Post-operative follow-up of 150 patients with sentinel lymph node biopsy under tumescence local anestheisa

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Summary

Background: Sentinel lymph node biopsy (SLNB) is useful for staging of patients with melanoma. Although SLNB is mostly performed under general anesthesia (GA), tumescence local anesthesia (TLA) can also be used. However, less data are available regarding feasibility of SLNB under TLA. Here we present a post-operative follow-up of 150 patients.

Patients and Methods: We prospectively analyzed data from 150 patients with primary cutaneous malignant melanoma. We assessed pain, post-operative complications and patients’ satisfaction after SLNB under TLA.

Results: 32% of the patients reported post-operative pain within the first 48 h after SLNB. Seroma was the most frequent complication, as 29 seromas after SLNB were observed. Wound infection was observed in 3.3% of the patients. 98.7% of the patients were satisfied with SLNB under TLA.

Conclusions: SLNB under TLA is a safe and feasible option and should be considered for patients with melanoma. Especially with multimorbid or elderly patients, the risks of GA can be avoided.

Introduction

Sentinel lymph node biopsy (SLNB) is an important diagnostic tool in patients with malignant tumors. In primary cutaneous melanoma, SLNB is useful for tumor staging and provides important prognostic information. SLNB is recommended in patients with primary cutaneous melanoma and a Breslow thickness of ≥ 1 mm or 0.8 mm, if individual risk factors such as a young age, ulceration or a high mitotic rate are present [1].

Patients with micrometastatic disease can be identified and may benefit from lymphadenectomy or adjuvant therapies [2–4]. As reported in the multicenter lymphadenectomy trial II (MSLT II) and other studies, completion lymph node dissection (CLND) does not improve melanoma-specific survival, but it was useful for regional disease control in patients with a positive sentinel lymph node (SLN) [5–7]. The importance of a CLND has to be assessed individually in the light of recent publications. However, the nodal status became highly important due to the availability of adjuvant therapies like checkpoint inhibitors or BRAF/MEK inhibitors improving the OS survival for patients with stage III melanoma [4, 8].

Sentinel lymph node biopsy can be performed under general anesthesia (GA), local anesthesia or tumescence local anesthesia (TLA) [9]. Especially in multimorbid and elderly patients GA can be associated with post-operative delirium, respiratory or cardiac complications [10, 11]. In our department, SLNB is performed under TLA. High volumes of a diluted solution with a combination of local anesthetics and epinephrine can be perfused into the operation area. The surgical technique is not affected by TLA and the preparation is easier because of a hydrodissection of the tissue. Using TLA-solution with added epinephrine, intraoperative bleeding is reduced, and both intra-operative and post-operative analgesia are ensured. Furthermore, TLA can be administered by the surgeons themselves and no anesthetist has to be present [12–14].
Several post-operative complications are reported for SLNB with a frequency of about 10 % [15, 16]. Seroma, wound infection, hematoma, lymphedema and nerve injury resulting in motor or sensory dysfunction have been described [15]. Male gender, diabetes and an inguinal location of the SLN have been described as risk factors for post-operative complications [16].

In this study we present 150 patients with malignant melanoma who underwent SLNB in TLA. Post-operative complications, pain and patient satisfaction were prospectively assessed.

Patients and Methods

Patient data

In this prospective observational study, we analyzed data from 150 consecutive patients with melanoma who underwent SLNB in the Department of Dermatology, University of Tuebingen, Germany, between July 2019 and January 2020. All patients included gave their written informed consent. We excluded 26 patients due to incomplete data (lost to follow up) and six patients with incomplete surgery. In these patients, the sentinel lymph node was either not found or extirpation of the lymph node was discontinued due to the risk of damaging anatomic structures. The study was approved by the local ethics committee (study number 312/2019BO2).

Surgical procedure

A preoperative lymphoscintigraphy with a technetium 99-nanokolloid (Tc 99) was performed in the Department of Nuclear Medicine to delineate the drainage to the SLN in the axillary, inguinal or cervical region.

