Short-Term Morbidity Associated with Ambulatory Sentinel Lymph Node Biopsy: A Spanish Tertiary Care Hospital Based Study and Literature Review

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Abstract

Aim: To determine the surgical morbidity of SLNB performed as a major surgery procedure in an ambulatory outpatient setting.

Methods: Observational, retrospective study of 303 consecutive patients undergoing SLNB for melanoma. Overall complication rate was 22.1% (67/303). Risk factors were the location of the primary tumor on limbs (49.2%) and groin SLNB (52.2%) At the last follow-up (median: 46 months), all complications had been resolved. No cases of lymphedema, systemic complications or mortality were detected.

Conclusions: Safety of ambulatory SLNB was demonstrated. The complication rate is slightly higher than reported, due to the overestimation of seroma incidence

Keywords: Sentinel lymph node biopsy, melanoma, ambulatory surgical procedures, morbidity.

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Introduction

Sentinel lymph node biopsy (SLNB) is a well-established method of staging the regional lymph nodes for patients with melanoma. The American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology released joint clinical practice guidelines in 2018 on the use of SLNB for patients with melanoma [1].

Although it is often stated that SLNB is a minimally invasive procedure associated with few complications, a lack of data exists to determine the morbidity associated with this procedure accurately. As other authors highlighted [2], the quality of melanoma surgery needs to be evaluated based on oncological outcomes and complication rate. There is no published agreement on complication rates for SLNB. Consequently, there are no agreed standards by which surgeons can audit their practices.

The purpose of this study was to determine the surgical morbidity of SLNB performed as major dermatological surgery procedure in an ambulatory outpatient setting, and to identify population demographics, histopathological features of melanoma and other preoperative or perioperative risk factors for complications following this technique.

Material and Methods

Patients and study design

This was an observational study of all patients who underwent SLNB for invasive cutaneous melanoma in the Ambulatory Mayor Surgery (AMS) unit of our tertiary hospital, during the period from 2008 to 2017. Retrospective review of medical records from procedures performed at Dermatology Department and other Departments (Oral and Maxillofacial Surgery, Plastic and Reconstructive Surgery and General Surgery/Breast Unit) were gathered.

Ethics and policy

Informed consent was obtained before surgery in all cases. The confidentiality of the information was guaranteed according to the effective Spanish legislation. The study was approved at the Institutional Review Boards of our center.

Treatment approach and follow-up

Patients of any age with pathologically proven cutaneous melanomas T 1b and clinically negative regional lymph nodes, were offered wide local excision with appropiate margins for tumor thickness and SLNB for surgical staging.

All patients underwent preoperative lymphoscintigraphy using 1-2 mCi of 99mTc sulfur colloid injected intradermally around the melanoma or biopsy site the morning of or the afternoon before the SLNB, to identify all draining nodal basins. A hand-held gamma probe was used during surgery to guide sentinel lymph node (SLN) detection. The protocol specified that all palpable adenopathies and all nodes 10% of the most radioactive, or hottest node should be removed and designated SLNs.

The patient was offered a complete lymph node dissection (CLND) if the result was positive with oncological appraisal at the time of admission for this procedure. The patient with a negative result had regular clinic follow-up. Retrospective evaluation of complications was performed by using detailed case report forms related to SLNB. Reports included details such as the site and severity of the complication and the extent of treatment, including the need for hospital admission or reoperation.

If a disease manifested in this group at a later date, then the patient was restaged and offered therapeutic lymph node dissection (TLND) if positive nodal involvement was confirmed.

Histopathology assessment

All SLNs underwent histological analysis with hematoxylin and

eosin staining at multiple levels, followed by immunohistochemical staining for S-100 protein. SLNs were divided into blocks on the basis of lymph node size; at least three sections per block were evaluated by hematoxylin and eosin staining, and two sections per block were stained for S-100 protein and Melanoma Triple Cocktail (HMB45; melan-A, tyrosinase) antibodies. Intraoperative frozen-section analysis of SLNs was not performed; therefore, patients undergoing CLND for positive SLNs returned to the operating room for a separate procedure at a later date.

Definitions

Regional lymph node basins were defined as parotid an neck, axilla, inguinal, and "others" (popliteal, elbow).

We broadly defined complications as any adverse event documented by any provider during postoperative follow up visits[3]. Complications specifically identified on the follow-up data forms included hematoma/seroma formation, lymphedema, wound separation, wound infection or "other" complications.

