinel lymphonodectomy; LCM, loco-regional cutaneous metastases; *vs.*, *versus*; WLE, wide local excision.

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doi:10.1016/j.ejca.2004.11.019

a potentially increased in-transit rate has been repeatedly reported [4–6]. Entrapment of melanoma cells has been described as "the most serious complication" after SLNE [3] and the 18–27% incidence of loco-regional cutaneous metastases (LCM) after the excision of tumour-positive SLNs has been interpreted as an "unnerving finding" [5].

LCM are believed to develop as a result of tumour cell emboli becoming entrapped in the dermal lymphatic vessels. Theoretically, the excision of a SLN might cause stasis in lymphatic vessels, promoting entrapment of melanoma cells. However, despite these assumptions, a higher incidence of LCM as a result of SLNE has not been proven. In the present work, we compare the groups with SLNE and with DLND in relation to LCM.

Unfortunately, most previous studies have only provided percentages of patients with in-transit recurrences. Since a considerable subset of the LCM becomes clinically apparent after more than 5 years [7,8], better information is provided by registering the time-course of the in-transit recurrences, instead of quantifying the number of patients with LCM alone. Therefore, a more sensitive assessment can be achieved by applying the Kaplan–Meier method, which is preferable from the biometric standpoint.

Another problem is that most investigators have considered only those LCMs which had become apparent as a first recurrence (for Review see [6]). However, there is no reason to assume that an increased in-transit risk, due to lymph node excision, ceases to exist after the diagnosis of nodal or distant recurrences. Moreover, SLNE prolongs the disease-free interval [9]; i.e., the time interval during which LCMs are able to manifest as a first recurrence. Therefore, the question of whether SLNE causes entrapment of tumour cells can be only answered by looking at the overall probability of developing LCM, taking into account also those in-transit recurrences which had occurred after the onset of nodal or distant metastases.

2. Patients and methods

2.1. Terminology

Loco-regional cutaneous metastases (LCM) of malignant melanoma are defined as metastases located between a primary melanoma and the regional lymph nodes. The terms LCM and in-transit metastases are used synonymously in this paper and are defined as any loco-regional cutaneous or subcutaneous metastasis, including satellite lesions, metastases in the scar of the primary tumour excision and true in-transit metastases. LCM which was completely excised at the time of the primary tumour excision (mostly microsatellites) was registered, but was not regarded as a recurrence. Recurrent disease within the scar of a complete regional lymphadenectomy (nodal and soft tissue) was defined as nodal basin recurrence and, thus, also was not regarded as LCM.

2.2. Patient population

The clinical records of 443 consecutive patients with cutaneous malignant melanoma, whose axillary or inguinal lymph nodes were operated upon, were reviewed. SLN-negative patients with a primary tumour less than 1.01 mm thick American Joint Committee on Cancer ((AJCC) stage I) were not considered in this study. Of the 244 patients with SLNE, 71 (29.1%) had histologically confirmed metastases. Six patients, who were upstaged by re-evaluation of their SLNs after the diagnosis of a tumour recurrence, did not undergo completion node dissection. These "false-negatives" were reassigned to the group with positive SLNE. Four patients did not receive a complete node dissection, because of increased general morbidity or refusal of the operation.

Patients with lymph node excision from the neck were not included in this study. Patients who already had palpably enlarged lymph node metastases at the time of their primary tumour, patients with palliative lymph node dissections and patients with unknown primary tumours were excluded. Thus, all patients included in this study had to be potential candidates for the SLN procedure at the time of the initial diagnosis. The data of patients with SLNE, performed between September 1993 and September 2003, was collected prospectively, using an electronic database. The control group consisted of 199 patients who received a DLND between September 1983 and August 2003.

2.3. Operative procedures

The day before SLNE, dynamic lymphoscintigraphy was performed. In 143 patients, both blue dye and a hand-held gamma probe were used to localise the SLNs. In 81 early patients, intraoperative lymphatic mapping was performed applying the blue dye alone. Lymph nodes that stained blue and had blue afferent lymph channels were generally defined as SLNs. Radioactive lymph node(s) which had first appeared at dynamic lymphoscintigraphy or for which there was lymphoscintigraphic evidence of an own afferent lymphatic vessel were also defined as SLN(s). The standard treatment for a primary melanoma was wide local excision (WLE) with adequate safety margins, depending on the tumour thickness.