First, a 0.11 %-TLA-solution was perfused in the axillary, cervical or inguinal region with rates of 50–750 ml per hour. For TLA, a highly diluted mixture of local anesthetics (lidocaine, ropivacaine) and epinephrine was used (Table 1). Typically, 150 ml to 250 ml are necessary during the follow-up period of this study.

| Isotonic complete electrolyte solution | 500 ml Jonosteril® |
|---------------------------------------|-------------------|
| Local anesthetics                     | + 20 mg/ml lidocaine 2 %, 10 ml |
|                                       | + 10 mg/ml ropivacaine 1 %, 10 ml |
| Epinephrine                           | + 0.5 ml epinephrine (1 : 1.000) |

Typically, 150 ml to 250 ml are necessary to anesthetize the axillary or inguinal region, less TLA-solution is required for the cervical region. If several sites are surgically treated (e.g. if lymph nodes have been marked at several locations), a 0.05 % TLA-solution can be used [14].

Before surgery a gamma probe collimated for Tc99 (Neoprobe GDS, Devico Medical; Norderstedt) was used to verify the position of the SLN. In addition, 0.5–1 ml of blue dye (acid blue 3) was injected intracutaneously into the tumor bed about ten minutes before surgery. The injection of blue dye was not performed for tumors located in the head and neck region; furthermore, we only used blue dye if another wide excision of the melanoma was performed as blue discoloration might be visible around the scar. The blue dye serves to identify the SLN, since it is transported to the lymph nodes and therefore marks the SLN optically to further facilitate the intraoperative identification of the correct lymph node.

Immediately before surgery anxiousness and stress of all patients were evaluated individually by the surgeon. The option of sedation in order to reduce anxiety and agitation was offered to the patients. The patients were informed about this option and the potential side effects as part of the pre-operative patients’ education. If sedation was desired by the patient, a total amount of 2.5 to 5.0 mg midazolam i.v. was fractionally injected after consideration of individual circumstances and under continuous monitoring of the patient’s vital signs.

The SLN was identified intraoperatively using a gamma probe by board-certified dermatologists with years of dermatosurgical experience. The SLN was then carefully dissected using Péan clamps; electrocoagulation was employed to seal lymphatic and blood vessels. After extirpation of the SLN the subcutaneous tissue was overstitched with Vicryl 2-0® depending on the surgeon’s assessment, however, this procedure was not mandatory. The wound was closed by dermal sutures with PDS 4-0®. We did not use any Redon drainage.

The removed SLN was examined by routine pathology including immunohistochemistry and by quantitative immunocytochemistry [17]. After extirpation of the SLN another wider re-excision of the primary melanoma was performed according to the German guidelines [18–20].

The vital parameters of the patients were continuously monitored. All members of the surgical team are continuously trained in emergency management, resuscitation and control of TLA-associated side effects. In addition, anesthetists are constantly on call in case of more serious complications that may require transfer to an intermediate care unit or intensive care unit. Fortunately, such interventions were not necessary during the follow-up period of this study.

Post-operative follow-up

Sentinel lymph node biopsy was performed as an inpatient surgery to provide post-operative monitoring. Thus, patients...
can be treated immediately in the case of severe bleeding, wound infection or pain. At the day of discharge, patients received a standardized questionnaire, and the wound was assessed by a dermatologist of our department. Post-operative pain, bleeding, wound infection, seroma and lymphedema within the first 48 hours were documented.

Patients presented to our hospital for clinical follow-up four weeks after surgery. The wound was again assessed by a dermatologist and patients answered a standardized questionnaire concerning post-operative complications, cosmetic satisfaction and pain. The extent of pain was indicated by the patient and correlated with the need for analgesics. A total of four months after the procedure, the patients were interviewed again using a standardized questionnaire concerning the points mentioned above. Demographic data (age, gender), tumor data (melanoma subtype, Breslow thickness, location, stage) and duration of the surgical procedure were collected from the electronic patient record.