As uniform criteria for all these complications are not available, we considered:

- *Seroma* as any palpable fluid collection, although it is debatable whether the criteria for seroma should be a certain diameter, since many small seromas will resolve without active treatment. As other authors[4], we consider that seroma should be defined as a condition requiring intervention, because as long as it does not impose a problem for the patient, it is questionable whether it should be regarded as a complication or just a natural part of the healing process.
- *Lymphedema* as any swelling of the involved limb/s and classified according to clinical severity. Mild (grade I) lymphedema was minor swelling with or without pitting, which reduced upon limb elevation. There was neither functional impact nor treatment necessary. Moderate (grade II) lymphedema was defined by the presence of pitting, which seldom reduced with limb elevation or required intermittent treatment. Severe (grade III) lymphedema was significant, irreversible limb swelling requiring continuous treatment, such as a compression garment [5]. Limb measurements were not performed.
- *Surgical site infection* (SSI) as any wound erythema prompting antibiotic treatment, being culture positive or clinically evident[4].

Data collection and statistical analysis

Patient demographics, clinicopathological characteristics of the primary melanoma and regional lymph nodes, complications and follow-up were gathered for analysis.

Statistical Package for the Social Sciences (SPSS, version 24.0) was used for the data analysis. Statistical comparison of continuous variables means was performed using the Mann–Whitney U or T-student test, while comparison of categorical variables was made by Ji- squared ($\chi 2$) analysis or Fisher's exact test, where appropriate. P values 0.05 were considered significant.

Limitations of the study

Information bias: Because of the retrospective design of the study, some important clinical characteristics (i.e., comorbidities) were not recorded.

Results

The database was created in 2008 and include 303 patients, 196 of which underwent SLNB in our Department and 107 patients in other departments.

The SLNB were all conducted on Caucasians; the sample group consisted of 182 women (60.1%) and 121 men (39.9%), aged from 1 to 93 years (mean of 61.2 years, median of 64.0 years). The primary tumor location was: 101 (33.3%) in the trunk, 119 (39.3%) in limbs, 38 (12.5) in hands and feet and 44 (14.5%) in the head and neck region. The mean thickness of the primary tumor was 2.66 mm. Two-hundred and thirty-nine (78.9%) had a negative SLNB whilst 52 (17.2%) had a positive result. Regarding the number of SLN excised, only one node was harvested in 113 cases (37.3%), two nodes in 102 (33.7%) and three or more nodes in the remaining 88 (29.0%). A single draining basin was identified in 301 patients (99.3%).

The overall complication rate was 22.1% with 67 complications. The most common complications was seroma formation (n=45; 14.9%), followed by wound infection (n=8, 2.6%), hematoma (n=6; 2.0%), perioperative hemorrhage (4 cases, 1.3%), nerve injury (n=2; 0.7%), wound separation (n=1, 0.3%) and Mondor disease (n=1, 0.3%) No cases of lymphedema were detected. By the last follow-up, all complications had been resolved. The median follow-up duration was 46 months.

Complications resulting in hospital readmission occurred in 8 cases (2.6%), 6 for serious wound infections that required intravenous antibiotics and 2 for perioperative hemorrhage. Systemic complications, perioperative and postoperative procedure-related mortality was zero. The univariate analysis, comparing patients with and without complications, only showed differences when the location of primary melanoma and lymph node basin were analyzed (p=0.03): The highest complication rate of 52.2% (35/67) was observed in patients undergoing SLNB of the groin for primary melanoma of the lower extremity. Primary melanoma of the lower extremity was also significantly related to a higher rate of wound complications (49.2%, 33/67). The strong statistical correlation between this location and drainage to the groin suggests the biopsy site in the groin, rather than the location of the melanoma on an extremity, is responsible for the wound morbidity.

Discussion

SLNB vs Elective lymph node dissection (ELND)

Lymphatic mapping with SLNB is the standard approach for the management of patients with melanoma in whom there is a significant risk of regional node metastasis. It is a less invasive alternative to ELND for pathologic nodal staging, provides important prognostic information and permits the identification of patients with a positive SLN who may be candidates for adjuvant therapy.

Recent meta-analysis[4] of 416 records of inguinal lymphadenectomy showed following complications rates: overall complications, 52% (44-60%); lymphorrhea, 29% (0-71%); seroma, 23% (18-29%); infection, 21% (15-27%); wound breakdown, 14% (8-21%); skin edge necrosis, 10% (6-15%); hematoma, 3% (1-5%); and lymphedema, 33% (25-42%).