Complete lymph node dissections were carried out according to established surgical techniques. In the case of axillary metastases, levels I–III of the axillary lymph nodes were excised. With reference to the extent of groin

dissection, the formal procedure was an ilioinguinal dissection. Generally, the surgical techniques of lymph node excision were very homogeneous, as the first author performed 80% of the node excisions.

2.4. Treatment of LCM

Our strategy for treatment of LCM was, whenever possible, surgical excision. After lymph node excision, only a few patients with massive in-transit-recurrences received hyperthermic cytostatic perfusion or irradiation therapy, with palliative intent.

2.5. Histological analysis of surgical specimens

Primary tumours and the specimens from complete lymphadenectomies were examined using routine histology. SLNs were submitted for step sections. Haematoxylin and eosin (H & E) staining, as well as immuno-histochemical methods with anti-protein S-100 serum (Dako, Denmark, diluted 1:5000), anti-HMB-45 (Dako, Denmark, undiluted) and anti-Mart-1 (ZYMED, USA, diluted 1:500) were applied.

2.6. Adjuvant therapy

After DLND, 90 patients received adjuvant chemotherapy without significant influence on the survival outcome [10]. It also appears very unlikely that the administration of low-dose interferon to a few patients might have biased our results [11,12].

2.7. Follow-up

According to guidelines in Germany, the patients were routinely monitored at three-month intervals for the first two years, every six months for the next three years, and annually thereafter. During the follow-up, the status of the in-transit area was known in 433 patients (97.8%). All of the 10 patients lost for follow-up were SLN-negative. The median follow-up after the primary tumour excision was 45 months (range 6–102 months) in patients with SLNE and 114 months (range 5–324 months) in patients with DLND.

2.8. Statistical analysis

Statistical comparison of the potential prognostic factors was performed using the non-parametric Mann–Whitney *U* test. The time until the appearance of the first LCM was generally calculated from the primary tumour excision, using the non-parametric Kaplan–Meier method. In the analysis of the time to LCM as a first recurrence, follow-up was interrupted at the time of the first nodal basin or distant recurrence. In contrast to others, we assessed not only the probability of LCM as a first recurrence, but also the overall probability of developing LCM during the whole course of the disease, also taking into consideration the LCM that appeared after nodal or distant recurrences. The log-rank test was used to determine differences in subgroups defined by different levels of risk factors. To control for confounding factors and interactions, multiple covariate analyses were performed using the Cox proportional hazards regression model, incorporating factors which have been previously reported to influence the in-transit probability. Individual model covariates were characterised with 95% Confidence Intervals (CI) on the hazard ratio scale. Significance was determined at the $P < 0.05$ level.

3. Results

3.1. Distribution of prognostic factors

Table 1 summarises the patients' characteristics according to the type of lymph node dissection. With regard to potential prognostic factors, there were no significant differences between the groups with positive SLNE and DLND. Compared with the node-positive patient groups, the SLN-negative patients had thinner primary tumours ($P < 0.000001$) that were less frequently ulcerated ($P = 0.03$). Notably, 8.5% of the patients with positive SLNE already had LCM at the time of the primary tumour excision.

Due to our less aggressive approach to the primary tumour in recent years, most of the patients with negative SLNE (66%) or positive (51.4%) SLNE had excision margins around the primary melanoma of less than 2 cm, whereas only 22% of the patients with DLND had safety margins of less than 2 cm. Paradoxically, the patients with margins $\geqslant 2$ cm had a significantly higher incidence of LCM ($P = 0.01$, log-rank test). As the margins were not a random feature, but strictly related to tumour thickness and to the treatment period, we did not analyse this aspect further.

