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Patients with lymphatic metastasis of cutaneous malignant melanoma benefit from sentinel lymphonodectomy and early excision of their nodal disease

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Abstract

Early versus delayed excision of lymph node metastases is still being assessed in malignant melanoma. In the present retrospective, multicentre study, the outcome of 314 patients with positive sentinel lymphonodectomy (SLNE) was compared with the outcome of 623 patients with delayed lymph node dissection (DLND) of clinically enlarged lymph node metastases. In order to avoid the lead-time bias, survival was generally calculated from the excision of the primary tumour. Survival curves were constructed using the Kaplan–Meier product-limit estimate. Cox's proportional hazards model was used to perform a multivariate analysis of factors related to overall survival. Compared with SLNE and early performed complete lymph node dissection, DLND yielded a significantly higher number of lymph node metastases. Median and mean tumour thickness were nearly identical in the two therapy groups. The estimated 3-year overall survival rate was $80.1 \pm 2.8\%$ ($\pm$standard error of the mean (SEM)) in patients with positive SLNs, and $67.6 \pm 1.9\%$ in patients with DLND (5-year survival rates 62.5 ± 5.5 and $50.2 \pm 5.4\%$, respectively). The difference between the two survival curves was statistically significant ($P = 0.002$). Using multifactorial analysis, SLNE ($P = 0.000052$), American Joint Committee on Cancer (AJCC) Breslow thickness category ($P < 0.000001$), age ($P = 0.01$) and gender ($P = 0.028$) were independent predictors of overall survival. The location of the primary tumour ($P = 0.59$) was non-significant. Considering only those centres with sufficient data for epidermal ulceration, this risk factor was also significant. In cutaneous malignant melanoma, early excision of lymphatic metastases, directed by the sentinel node procedure, provides a highly significant overall survival benefit.

Keywords: Melanoma; Lymph node metastases; Delayed excision; Sentinel lymphonodectomy; Prognostic factors

1. Introduction

The sentinel lymph node (SLN) is defined as the first lymph node on the lymphatic drainage pathway from the primary tumour site. For sentinel-lymphonodectomy (SLNE) in patients with malignant melanoma, blue dye and radioactive colloid are injected into the dermis around the primary tumour or biopsy site. These substances are taken up by the lymphatic system and transported to the tumour-draining lymph nodes. During surgery, the SLNs can be identified by radioactivity and by blue staining. The histological status of the SLN has been shown to reflect accurately the status of the whole nodal basin [1,2]. Studies worldwide have established the pathological status of the SLN as the most important prognostic factor for recurrence and survival after excision of the primary melanoma. Consequently, the SLN status has strongly influenced the completely revised staging system for cutaneous malignant melanoma [3].

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Before the introduction of the minimally invasive SLN procedure, the staging of the regional lymph nodes required excision of the entire regional lymph node basin (elective lymph node dissection (ELND)), a procedure that was accompanied by significant morbidity. Using the SLN technique, patients with lymph node metastases can be distinguished at the time of primary tumour excision and a complete lymph node dissection can be avoided in patients with histologically-negative SLNs.

On the other hand, there are possible limitations to the SLN concept. Firstly, there is no definite proof that early excision of lymph node metastases would improve the survival chances of melanoma patients [4–6]. Secondly, the impact of a complete lymph node dissection after positive SLNE on survival or local disease control has not yet been clarified. Thirdly, several trials of adjuvant immunotherapy and chemotherapy have failed to show a significant survival benefit for node-positive patients. Taking into consideration this lack of an unequivocally proven therapeutic consequence of a histologically-positive SLN, Thomas and Patocskai [7] have argued that the routine use of SLNE, if its purpose is simply to identify high-risk patients, should currently be restricted to controlled trials.

The alternative to early excision of lymphatic micrometastases is performing a so-called delayed lymph node dissection (DLND). This type of therapeutic lymph node dissection is reserved for those patients who have actually developed clinically enlarged lymph node metastases (macrometastases) in the later course of their disease. The advantage of this 'wait and watch strategy' is that the majority of patients without lymphatic metastasis are spared any unnecessary operation on their lymph nodes.