Although most centers have accepted the premise that SLNB is associated with low surgical morbidity when compared with ELND, limited evidence is available to support this assertion. The only study that directly examines the complications of SLNB with those of ELND is Schrenk et al[6]. The study compared the morbidity rate of two groups of 35 women with breast cancer. The first group underwent

SLNB whereas the second group had level I and II axillary dissection. Formal axillary node dissection was associated with significantly increased arm circumference and higher rate of subjective arm lymphedema, numbness, pain, and motion restriction.

SLNB vs SLNB followed by CLND

In the case of melanoma, at least seven studies have shown reduced SLNB morbidity compared with SLNB followed by CLND (Table 1):

- The first report regarding the complications of SLNB from a large multicenter prospective study was the Sunbelt Melanoma Trial (SMT) which showed that SLNB is associated with fewer complications than regional lymphadenectomy[7]. At a median follow-up of 16 months, the overall complication rate was significantly lower when only SLNB was performed (5% vs 23% for SLNB plus completion lymphadenectomy). The lower rate of complications included wound infection, lymphedema, hematoma/seroma, and sensory nerve injury. As we discuss later, this incidence of complications reported by SMT for SLNB is lower than that those reported by several smaller single institution series[8]:
- Initial report about morbidity of SLNB published by Morton et al[9] with data from MSLT-1 showed that the low (10.1%) complication rate after SLNB increased to 37.2% with the addition of CLND; CLND also increased the severity of complications.
- In other prospective study[5], 1521 patients who underwent SLNB, CLND following a positive SLNB and TLND in the axilla and groin were included. The overall rate of early complications associated with SLNB was significantly higher in the groin compared with the axilla (14% versus 5%, P = 0.0001) and fewer than for lymphadenectomy. Early complications were similar for CLND and TLND in the groin (49% versus 43%, P = 0.879) and axilla (28% versus 33%, P = 0.607).
- - A retrospective study[10] of 493 SLNB and 147 SLNB followed by CLND also detected higher early and late incidence of complications for SLNB in the groin (24%) than the axilla (10%) and fewer than for CLND (84% and 60%, respectively).
- Another retrospective study of 416 patients[8], showed not only an overall rate of complications significantly higher than that observed for SLNB (19.5% vs 5.9%), but also a predominance of chronic vs auto-resolved lymphedema in those who also underwent CLND (5/6 vs ½).

Smaller series have found similar differences, but the relation with lymph node basin was not specifically studied:

- A retrospective study[11] of 203 patients found post-operative complications of SLNB (neuropathic pain, infection, seroma, hematoma, lymphedema) in 12% of patients (24/197) and in 14% of patients (6/ 42) who underwent additional CLND, including lymphedema[3], hematoma[1], neuropathic pain[1] and complex regional pain syndrome[1].
- Mixed prospective and retrospective study[12] of 241 patients showed that the complication rate was 6% after SLNB and 29% after CLND.
- A retrospective study[13] showed that persistent sequelae were less frequent after SLNB (7.5%) than after SLNB plus CLND (30%), being lymphedema the most common in both groups.

One caveat regarding these analyses should be mentioned: the comparison was not between SLNB and ELND, but between SLNB alone and SLNB followed by CLND. Although it is possible that CLND after SLNB, which involves two operative procedures, is more morbid than ELND alone, the rate of complications in the SLNB plus CLND group in these studies was similar to that reported for ELND in other studies[7].

CLND vs TLND

Two different types of lymph node dissection could be considered in melanoma patients with demonstrated lymph node metastasis:

- CLND: lymphadenectomy of all remaining lymph nodes in the affected basin following a positive SLNB in the absence of clinically palpable disease[13].
- TLND: lymphadenectomy presented as an option for those who have clinically palpable lymph node involvement, either following SLNB or in the absence of SLNB[14].

A paucity of literature exists comparing the morbidity of CLND and TLND[15]. In 2010, published data from MSLT-1 [16] showed no significant difference in acute morbidity, but lymphedema was significantly higher in the TLND group (20.4% vs. 12.4%, p=0.04). Length of inpatient hospitalization was also longer for TLND.