3.2. LCM as first recurrence after the primary tumour excision

For sentinel-negative patients with a primary melanoma >1 mm thick, the 5-year probability of developing LCM as a first recurrence was $6.9 \pm 0.02\%$. Calculated from the excision of the primary tumour, in the DLND group, the probability of developing LCM was $17.6 \pm 0.03\%$. The highest probability of developing LCM after the excision of the primary melanoma was observed in patients with positive SLNs ($27.3 \pm 0.05\%$). As shown in Fig. 1, these differences were statistically significant. The 61 SLN-positive patients with subsequent complete lymph node dissection had a slightly lower in-transit probability of $22.4 \pm 0.06\%$.

Table 1
Clinical and pathological features of the patient population

Patient's characteristics	Negative SLNE (n = 173)	Positive SLNE (n = 71)	DLND (n = 199)
Age (median/years)	58.5 (22–86)	59 (17–84)	57 (19–85)
Gender			
Male	86 (49.7%)	40 (56.3%)	110 (55.3%)
Female	87 (50.3%)	31 (43.7%)	89 (44.7%)
Site of the primary tumour			
Extremity	106 (61.3%)	46 (64.8%)	103 (51.8%)
Trunk	67 (38.7%)	25 (35.2%)	96 (48.2%)
Distribution of Breslow thickness (mm)			
⩽1.0	0 (0%)	2 (2.9%)	8 (4.6%)
1.01–2	84 (49.7%)	17 (24.3%)	37 (21.3%)
2.01–4	61 (36.1%)	27 (38.6%)	75 (43.1%)
⩾4.01	24 (14.2%)	24 (34.3%)	54 (31.0%)
Not available	4	1	25
Median tumour thickness (range)/in (mm)	2.0 (1.01–10.8)	2.9 (0.8–13.0)	3.0 (0.4–30.0)
Epidermal ulceration			
Ulceration present	55 (34.2%)	30 (42.9%)	79 (44.1%)
Ulceration absent	106 (65.8%)	40 (57.1%)	100 (55.9%)
Not available	12	1	20
LCM at the time of primary tumour excision	3 (1.7%)	6 (8.5%)	6 (3.0%)

SLNE, sentinel lymphonodectomy; DLND, delayed lymph node dissection; LCM, loco-regional cutaneous metastases.

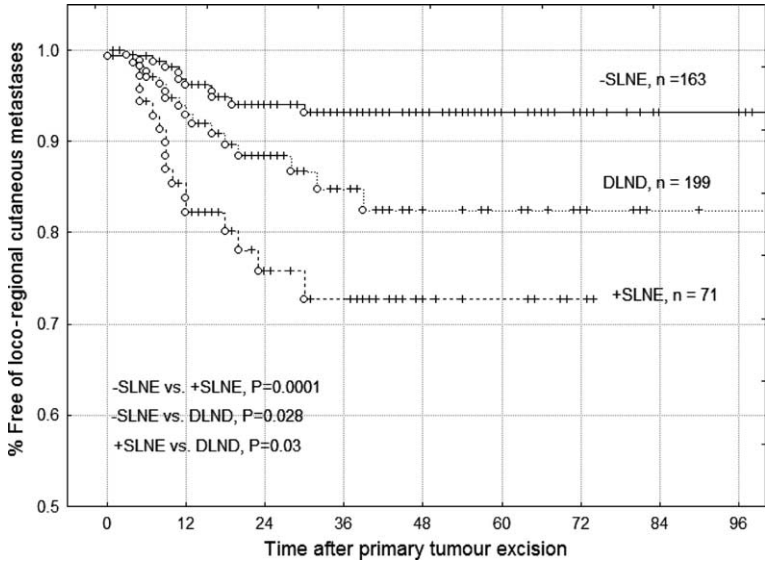

Fig. 1. Loco-regional cutaneous metastases (LCM) as a first recurrence after primary tumour excision. The probability of developing loco-regional cutaneous metastases as a first event was significantly increased for patients with histologically positive sentinel lymphonodectomy (+SLNE), compared with the groups with negative sentinel lymphonodectomy (−SLNE) and with delayed lymph node dissection (DLND).