Until now, three prospective multicentre studies have failed to demonstrate a beneficial effect of ELND [4–6]. However, compared with ELND, the SLN procedure is an anatomically more accurate approach. Although controlled, the prospective ELND studies have been criticised as statistically underpowered since less than 25% of the patients included had regional lymph node metastases. This actual target group of the lymph node dissection possibly has been submerged by the majority of patients with tumour-free lymph nodes, obscuring any potential benefit of early treatment of nodal metastases [8].

For that reason, we focus here on the only subpopulation that theoretically may benefit from any lymph node dissection, namely the patients who actually have lymphatic metastases. In the present multicentre study, the survival outcome of patients with early versus delayed excision of regional lymph node metastases (SLNE versus DLND) was compared. Many studies have demonstrated that microscopic tumour burden is associated with longer survival than macroscopic tumour burden. What is controversial is whether this is solely due to the so called lead-time bias, which is associated with the different time points of diagnosis of the nodal disease in patients with micro- and macrometastases. Therefore, in the present study, the survival was calculated from the excision of the primary tumour in both groups, which is the only way to establish whether the SLN procedure itself yields a true therapeutic benefit. Possible biases that might obscure our approach will be discussed.

2. Patients and methods

2.1. Patients

The present study includes 937 consecutive patients with regional lymph node metastases from five clinical centres in Germany (Table 1). Applying the SLN procedure, 314 patients had early diagnosis and treatment of their nodal disease, whereas 623 patients underwent DLND of clinically enlarged metastases. The SLNEs were performed between 1993 and 2002, while the DLNDs were performed between 1983 and 2002. All patients had to have histologically-proven regional lymph node metastases. In addition, they had to be potential candidates for the SLN procedure at initial diagnosis, i.e. they had to have a known primary melanoma and no clinical evidence of nodal or systemic disease. Patients with clinically detectable distant metastases at the time of DLND are not considered in this study, whereas patients with loco-regional cutaneous metastases prior to the lymph node excision were included.

3. Methods

3.1. Lymphatic mapping and operative procedures

Dynamic and static lymphoscintigraphy were performed using 99mTc- human albumin or sulphur colloid. Except for a few early cases, SLNE was performed applying both blue dye and radio-localisation

Table 1
Number of patients according to the clinical institution

Institution	DLND	Positive SLNE
Augsburg	51	98
Göttingen	25	40
Halle	173	7
Munich	–	131
Tübingen	374	38
Total	623	314

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

using a hand-held gamma probe. Lymph nodes that stained blue and had blue afferent lymph channels were defined as SLNs. Radioactive lymph node(s) that had appeared first at dynamic lymphoscintigraphy or had lymphoscintigraphic evidence of an own afferent lymphatic vessel were also defined as SLN(s).

Standard treatment of the primary melanoma was local excision with adequate safety margins, depending on the tumour thickness. Complete lymph node dissections were carried out according to established surgical techniques. Of the 314 patients with positive SLNE, 58 (18.5%) (for various reasons) could not receive a subsequent complete lymph node dissection. All patients of the observation group who developed clinically-evident lymph node metastases in the further course after primary tumour excision underwent complete regional DLND. Patients with neck metastases underwent radical, modified or selective neck dissection, depending on different approaches in the various institutions. In the case of axillary metastases, the levels I–III of the axillary lymph nodes were excised. Regarding the extent of groin dissection, the formal procedure was a superficial inguinal dissection in Tübingen, whereas an ilioinguinal dissection was the formal procedure in Augsburg, Halle, Munich and Göttingen. The Tübingen DLND series did not include patients with clinically-evident iliac metastases, as these patients were operated upon in another department.

3.2. Histological analysis of surgical specimens

Primary tumours and the specimens from complete lymphadenectomies were examined using routine histology. The excised 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) and anti-HMB-25 (Dako, Denmark, undiluted) were applied. In the University of Tübingen, one half of the SLN was used for polymerase chain reaction (PCR) studies. The specimens of the complete lymph node dissections were examined using routine histology.

3.3. Adjuvant therapies

The modalities of adjuvant treatment are not explicitly recorded. Since high-dose interferon has not been applied, it appears very unlikely that the administration of low-dose interferon or of various chemotherapies in the different institutions might have biased the survival curves solely [9].