Statistical analysis

All data collected were analyzed using JMP (SAS Institute Cary/NC, USA). Clinical, histopathological and demographic features were statistically evaluated. Numerical variables were described by the mean and by the median value. A Chi-squared test was used to calculate the \( P \)-values. \( P \)-values below 0.05 were considered statistically significant.

Results

Description of the sample

Patients: We collected data from 150 patients who underwent SLNB in our department. Ninety-five (63.3 %) were male and 55 (36.7 %) were female. The mean age of all patients was 60.1 (± 14.7) years (Table 2).

Tumor parameters: The tumor parameters are summarized in Table 2. All patients suffered from primary cutaneous melanoma. In 67 patients (45.3 %) superficial spreading melanoma (SSM) was diagnosed, in 42 patients (28 %) nodular melanoma (NM) and in seven patients (4.7 %) acral lentiginous melanoma (ALM). A lentigo maligna melanoma was observed in three patients (2 %). Rare melanoma subtypes like desmoplastic, amelanotic, spitzoid, nevoid or unclassified subtypes are summarized as “others” and were present in 31 patients (20.7 %). The primary tumor was located at the extremities in 68 patients and on the trunk in 67 patients. A lentigo maligna of the head and neck region was observed in 15 patients.

The median tumor thickness was 1.9 mm (min. 0.8 mm, max. 13 mm). Ulceration was found in 40 of 150 (26.7 %) cases.

| Table 2 Epidemiologic data and tumor parameters of 150 patients with malignant melanoma. |
|---------------------------------|------------------|------------------|
| Gender                         | Patients, n ( %) |
| Male                           | 95 (63.3 %)      |
| Female                         | 55 (36.7 %)      |
| Melanoma subtype               |                  |
| SSM                            | 67 (45.3 %)      |
| NM                             | 42 (28 %)        |
| ALM                            | 7 (4.7 %)        |
| LMM                            | 3 (2 %)          |
| Others                         | 31 (20.7 %)      |
| Localization                   |                  |
| Scalp                          | 11 (7.3 %)       |
| Neck                           | 4 (2.7 %)        |
| Upper extremity                | 28 (18.7 %)      |
| Trunk                          | 67 (44.7 %)      |
| Lower extremity                | 40 (26.7 %)      |
| Breslow thickness              |                  |
| 0.8–1.0 mm                     | 28 (18.7 %)      |
| > 1.0–2.0 mm                   | 54 (36.0 %)      |
| > 2.0–4.0 mm                   | 45 (3.0 %)       |
| > 4.0 mm                       | 23 (15.3 %)      |

Abbr.: SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma.

Sentinel lymph node biopsy (SLNB)

In 102 of 150 (68 %) patients the SLN was located in the axillary region, in 49 patients (32.7 %) in the inguinal region and in 17 patients (11.3 %) it was located in the neck. In 18 patients (12 %) the SLNs were located in two different locations (both axillae n = 12, both groins n = 2, axilla and groin n = 3, axilla and neck n = 1). Thus, 168 SLNBs were performed.

In 29/150 patients (19.3 %) solid or single cell metastases were found and the SLN was therefore rated as positive. The results of the SLNB are represented in Table 3.

In the axillary region, 133 SLNs were excised, 19 lymph nodes were positive (positivity rate 14.3 %). In the inguinal region 67 SLNs were excised and in eleven SLNs metastases were found (positivity rate 16.4 %). 18 SLNs were excised in the neck region. No metastases were found.
123/150 patients (82 %) received midazolam additionally. The mean time of surgery was 38.4 ± 15.0 min including wide re-excision of the melanoma.