3.3. Overall probability of developing LCM

In contrast to the first recurrences, the overall-probability of developing LCM (also taking into consideration the LCM which appeared after nodal or distant recurrences) did not differ in the node-positive subgroups (33.3% in the DLND group versus (*vs.*) 33.7% in patients with positive SLNs (Fig. 2)). The SLN-positive patients with completion lymph node dissection had a similar probability of 33.9 ± 0.07%. As was expected, the overall probability of developing LCM was significantly lower for patients with negative SLNE (12.9 ± 0.03%).

In order to evaluate possible confounding factors influencing the in-transit risk, the therapy groups with positive SLNE and DLND were analysed together. Using univariate analysis, the overall probability of developing LCM was positively correlated with thicker primary tumours (P<0.001), epidermal ulceration (P = 0.01) and older age (P = 0.02). Localisation of the

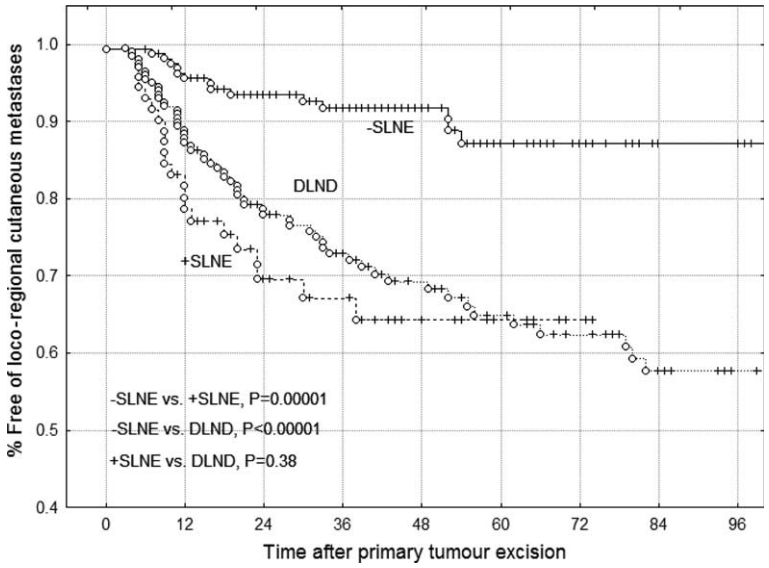

Fig. 2. Overall probabilities of developing loco-regional cutaneous recurrences. When compared with patients with negative sentinel lymphonodectomy (−SLNE), the overall probabilities of developing loco-regional cutaneous metastases (LCM) were significantly increased for patients with positive sentinel lymphonodectomy (+SLNE) and for patients with delayed lymph node dissection (DLND) of palpable metastases. In contrast, there was no significant difference between the node-positive groups with SLNE and DLND.

Table 2
Prognostic factors for the overall probability of developing loco-regional cutaneous metastases in the node-positive therapy groups with either SLNE or DLND (multifactorial analysis including 238 patients with complete data)

Factor	Category	Adjusted relative risk	95% Confidence interval	*P* value
Treatment group	1 – Positive SLNE 2 – DLNE	0.835	0.16–4.30	0.50
Breslow thickness	mm	1.065	1.02–1.12	0.009
Epidermal ulceration	1 – Present 2 – Absent	0.689	0.43–1.10	0.125
Site of primary tumour	1 – Extremity 2 – Trunk	0.666	0.39–1.14	0.14
Gender	1 – Female 2 – Male	0.832	0.49–1.40	0.49
Age	Years	1.013	0.996–1.03	0.12
Likelihood ratio test for the model/$P < 0.01$				

SLNE, sentinel lymphonodectomy; DLND, delayed lymph node dissection.

primary tumour, site of node excision, gender and also early excision of the nodal metastases by SLNE were non significant. Using a multifactorial analysis (Table 2), only Breslow thickness retained its significance. It is important to note that, also after adjustment for possible confounding factors, the time of node dissection (SLNE *vs.* DLND) did not significantly influence the overall risk of developing LCM.