3.4. Statistical analysis

The following prognostic variables with possible influence on overall survival were analysed: gender, age at the time of primary diagnosis, anatomical location of primary melanoma (extremity versus axial), American Joint Committee on Cancer (AJCC) Breslow stage (<1.0 mm versus 1.01–2.0 mm versus 2.01–4.0 mm versus >4 mm), epidermal ulceration, and the total number of lymph node metastases. In patients with SLNE, the number of lymph node metastases was composed of the number of positive SLNs and the number of lymph node metastases excised at the subsequently performed complete lymphadenectomy. Mean testing was performed with the non-parametric Mann–Whitney U-test. Overall survival curves were constructed using the Kaplan–Meier product-limit method and were analysed by the log-rank test. Death from other causes or unknown outcome were categorised as censored observations. Multiple covariate analyses of overall survival were performed using Cox proportional hazards regression model incorporating factors that have been previously described to influence the survival outcome of melanoma patients with positive regional lymph nodes. Individual model covariates were characterised with 95% confidence intervals (CI) on the hazard ratio scale. Significance was determined at $P<0.05$.

3.5. Follow-up

According to guidelines in Germany, the patients were routinely monitored at 3-month intervals for the first 2 years, every 6 months for the next 3 years, and annually thereafter. The median follow-up after the primary diagnosis was 32 months (range 3–94 months) in patients with a positive SLN biopsy, and 121 months (range 4–324 months) in patients with DLND.

4. Results

4.1. Distribution of the prognostic factors among the therapy groups

The clinical and histological data of the patients according to the two treatment groups are shown in Table 2. The tumour thickness was nearly identical in both groups (Fig. 1). In addition, age, gender and primary tumour location were well-matched. Epidermal ulceration was recorded only in Göttingen, Halle and Tübingen. In these centres, the percentage of ulcerated tumours was higher in the SLNE group, which may be attributed to an increased awareness of the more recently treated SLNE patients.

Compared with patients with positive SLNE and subsequent regional lymphadenectomy, a significantly higher number of metastatic lymph nodes were excised in the patients with DLND (2.46 ± 2.35 nodes in patients with DLND versus 1.54 ± 1.42 nodes in patients with early lymph node dissection, $P<0.00001$). However, in the DLND group, the number of lymph nodes

carrying micrometastases at the time of primary tumour excision remains unknown. Therefore, this risk factor could not be considered as a covariate in the survival analyses.

4.2. Univariate survival analysis

As shown in Fig. 2, the overall survival rate was significantly better for the patients with SLND and early diagnosis of the lymph node metastases ($P=0.002$). The estimated 3-year overall survival rate was 80.1±2.8% (±standard error of the mean (SEM)) in patients with positive SLNs, and 67.6±1.9% in patients with DLND (5-year survival rates 62.5±5.5 and 50.2±5.4%, respectively).

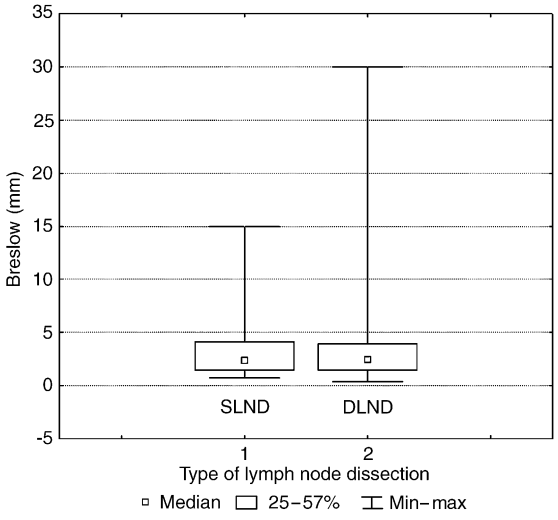

Fig. 1. Distribution of Breslow thickness among the treatment groups.

Besides SLNE, AJCC T-stage grouping ($P<0.000001$), epidermal ulceration ($P=0.0001$), age ($P=0.0001$), and gender ($P=0.04$) were univariate predictors of overall survival. The primary tumour location (extremity versus other) was non-significant.