A recent systematic review of complications following CLND versus TLND for melanoma was published[17] and 18 articles were included. Comparing the group of 1627 patients who underwent TLND (1627 patients) vs the group of CLND (1929 patients), the overall incidence of surgical complications was 39.3% (95% CI 32.6-46.2) vs 37.2% (95% CI 27.6-47.4). were as follows: wound infection 25.4% (95% CI: 20.9-30.3) vs 21.6% (95% CI: 13.8-30.6); lymphedema 20.9% (95% CI: 13.8-29.1) vs 18% (95% CI: 12.5-24.2) and seroma 20.4% (95% CI: 15.9-25.2) vs 17.9% (95% CI: 10.3-27). The complication rate was sightly lower for CLND, but without any statistical significance.

There are few prospective studies examining lymphoedema incidence when radiotherapy is added to TLND [18], but some of them showed that rate was increased[5].

Overall complications of SLNB

Although SLNB is not without morbidity, most of the complications associated are minor. In their original description of the procedure, Morton et al[19] quote an incidence of 5.5% seroma and 4.8% infection for all lymph node basins. We reviewed a meta-analysis[20] with 9047 patients from 21 individual studies published between 2000-2015. The overall incidence of complications was 11.3% with a highly variable range reported (from 1.8 to 30). These variations likely stem from a considerable heterogeneity in available studies. Difficulties for analyzing data reported are mainly due to[20]:

- Design of the studies: Many of the studies presenting morbidity data are small in scale, retrospective in design, with a lack of high quality evidence available.
- Poor reporting information: complications presented as a secondary measure, with imprecise definitions and grouped complications (presenting data as "wound complications") means that the data is not standardise and results are impractical to establish conclusive comparitions.
- Length of follow up periods across the studies is heterogeneously presented as the mean, median or range. Some studies omit the length of follow up, or it is not transparently presented.

In 2015, the Cochrane Collaboration published a systematic review[21] with the primary outcome measure being overall survival after lymph node dissection for melanoma in 2001 patients. A subgroup analysis of risk ratios was performed comparing surgical morbidity (within 30 days) in the dissected lymph node basin between patients treated with wide excision and SLNB versus wide excision and observation, which unsurprisingly showed zero complications in

Table 1 Complication rates for SLNB compared with SLNB followed by CLND.

Reference	Design	n	Age of patients included	Type of complications	SLNB (%)	SLNB + CLND (%)
Theodore et al [5]	Prospective, single centre	SLNB: 847 SLNB+ CLND: 100	12-85	TOTAL Seroma Surgical-site-infection	8 4 2	40 26 22
Wrightson et al [7]	Prospective randomised	SLNB: 1676 SLNB + CLND: 444	18-70	TOTAL Wound separation Wound infection Severe infection Haemorrhage Lymphoedema Haematoma/seroma Skin graft requirement Thrombophlebitis Deep venous thrombosis Pneumonia Urinary tract infection Cardiac complication Pulmonary complication Sensory nerve injury Motor nerve injury Other	4.6 0.24 1.08 0 0.09 0.66 2.31 0 0.09 0.09 0 0 0 0.14 0.14 0.09 0.42	23.2 1.58 6.98 1.35 0.45 11.7 5.9 0 0 0.23 0 0.23 0 0 1.8 0.45 4.1
Roaten et al [8]	Retrospective, single centre	SLNB: 339 SLNB + CLND: 77	NA	TOTAL Seroma Nerve injury Wound infection Lymphoedema Haematoma Dehiscence Postoperative pain Suture granuloma Myocardial infarction Thoracic duct injury Lymphocoele	5.9 1.2 0.9 0.9 0.6 0.6 0.6 0.6 0.3 0.3 NA NA	9.5 NA 1.3 6.5 7.8 NA 1.3 NA NA NA 1.3 1.3
Morton et al [9]	Phase III RCT	SLNB: 937 SLNB + CLND: 234	18-75	TOTAL Wound separation Seroma/haematoma Infection	10.1 1.2 5.5 4.6	37.2 3.0 23.1 15.8
Jørgensen et al [10]	Retrospective, single centre	SLNB: 493 SLNB+ CLND: 147	NA	TOTAL Lymphoedema Seroma Reoperation Surgical-site-infection	22.3 4.1 9.3 0.4 8.5	72.8* 34 57.1 16.3 46.2
Chakera et al [12]	Mixed prospective and retrospective	SLNB: 241 SLNB + CLND: 49	18-85	TOTAL Infection Seroma Lymphoedema Haematoma	6* 2.1 4.7 0.8 0.8	29* 14.3 16.3 14
Van den Broeck[45]	Mixed prospective and retrospective	SLNB: 241 SLNB + CLND: 49	17-85	TOTAL Infection Seroma Haematoma Lymphoedema Bleeding Neuralgia	11 1.6 7.2 1 1.3 - 1	78 38 58 - 11 4.4 -
Espinosa-Pereiro [13]	Retrospective	SLNB: 94 SLNB + CLND: 30	Average: 56	TOTAL Impaired scarring Infection Seroma Lymphoedema Wound separation	30.9 10.6 9.6 5.3 4.3 4.3	60.0 13.3 13.3 20.0 26.7 0