3.4. Overall- and recurrence-free survival.

The 5-year overall survival rates after the primary tumour excision for patients with negative SLNE, positive SLNE and DLND were 90.1 ± 0.03%, 54.4 ± 0.09% and 37.4 ± 0.03%, respectively. The 5-year disease-free survival rates were 77.7 ± 0.04%, 38.6 ± 0.08% and 11.6 ± 0.02%, respectively. Fig. 3 demonstrates the probabilities of remaining free of nodal or distant recurrences. These events are important, because they serve as endpoints of the follow-up, when the probability of developing LCM as a first recurrence is calculated. The median interval between the primary tumour excision and nodal recurrence was 12 months for patients with DLND. In patients with positive SLNE, where nodal recurrences are reduced to a negligible number, the interval to the first nodal or (mostly) distant recurrence was significantly prolonged (47.5 months).

4. Discussion

After the excision of a primary melanoma, Breslow thickness, Clark's level, epidermal ulceration, lymphatic invasion, the presence of microsatellites, leg location of

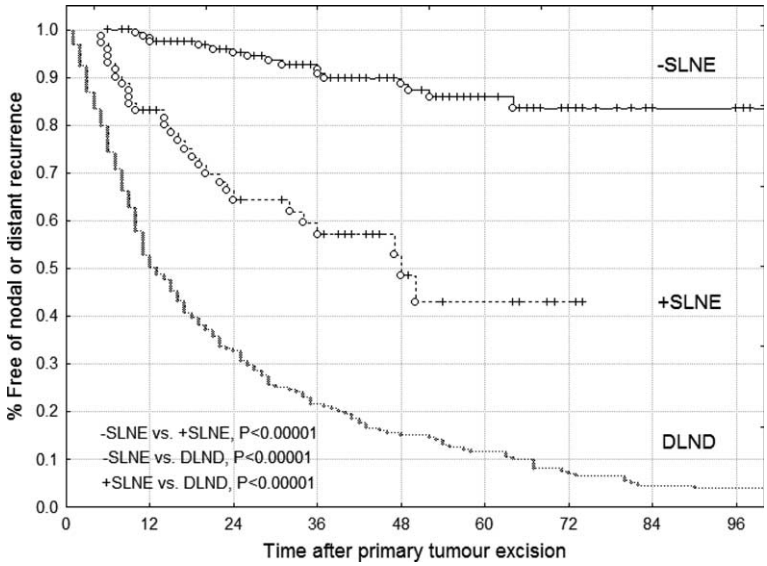

Fig. 3. Probability of staying free from nodal or distant recurrences as a function of the type of lymph node surgery. Nodal and distant recurrences form the endpoints of the follow-up, for which the probability of developing loco-regional cutaneous metastases (LCM) as a first recurrence is calculated. The time period during which LCM may manifest is longest after negative sentinel lymphonodectomy (−SLNE). Patients with positive sentinel lymphonodectomy (+SLNE), in whom nodal recurrences are practically avoided, have a significantly longer recurrence-free interval than patients with DLND, in whom palpable lymph node metastases usually represent the first recurrence.

the primary melanoma and older age have been reported to increase the risk of developing LCM [7,13–16]. In addition, therapeutic modalities, for example, safety margins around the primary melanoma [17,18], elective lymph node dissection (ELND) [19–21] or adjuvant cytostatic limb perfusion [22] have been shown to influence the incidence of LCM. Moreover, as confirmed by the present study, the risk of LCM is increased in patients with lymphatic metastasis [16,23–27]. This points to the importance of carrying out a SLNE which allows node-positive and node-negative patients to be differentiated. By contrast SLNE itself has repeatedly been suspected of causing in-transit metastases by inducing lymphatic stasis or entrapment of melanoma cells. Therefore, it is of great importance to appropriately address this issue.