Pain

Forty-eight of 150 patients (32 %) reported to have post-operative pain within the first 48 hours. Analgesics were offered to all patients who reported any pain but only 26 of 150 patients (17.3 %) required analgesics. Four weeks after surgery, 39 of 150 patients (26 %) reported having pain, whereby only nine patients (6 %) needed analgesics. After four months 14/150 patients (9.3 %) reported a pulling type of pain in the operated area. None of the patients needed analgesics after four months. Post-operative paresthesia was reported in 20/168 patients (11.9 %) after four months.

Patient satisfaction

Overall patient satisfaction with the surgery is represented in Table 4. 146/150 patients (97.3 %) would recommend SLNB under TLA; 80 % (120/150) of patients were very satisfied with SLNB under TLA and none of the patients were very dissatisfied.

We also evaluated patient satisfaction concerning the cosmetic result after four weeks and four months. Most of the patients (88 % after 4 weeks, 88.7 % after 4 months) stated that they were satisfied or very satisfied with the cosmetic result. Only 2.7 % were dissatisfied or very dissatisfied after four months.

Post-operative complications and risk factors

Post-operative side effects defined as bleeding, seroma or wound infection were most frequently observed in the inguinal region. We did not observe side effects after SLNB of the cervical region. No post-operative lymphedema was observed during follow-up. All post-operative complications are presented in Table 5.

Bleeding: Minor post-operative bleeding within the first 24 hours occurred in two patients (1.3 %) in the axillary region. The bleeding was stopped by compression only, no surgical intervention was necessary. No seroma or wound infection was observed within the first 24 hours after surgery.

Seroma: Seroma was the most common side effect, occurring in 29/168 patients (17.3 %). 3/29 seromas (10.3 %) were not symptomatic, defined as painful or limiting the mobility of the patient. 17 seromas (58.6 %) were observed in the inguinal region. After four months, only three (10.3 %) of them were still present but decreased in size. Eleven seromas (37.9 %) were reported in the axillary region after four weeks. Only one seroma (3.4 %) in the axillary region developed later and was not yet present after four weeks. After four months three of these seromas (10.3 %) were still present. Twelve of 150 patients (8 %) were smoking cigarettes before surgery and 18/150 (12 %) had a history of diabetes. Only one patient (0.3 %) who developed a seroma was a smoker and 3/28 patients (10.7 %) with seroma suffered from diabetes. Smoking or diabetic patients did not significantly increase the risk for a seroma. The pathological result of the SLNB did not significantly increase the seroma frequency. When the lymph node basin was overstitched using self-resorbing suture material, significantly less seroma occurred in the inguinal region ($P < 0.001$). In the axillary region, a trend towards lower seroma frequency was observed when sutures were applied, although this was not significant. Seroma was
mostly treated by compression (n = 14, 48.3 %). However, a drainage of the seroma was necessary in twelve patients (41.4 %).

Infection: A wound infection in the SLNB area was observed in five of 150 patients (3.3 %). These patients developed seroma with consecutive infection and were all treated with antibiotics. Infected seromas were more frequent in the inguinal (n = 4) than in the axillary (n = 1) region.

Discussion

Sentinel lymph node biopsy provides an important diagnostic tool for patients with primary cutaneous melanoma to assess the regional node status. In the case of micrometastases the patients might benefit from adjuvant therapies with checkpoint inhibitors or BRAF/MEK inhibitors. Sentinel lymph node biopsy can be performed in GA and in LA.

Even though GA is a well-established method, it can be burdensome for patients. Not all patients are suited for GA, with pre-existing conditions in particular affecting the patient’s ability to undergo GA. The fear of anesthesia and side-effects such as post-operative nausea and vomiting (PONV) are further issues that patients have to deal with. The incidence of PONV after anesthetic procedures is described to be between 30 % and 80 %, and there is currently no drug available that is fully effective against PONV [21, 22]. Indications for SLNB under GA are allergies to components of the TLA-solution or an explicit patient request due to a pronounced fear of surgery under TLA. For these patients, GA with complete loss of consciousness and amnesia is more suitable than TLA.