the unoperated observation group versus 106 complications in 937 patients of the SLNB group (11.3%). This result is equal to the pooled proportion of complications in the meta-analysis[20], although in a much smaller sample size.

Comparing our series with both reviews, we detected a higher overall rate of complications of 22.1%, which is most probably due to the inclusion of very small seromas (Table 2).

Specifical complications of SLNB

Meta-analysis[20] calculated that the incidence of seroma was 5.1% (95% CI: 2.5-8.6); infection was 2.9% (95% CI: 1.5-4.6); lymphoedema was 1.3% (95% CI: 0.5-2.6); haematoma was 0.5% (95% CI: 0.3-0.9) and nerve injury was 0.3% (95% CI: 0.1-0.6).

Hematoma and seroma formation are the most frequent complication, which usually is of no long-term consequence. Ligatures or metal clips to control lymphatic dissection field may help to minimize the incidence of haematomas and seromas, although some authors related their use to higher risk of sensitive nerve entrapment and temporary postoperative pain[22]. A meta-analysis[20] showed that the most common reported complication was seroma in 16 articles (n = 386 of 6750 patients, 5.72%), with a crude rate ranged from 0% to 38%. Our data revealed a 14.9% incidence of seroma after SLNB, but comparison cannot be established as we considered any palpable fluid collection. In contrast, only 2% developed haematoma.

We only had one case with persistent seroma after six months in a patient with congestive heart failure. Some authors[23] found persistent seromas at the SLNB site (7%) in patients who did not had CLND. Concomitant medical illness that can cause persistent seromas such as congestive cardiac failure, renal failure or low blood protein were not reflected.

SSI: We detected a rate of wound infection after SLNB of 2.6%, consistent with meta-analysis reported (1%), which showed that it was the second most common reported complication in 16 articles (n = 242 of 7687 patients), with a crude rate ranged from 0.3% to 19%[17]. It is comparable to that of a clean operative procedure and is significantly less than that of the CLND (6%[24] to 29%[25]).

As previously commented, the number of seroma aspirations increased the risk of SSI and lymphoedema[10]. We could not evaluate the influence of this variable, as it was not recorded in most cases.

Similar to other studies[7], the most frequent complication resulting in hospital readmission in our series was serious wound infections that required intravenous antibiotics.

Lymphoedema after axillary or inguinal lymphadenectomy is not infrequent and is perhaps the most dreadful complication associated with nodal staging procedures. Meta-analysis showed that it was the third most commonly reported complication of SLNB, included in 18 reports (n = 135 of 7770 patients, 1.3%), with a crude rate ranged from 0% to 17%. In our series, no cases of lymphoedema after SLNB were detected.

Although lymphoedema was attributed to the externt of lymphatic disruption and the number of lymph nodes excised during the SLNB or CLND procedure, wide local excision of extremity melanomas could contribute to this incidence of lymphedema[22]. Also, lymphoedema was not evaluated (in our and most studies) by prospective measure of limb volume or circumference, but was defined as clinically apparent swelling of the extremity on the basis of history and physical examination, so some cases of minor limb swelling could have been missed[7].

SMT[7] found a 0.7% risk of lymphoedema among patients undergoing axillary or inguinal SLNB (14 of 2083 patients), while the rates of lymphedema after axillary and inguinal CLND were 4.6% and 31.5%, respectively. Ten (71%) of these 14 patients had lymphedema of the lower extremity after inguinal SLNB. Lymphoedema was also significantly more common for patients undergoing inguinal CLND compared with axillary CLND (31.5% vs 4.6%; $P < 0.0001$).