4.3. Multifactorial analysis

Using a Cox proportional hazards model, SLNE ($P=0.000052$) turned out to be an independent prognostic factor of overall survival. Delayed excision of the regional lymph node metastases added a relative risk of 1.82. As shown in Table 3, AJCC T-category ($P<0.000001$), age ($P=0.01$) and gender ($P=0.028$) were also independent predictors of overall survival, whereas the primary tumour site ($P=0.59$) was non-significant in this model.

In a separate multifactorial analysis, only the three centres with data for epidermal ulceration were considered (results not shown in Table 3). In this sub-set analysis of 450 patients, the absence of epidermal ulceration (adjusted relative risk (RR) 0.72, 95% confidence interval (CI) 0.54–0.969) was also a significant predictor of overall survival, as well as delayed lymph node excision (RR 1.73, 95% CI 1.05–2.85), Breslow thickness category (RR 1.2, 95% CI 1.04–1.44) and female gender (RR 0.76, 95% CI 0.59–0.98).

5. Discussion

Until now, three prospective multicentre trials have failed to demonstrate a survival benefit resulting from ELND [4–6]. These trials have primarily focused on the

Table 2
Patients' characteristics according to the treatment groups

	Positive SLNE ($n=314$)	DLND ($n=623$)	P value (U-test)
Breslow	Mean—3.15±2.2 mm ($n=311$) Median—2.40 mm (0.7–15 mm)	3.13±2.5 mm ($n=568$) 2.49 mm (0.7–25 mm)	0.46
AJCC Breslow category			0.32
⩽1 mm	20 (6.4%)	69 (12.1%)	
1.01–2 mm	112 (36.0%)	169 (29.8%)	
2.02–4 mm	101 (32.5%)	207 (36.4%)	
>4 mm	78 (25.1%)	123 (21.7%)	
Ulceration[a]	39 (48.7%) ($n=80$)[a]	128 (29.4%) ($n=435$)	0.006
Age (years)	Mean—54.7±14.4 Median—57 (18–88)	54.2±15.3 54 years (13–92 years)	0.57
Male sex	185 (58.9%)	331 (53.1%)	0.15
Number of metastatic lymph nodes	Mean 1.54±1.42 ($n=256$)[b] Median 1 (range 1–14)[b]	2.46±2.35 ($n=435$)[c] 2 (range 1–18)[c]	<0.000001
>1 metastatic lymph node	75 (29.3%)[b]	223 (51.3%)[c]	<0.000001

AJCC, American Joint Committee on Cancer; SLNE, sentinel lymphonodectomy; DLND, delayed lymph node dissection; n, number of patients with available data.

[a] Data only from Göttingen, Halle and Tübingen.

[b] Yielded by SLNE plus complete regional lymph node dissection.

[c] Yielded by DLND.