Tumescence local anesthesia is almost painless and intra-operative and post-operative bleeding is reduced by administration of epinephrine. With this technique, preparation under direct view is possible because of reduced bleeding and because hydrodissection of the tissue facilitates the preparation. By using a mixture of short-lasting and long-lasting local anesthetics, post-operative analgesia is ensured [23]. TLA was introduced by Jeffrey A. Klein for liposuction and has since been widely used. It has been shown to be safe for tumor surgery as well as for lymph node dissection [23].

Methemoglobinemia is a rare side effect after LA and is mostly described following the use of prilocaine [24]. We use a mixture of lidocaine and ropivacaine, which has a favorable safety profile. No case of methemoglobinemia has been recorded in our hospital in the last twenty years using TLA.

Tumescence local anesthesia can be perfused into the operation area by the surgeons themselves. Stoffels et al. showed in their retrospective analysis that the costs for SLNB under TLA (mean €30.64) were significantly lower than in an operating room under GA (mean €326.14, P < 0.0001) [25]. The duration of surgery is also lower for TLA compared to GA [9]. The available data on the feasibility of SLNB under TLA are from retrospective studies, as are the data on lymph node dissections under TLA [9, 23]. To the best of our knowledge, no prospective data on SLNB under TLA are available to date. In particular, there are no prospective results regarding complications for SLNB under TLA and of patient satisfaction with this procedure.

The mean age of all patients in this study was 60.1 (± 14.7) years and most of our patients (63.3 %) were male. Our results are consistent with the literature as melanoma are mostly diagnosed in patients between 50 and 60 years of age, with SSM being the most frequent subtype [26]. In Germany the gender ratio is equal but in other countries a dominance of the male gender is described in melanoma patients.

Table 5 Post-operative complications at 48 hours, four weeks, and four months (168 sentinel lymph node biopsies in 150 patients).

| Complications | 48 hours post-operative, n (%) | 4 weeks post-operative, n (%) | 4 months post-operative, n (%) |
|---------------|-------------------------------|-------------------------------|-------------------------------|
| **Axillary**  |                               |                               |                               |
| Bleeding      | 2 (1.2 %)                     | 0 (0 %)                       | 0 (0 %)                       |
| Infection     | 0 (0 %)                       | 1 (0.6 %)                     | 0 (0 %)                       |
| Seroma        | 0 (0 %)                       | 11 (6.5 %)                    | 3 (1.8 %)                     |
| Lymphedema    | 0 (0 %)                       | 0 (0 %)                       | 0 (0 %)                       |
| **Inguinal**  |                               |                               |                               |
| Bleeding      | 0 (0 %)                       | 0 (0 %)                       | 0 (0 %)                       |
| Infection     | 0 (0 %)                       | 4 (2.4 %)                     | 0 (0 %)                       |
| Seroma        | 0 (0 %)                       | 17 (10.1 %)                   | 3 (1.8 %)                     |
| Lymphedema    | 0 (0 %)                       | 0 (0 %)                       | 0 (0 %)                       |
In the 8th edition of the American Joint Committee on Cancer (AJCC) melanoma guidelines an SLNB is recommended for patients with a Breslow thickness of ≥ 1 mm if there are no lymph node macrometastases or distant metastases present, and with a thickness of 0.8–1 mm if risk factors such as a young age and/or ulcerations and/or a high mitotic rate exist as additionally [1]. According to the American melanoma guidelines an SLNB can be performed in melanomas with a Breslow thickness ≥ 0.8 mm and without further risk factors [27]. The median Breslow thickness in our study cohort was 1.9 mm. In this patient collective no unusual SN locations such as interval, cubital or popliteal nodes were observed. For these patients, GA might be more suitable.