A previously mentioned retrospective study[10] comparing 493 SLNB vs 147 SLNB followed by CLND cases also showed that the incidence of lymphoedema after CLND (34%) was substantially higher than after SLNB (2%), and is related to the extent of lymphatic disruption, the number of lymph nodes removed, the number of metastatic lymph nodes, SSI, reoperation and number of seroma aspirations. SSI was the most significant independent risk factor for developing lymphoedema. Additionally, patients that developed postoperative seroma were at an increased risk of also developing SSI. The risk of lymphoedema was significantly larger following inguinal incisions compared to axillary incisions for both SLNB and CLND. Although obesity and increasing age has previously been associated with a risk of lymphoedema[25], these parameters were not found to be independent risk factors.

Other local complications (reported but not fully enumerated) included nerve injury (motor or sensory dysfunction), wound dehiscence, post-operative pain, keloid scar, suture granuloma, skin graft requirement, lymphatic fistula and persistent skin staining of blue dye[20].

Out of this group of post-operative complications, we only detected wound dehiscence in 0.2% of patients. Our study also included patients with melanoma in the head and neck region undergoing SLNB involving the parotid basin. Albeit some surgeons have proposed that SLNB may limit complications associated with parotid dissection—specifically, facial nerve injury—others have disproved this argument because the facial nerve is not exposed properly,

Table 2 Complications of SLNB in patients with melanoma.

Type of complication	Cochrane Collaboration [21] N=937)	Meta-analysis[20] (95% CI) (N=9047)	Our series (N=303)
Infection	4.59%	2.9% (1.5-4.6)	2.6%
Seroma	5.54%	5.1% (2.5-8.6)	14.9%
Haematoma		0.5% (0.3-0.9)	2.0%
Lymphoedema	0.6%	1.3% (0.5-2.6%)	0.0%
Nerve injury	-	0.3% (0.1-0.6)	0.7%
Wound separation	1.2%	-	0.3%
TOTAL	11.3%	11.3% (8.1-15.0)	22.1%

and, therefore, unintentional damage could occur because of the limited dissection field. The morbidity associated with SLNB of the parotid has been reported to be 2.6% [26] to 4%[27]. Some authors have identified facial nerve dysfunction in 10% patients, but in all of them returned to preoperative status[28]. In this study, we also found minor, transient facial nerve paresis in 1.2% of patients as complication associated with parotid SLNB. However, we did not see any cases of seroma, infection, definitive section, or paresis.

We not detected other sensory complications in our series. Wasserberg et al[29] observed a significant relation between nerve-related complications and age younger than 50 years, axillary site, and number of excised sentinel nodes (p=0.003, 0.04 and 0.02, respectively).

AWS (Axillary web syndrome) or Mondor disease of the axilla is a complication frequently described in the breast cancer literature. It is characterized by a palpable cord that arises in the axilla that may extend distally to involve the medial arm, antecubital fossa, and forearm and is associated with pain and restriction of movement across the involved joint space. AWS has been reported as having an incidence as high as 20% after SLNB and 72% after CLND for breast cancer and usually presents within 12 weeks of the operation. AWS has also been reported after trauma, infection, excessive physical activity, and inflammatory conditions. The incidence of AWS in the unique retrospective study[30] with patients undergoing SLNB for clinically node-negative melanoma of the upper extremity and trunk, was equal or higher than "standard" complications at 4.5% (21/465). There was no statistical difference regarding tumor thickness, the location of primary (upper extremity vs trunk), average number of sentinel nodes removed, positive SLNB rates (10% vs 12%), patient age, or gender. All cases of AWS solved with expectant management; none required surgical intervention. We detected only one case of AWS in our series.

Other, rare, systemic reported complications were detected in 26 cases (0.29%) in the meta-analysis[20], and included :

Allergic reactions to sulfan blue dye reportedly appear in approximately 1.5% of cases, although most are mild allergic reactions. A systematic review[32][33] A of reports of anaphylactic responses to isosulfan blue dye and patent blue V dye during SLNB for any tumor, reported that incidence of anaphylaxis varies between 0.06 and 2.7%, with a mean value of 0.71%.