As far as we are aware, a comparison with a group of patients undergoing DLND for palpably enlarged node-recurrences has not yet been made. However, with respect to an increased risk of LCM in patients with positive SLNE, those with DLND would constitute the most appropriate control group. For SLN-positive patients, others have observed percentages of patients with (first) in-transit recurrences ranging from 4% to 31% [23–27]. In our study, the estimated 5-year probability of developing LCM (as a first event after the excision of the primary melanoma) was significantly lower in the DLND group than in the group with positive SLNE (17.6% *vs.* 27.3%, $P = 0.03$, Fig. 1).

What is the explanation for this observation which, at first sight, seems surprising? We hypothesise that, with regard to a first recurrence, LCM compete with lymph node metastases in the DLND group while, in patients with positive SLNE who have preventive node-dissection, LCM have an advantage. In agreement with this hypothesis, we found that the overall probabilities of developing LCM did not differ significantly between the two groups. The slightly (but non significantly) higher overall probability of developing LCM after positive SLNE (Fig. 2) might be explained by entrapment due to the earlier node excision, but also by a higher proportion of patients with LCM at the time of the primary tumour, the narrower resection margins in the SLNE group, and by the fact that a few patients with massive LCM and subsequent development of nodal metastases were not subjected to DLND. Tumour thickness, which was the only independent variable influencing the overall probability of developing LCM, did not differ significantly between the groups with DLND and with positive SLNE.

It is important to note that, in the present study, the median interval between the primary tumour excision and palpable node metastases was 12 months in the DLND group, whereas in the group with positive SLNE, the median time interval to the occurrence of a first distant or (very rare) nodal recurrence was 47.5 months (Fig. 3). Thus, the time during which LCM may manifest as a first recurrence is nearly four times longer, if nodal recurrences are avoided by the use of SLNE. This explains quite impressively why we observed an increased probability of developing LCM as a first event after positive SLNE.

More LCMs (as a first event) have also been observed in patients with preventive node dissection [6,19–21] compared with patients who received wide local excision

(WLE) of the primary tumour alone. Again, this comparison is inadequate because, in the node-positive subsets, the recurrence-free interval will be shorter after WLE alone than after WLE plus preventive node-dissection.

Calabro and colleagues [28] have analysed 1001 node-positive patients with a minimum follow-up of 10 years. The authors also found a lower incidence of LCM after DLND than after ELND (10% *vs.* 27%). However, since they only considered the first recurrences which occurred after DLND, they missed those LCMs which appeared between primary tumour excision and DLND. The latter have been shown to constitute a significant proportion of cases [29].

After negative SLNE, we found a 5-year probability of developing LCM as a first event of 6.9%. This is in agreement with a recent review which reported an average in-transit recurrence rate of 5.7% following negative SLNE [6]. In our study, the overall in-transit probability of the SLN-negative patients reached 12.9%.

However, the question of a possible entrapment of melanoma cells can not be answered for the patients with negative SLNE, since proper controls are lacking. Essner and colleagues [19] found similar incidences of LCM in node-negative patients with SLNE and ELND (2.6% *vs.* 3.8%), although the degree of lymphatic disruption is much greater after ELND. The question remains whether entrapment of melanoma cells, provided it exists, might place the SLN concept in question. Extended safety margins around the primary melanoma [17,18], as well as adjuvant limb perfusion [22], have been shown to reduce not only LCM, but also the frequency of lymph node recurrences. These observations suggest that, after the excision of a primary melanoma, occult tumour cells may continue to migrate from the loco-regional skin to the regional lymph nodes, causing LCM and node metastases later on. Theoretically, SLNE might promote entrapment of occult melanoma cells and the subsequent development of LCM. However, surgically amenable LCMs are mostly easier to treat than lymph node recurrences, which require a complete regional node dissection, associated with high levels of morbidity. In this paper, we have demonstrated that SLNE avoids nodal recurrences, thereby prolonging the recurrence-free interval; i.e., the interval during which LCM are able to manifest as a first recurrence. However, when compared with delayed excision of palpable node metastases, the overall probability of developing LCM was not increased after positive SLNE. These considerations imply that a potential entrapment of melanoma cells cannot be regarded as an argument against the sentinel procedure.

Conflict of interest statement

None declared.

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