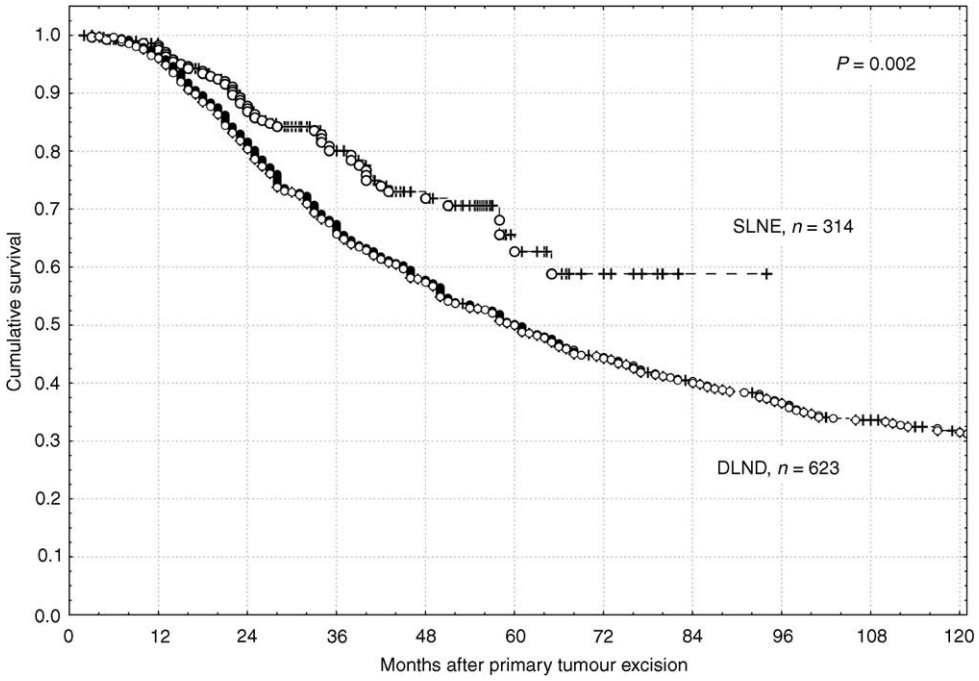

Fig. 2. Overall survival after primary tumour excision according to the time point of the excision of lymph node metastases: early lymph node excision (upper curve) appears to provide a significant survival benefit. SLNE, sentinel lymphonodectomy; DLND, delayed lymph node dissection.

Table 3
Prognostic factors of overall survival by multifactorial analysis (including 879 patients with complete data)

Factor	Category	Adjusted relative risk	95% Confidence interval	*P* value
Treatment group	1. SLNE 2. DLND	1.82	1.38–2.44	0.000052
Breslow thickness	⩽1 mm versus 1.01–2 mm versus 2.01–4 mm versus >4 mm	1.42	1.27–1.58	<0.000001
Age	/Year	1.01	1.002–1.02	0.01
Gender	Female versus male	0.79	0.64–0.97	0.028
Site of primary tumour	Extremity versus trunk	1.06	0.86–1.30	0.59
Likelihood ratio test for the model/$P<0.00001$				

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

total population of high-risk patients with primary melanoma. Thus, their study populations have contained 70–80% of patients with tumour-free regional lymph nodes. Considering the sub-groups of node-positive patients, two trials have yielded conflicting results. In the World Health Organization (WHO) trial 1, the subgroup of patients with lymphatic micrometastases has not benefited from ELND [4]. In contrast, WHO-trial 14 has demonstrated a significant benefit in overall survival for 27 patients who received ELND with confirmed micrometastases compared with 36 patients with delayed excision of clinically- and histologically-positive nodes [5]. In the American Intergroup study, certain prospectively defined sub-groups have also appeared to benefit from ELND [6]. Based on this data and considering the low morbidity of SLNE, the WHO has recommended SLNE as the standard procedure for patients with primary tumours >1 mm thick [10]. However, the data is still conflicting and this recommendation clearly needs further confirmation.

Studies dealing with SLNE have recently revealed the excellent prognosis of patients with histologically-negative regional lymph nodes [11,12]. Thus, in the quoted ELND studies, the node-negative patients have diluted and possibly confounded the specific minority of patients of actual interest, namely the patients with regional lymph node metastases. Consequently, these studies have been criticised as being statistically underpowered [8,13] and their failure to reveal any beneficial effect of early excision of regional lymph nodes may not be surprising.

Here, we chose an alternative approach, namely to focus on the sub-populations of patients with proven lymphatic metastasis. Undoubtedly, patients with regio-

nal lymph node metastases constitute the only target group that may benefit from any type of lymph node dissection. The present multicentre study is one of the largest dealing with therapeutic lymph node dissection and the first one that compares the overall survival, as calculated from primary melanoma excision, of patients undergoing DLND for clinically enlarged metastases to the overall survival of patients with histologically-positive SLNE and (in 81.5% of the cases) subsequent complete lymphadenectomy. Previous retrospective studies have shown that patients with ELND and micrometastases of their regional lymph nodes fare better than patients with clinically enlarged lymph node metastases (macrometastases) [3,19,20]. Obviously, this survival benefit must be attributed, at least to some extent, to the so-called lead-time bias, i.e. the time that melanoma metastases remain clinically occult in the lymph nodes. Consequently, in a homogeneous group of patients with DLND a highly significant difference was observed when the survival after primary tumour excision was compared with the survival after the lymph node dissection [15]. In order to avoid the lead-time bias, in the present study survival rates were generally calculated from primary tumour excision.