Trials for measure this complication are mainly focused in breast cancer patients. In the ALMANAC trial[33], the authors reported minor reactions after blue dye injection in 51 of 5853 (0.9%) SLNB procedures. Severe allergic reactions, requiring administration of a vasopressor or a change or cessation of the procedure occurred only in 4 of 5853 (0.07%) procedures. In NSABP B-32, allergic reactions secondary to blue dye occurred in 0.7% (37 of 5588) of patients for whom data on toxic effects were available[34]. Anaphylactic shock after administration of blue dye for SLNB is potentially lethal and must be considered a medical emergency. Different grades have been described: grade I (allergic skin reaction only); grade II (transient hypotension not requiring vasopressor support); and grade III (transient hypotension requiring vasopressor support)[34]. In some cases, a biphasic anaphylactic reaction has been described, with hypotensive episodes occurring at 15 min and 2 h after blue dye injection[35]. This reaction must be recognized to manage the patient effectively in the post-operative period. As for other authors' knowledge, no cross-reactivity has been described between blue dye and any other drugs. In the same way, there is no test available to predict allergy, because specific antibodies only appear in the event of an anaphylactic reaction and do not exist beforehand.

Meta-analysis of complications of SLNB in melanoma patients detected 13 cases of 'allergy' to the radiocolloid or blue dye, however the term 'allergy' was not often defined, and therefore the true rate of hypersensitivity or anaphylaxis cannot be reported.

Some series described a well-documented inmediate-hypersensivity rash:

Leong et al[36] reported a 1% incidence of anaphylaxis to isosulfan blue dye: 3 cases in a series of 406 melanoma patients during lymphatic mapping.

Lock-Andersen[23] described 2 cases (among 198 patients who underwent SLNB) of universal urticarial rashes, 20-30 minutes after injection of the dye. Vital signs were not afected.

However, SMT[7] not identified any complications directly associated with blue dye in >2100 cases. Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1)[9] found allergic reactions (0.17%) but not cases of anaphylaxis. We could not measure this specific complication given that blue dye was not used in our centre.

In a series of SLNB for breast cancer[37], intradermal injection of methylene blue dye caused skin lesions at the injection site, which was avoided using deep breast parenchymal injections. Because SLN mapping for melanoma surgery involves a more superficial injection, use of methylene blue dye in this setting carries a relative contraindication unless overlying skin is being excised where the injection took place.

Extremely infrequent complications included urinary complications (five patients), deep vein thrombosis (four patients), myocardial infarction (two patients), pulmonary embolism (one patient) and cerebral vascular accident (one patient). There were no deaths secondary to SLNB reported. None of our patients suffered these serius, systemic adverse events nor anaesthetic complications.

What are the expected or acceptable complication rates for SLNB?

At present, there is no consensus on surgical performance indicators and complication rates in melanoma surgery. Consequently, there are no standards with which individual surgeons and units can compare their own audited outcomes. Surgical standards published in 2008, following a review of the literature and expert opinion, proposed a threshold of <5% for SLN site infection or seroma requiring aspiration [2]. Our rates of seroma was higher, but it was probably overestimated.

Risk factors for SLNB morbidity

Most studies not include clinically relevant information regarding relationships between complications and patient-specific risk factors for complications. Identification of such risk factors may ultimately allow for a reduction in complications[8].

Age

We did not find differences in complication rates based on age. Meta-analysis detected that the average age of patients at the time of SLNB was presented only in 17 studies and age at melanoma diagnosis in two studies. Therefore, no accurate comparison or conclusions can be made regarding the age of the patients and complication rates[20].

Nodal basin

In our series, the location of the primary melanoma and lymph node basin are the two factors significantly related to a higher risk of complications. As we previously mentioned, a significantly increased rate of complications with inguinal nodal basins compared with cervical or axillary nodal basins was detected in the literature. In the meta-analysis[20], the percentage of complications reported in each lymph node basin was extractable only from 10 studies [5][7]

[8][10][22][29][38][39][40][42] (Table 3). Overall, there were 257 complications reported in 3541 biopsies. With respect to lymph node basin, there were 118 complications in 1922 axilla biopsies; 110 complications in 992 groin biopsies; 21 complications in 594 neck biopsies and eight complications in 73 'other' site biopsies. Separate pooled estimates were figured for the rate of complications per lymph node basin site in order to identify any significant differences. The site with the highest incidence of complications was the groin with a rate of 14.9% (95% CI: 6.1-26.7), followed by the axilla at 9.8% (95% CI: 4.7-16.6). The neck had the fewest complications with a rate of 5.1% (95% CI: 2.2-9.3). There was no significant difference in complication rate between the lymph node basins .