In our study collective, patients showed overall satisfaction with the surgery, and the majority did not suffer post-operative pain. 88.7% of the patients were very satisfied with the surgery. Only 32% of our patients reported pain within the first 48 hours post-operatively. 26% of patients reported pain after four weeks but only 6% needed analgesics. After four months, less than one in ten patients reported pain, especially when moving the corresponding extremity, but none of them required analgesics. Patient satisfaction with the cosmetic outcome of the wound was also assessed. Most of the patients (96% after 4 weeks, 97.3% after 4 months) were somewhat satisfied, satisfied or very satisfied with the scar.

These results clearly indicate that patient satisfaction with TLA, the surgery itself and the cosmetic result after SLNB was high, while post-operative pain was rarely reported and even decreased further after surgery.

Moody et al. reported an overall complication rate of 11.3% with the most frequent complication being seroma (incidence of 5.1%) followed by infection (2.9%) [15]. In our study the most frequent complication was also seroma (17.3%). Our results are therefore comparable with the results of Gunn et al. [28]. Although no seromas were observed during the first two post-operative days, the highest number was found during the follow-up examination after four weeks. In our study, most seromas were observed in the inguinal region. Our results are in agreement with the study of Hettiaratchy et al. [29]. These findings are most probably related to insufficient compression in the inguinal region due to anatomical structures, a higher hydrostatic pressure on the lower extremities compared to the axilla and an early post-operative mobilization. In addition, more lymphatic fluid is drained in the inguinal region than in the axillary region due to the larger drainage area. Seroma was mostly treated by aspiration (41.4%) and compression with an elastic bandage (48.3%). After four months, 79.3% of all seromas were completely resorbed, whereby predominantly conservative measures were sufficient as therapy. Wasserberg et al. also reported a higher wound complication rate (fluid collection, hematoma, infection) in the inguinal region than in the axillary or neck region [30].

An important observation was the lower frequency of seromas when the lymph node basin was overstitched and thereby compressed. In the inguinal region, significantly fewer seromas were observed when the lymph node basin was overstitched (P < 0.001). Fewer seromas were also observed in the axilla after suturing, though the trend did not reach significance (P = 0.085). This effect might be explained by tissue compression and a resulting reduction in the size of the wound cavity. The present study was not designed to investigate the effect of lymph node bed suturing on the frequency of seroma. Further prospective studies are needed to clarify the impact of suturing the lymph node base on SLNB under TLA.

In contrast to Wrone et al. and Moody et al. we did not observe any lymphedema after SLNB [15, 31]. Lindqvist et al. showed that the risk for post-operative complications was higher in patients with diabetes [16]. However, we did not observe a correlation of post-operative complications with diabetes, nicotine abuse or age. No major complication was observed after neck SLNB in our study cohort. This could be due to smaller wound cavities and a lower hydrostatic pressure compared to the inguinal and the axillary region. SLNB of the head and neck region is challenging due the anatomical proximity of important vascular and nerve structures. The highest false negative rates for SLN are reported for this area. This could be related to the high lymphatic drainage, the technically demanding surgery and the alteration of the lymphatic drainage after previous surgeries with local flap plasty [32–34].

Limitations

This prospective observational study has several limitations. The study was not placebo-controlled. In addition, this study was conducted without a control group using a different anesthesia technique such as GA, as SLNB is only performed under TLA in our hospital. A direct comparison of both anesthesia techniques is therefore not possible based on the available data. Another limitation is the evaluation of pain and satisfaction through a questionnaire-based survey; however, since both parameters are highly subjective, we decided to use this approach to evaluate the patients’ perspective. Additionally, the case numbers in this study were too small to assess the impact on complications of smoking, diabetes and overstretching of the lymph node basin.

Conclusions

To the best of our knowledge, no prospective data are currently available on SLNB under TLA. In this study it is shown prospectively for the first time that SLNB under TLA is safe
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and feasible in melanoma patients. Patient satisfaction was high, and only a minority of patients reported post-operative pain. Seroma was the most frequent post-operative complication. An over stitching of the lymph node basin appeared to reduce the frequency of seromas.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

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