Here, we are able to demonstrate a highly significant overall survival benefit in favour of early excision of lymphatic metastases using the SLN procedure. The difference between the two survival curves was 12.5% at 3 years and 12.3% at 5 years. The 5-year survival rate of SLN-positive patients was 62.5%. This supports a recent study demonstrating a survival rate of 67% for 40 SLN-positive patients with long-term follow-up [14]. In patients with DLND, we observed a 5-year overall survival rate of 50.2%, which compares favourably with other series [4,5,15].

The beneficial effect of SLNE was confirmed by multifactorial analysis. Early excision of nodal metastases was an independent prognostic factor, as well as Breslow thickness, age and gender. DLND added a relative risk of 1.82, when compared with early treatment. The significance of Breslow thickness suggests that patients who already have lymphatic metastasis still benefit from early excision of their primary melanomas. Other large studies, dealing with survival after therapeutic lymph node dissection, have also confirmed the significance of tumour thickness [16,17].

If the data of the two centres that had not regularly recorded epidermal ulceration were excluded, the latter risk factor also turned out to be significant. This is in agreement with the AJCC-classification, which is also based on a study population including patients with micro- and macrometastases [3]. Other studies that have focused on survival after primary tumour excision in the homogeneous sub-group of patients with clinically-detectable lymph node metastases have not confirmed the significance of ulceration [15,18].

A further important result of our study is the significantly higher number of lymph node metastases at the time of DLND, compared with the number of metastases yielded by SLNE plus excision of the entire nodal basin. Many previous studies have established the number of node metastases as a key prognostic factor in stage III melanoma. Consequently, an increased number of metastatic lymph nodes seems to reflect both a more aggressive disease and a later time point of surgical intervention.

Possible biases that may have influenced our results have to be discussed. In our study, tumour thickness, age, gender and primary tumour site were well-matched between the two therapy groups. However, epidermal ulceration was recorded in only three of the five participating centres. In these three institutions, the percentage of epidermal ulceration was even higher in the SLNE group. Since tumour thickness was nearly identical in both therapy groups (Fig. 1), this higher percentage of epidermal ulceration most likely indicates a more careful histological examination in the more recently treated patients with SLNE.

A possible improvement of the prognosis of the DLND group could have resulted from the exclusion of patients with clinically-enlarged iliac metastases from the Tübingen series. Moreover, in this institution, lymph node sonography was routinely performed during the follow-up examinations, which led to the excision of non-palpable macrometastases in 21% of the patients [21].

In addition, one could argue that not all patients with nodal micrometastases will develop macrometastases later on. However, in two prospective ELND studies, the percentage of patients who developed macrometastases in the course of their disease has clearly exceeded the percentage of patients with micrometastases at the time of their primary tumours [4,5]. Moreover, a significant downregulation of antigen-presenting cells in SLNs has been observed [22], damping the hope for spontaneous regression of already established lymph node metastases.

A more important criticism might be that some patients will develop distant metastases prior to enlarged lymph node metastases. Seven per cent of the node-positive patients have shown this metastasising pattern in the observation group of WHO-trial 14 [5]. These patients with a poor prognosis, who cannot be distinguished at the time of primary tumour excision, worsen the outcome of the SLNE group. Vice versa, the prognosis of the DLND group will improve, as patients with lymph node metastases and synchronous visceral metastases are not subjected to DLND.

A further criticism could be that the pathologists probably miss a certain percentage of the micrometastases in SLNs. This will happen preferentially in patients with small clusters of melanoma cells who,

most likely, have a relatively good prognosis [23,24]. Consequently, this kind of bias would also worsen the prognosis of the group with actually diagnosed metastases in the SLNs.

In our study, 18.5% of the patients with positive SLNs did not receive a subsequent complete lymphadenectomy. This theoretically could impair their survival chances since up to 30% will have lymph node metastases beyond the SLNs [25–27].

Taken together, all conceivable biases contribute to diminish a possible survival benefit of early over delayed excision of regional lymph node metastases. Nevertheless, we observed a highly significant survival benefit in favour of early treatment. Moreover, the number of lymph node metastases, was significantly higher in the DLND group. These observations strongly support the view that, as long as the results of prospective trials [28] are not available, SLNE should be considered as the standard procedure for patients with AJCC stage II cutaneous melanomas.

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