At least two studies[12][39] found that the more SLNs removed, the greater the risk of complications at the SLNB site, but differences were not statistically significant. Wasserberg et al[29] demonstrated not only that number of excised nodes was significantly associated with an increased rate of total complications, but also that it was the only independent factor to predict them (2 nodes, sentinel or other) (p=0.007). Sampling of more than one basin site did not affect morbidity. One year later, Roaten et al[8] showed that patients having 2 nodes (n = 107; 7.5%) or 3 nodes (n = 62; 11.3%) excised at SLNB were at significant higher risk of complications than those patients having a single node (n=156; 3.2%) excised at SLNB (p = 0.02). We could not find this trend in our series.

Comorbidities

As we previously commented, the retrospective design of the study did not allow reaching a conclusion about comorbidities and SLNB complication risk.

Ling et al[38] studied the relation between complication rate and being overweight. The mean weight for those who developed a complication was significantly greater than that for those without complications (91.9 kg vs 78.6 kg, P = 0.03). Likewise, the mean body mass index for those with complications was greater compared with those who did not develop a complication (31.04 vs 27.29, P = 0.05) We did not gathered weight nor body mass index in our study. They also detected that not increase the risk of a complication was related to age the type, level or thickness of the primary melanoma, smoking, alcohol, diabetes mellitus nor use of aspirin or warfarin. The use of intravenous intra- operative or post-operative oral antibiotics did not significantly decrease the risk of a complication (P-values 0.34 and 0.63 respectively). However, other authors[13][42] detected an increased risk of complications associated to smoking.

Roaten et al[8] identified 16% of patients with preoperative comorbidities including diabetes, obesity, cardiac disease, or a history of smoking. They showed no significantly increased risk for complications (9.3% vs 5.2%).

Ascha et al[41] used the National Surgical Quality Improvement Program (NSQIP) database to explorate predictors of 30-day readmission for surgical complications of SLNB and CLND. Of 3006 patients included, 151 (5.0%) returned to the hospital. No significant differences were found between readmission rate of CLND patients (5.3%, 65/1235) and SLNB patients (4.9, 86/1771). Predictors of hospital readmission were smoking for overall SLNB and cervical SLNB on multivariate analysis, age for cervical and inguinal CLND, and hypertension for cervical CLND. Diabetes, preoperative hematocrit and male sex were predictors for inguinal SLNB. There were no significant predictors for axillary SLNB nor overall CLND procedures.

The median follow-up for our study was 46 months, and we believe that most late complications like lymphoedema, hypertrophic/painful scars or chronic seroma were captured during this follow-up period. The minimum follow-up was extracted in the meta-analysis[24] from the data reported in 12 studies, ranging from 11 days[23] to 12 months[42][43], although the study[23] with 187 patients, reporting a minimum follow-up of 11 days, did have a mean follow-up period of 24 months. Althought most were early operative complications, some late complications could be missed because they become apparent during more extended follow-up periods. Several articles report complete resolution of complications within the follow-up period[3][8][44][45]. One study[46] reported that 3% of their patients had 'permanent' lymphoedema and two papers[23][39] reported two cases of persistent staining from the blue dye. However, most of the studies partially reported or failed to report whether or not the complications had been resolved. In our series, lymphoedema was not completely solved at the end of follow-up.

Technical aspects of surgery

No differences among specialities were detected in our study. We could not find previous studies that compare the risk of complications

Table 3 Distribution of nodal basin sites in SLNB and complications (percentage of complications for each location).

Series/Nodal basin	Neck	Axilla	Groin	p
Theodore et al [5]	-	5%	14%	0.0001
Wrightson et al [7]	2.4%	4.4%	8.1%	-
Roaten et al[8]	3.6%**	4.8%	5.3%	>0.05
Jørgensen et al [10]	-	10%	24%	-
Cigna et al [22]	2.6%	6.9%	4.4%	-
Wasserberg et al[30]	8.5%	17.1%	28.2%	0.001
Ling et al[39]	0%	31.2%	68.8%	0.04
Hettiaratchy et al[40]	19%	22%	41%	<0.04*
Verdier et al[41]	17%	17%	32%	-
Persa et al[42]	-	33.9%	66.1%	<0.0001
Total(21)	5.1%	9.8%	14.9%	>0.05
Our series	13.6%	17.8%	31.3%	0.03

considering type of surgeon or ambulatory versus hospital-based surgery.

There are controversial results with regards to the surgeon's experience: one study[39] observed that complication rates not decrease with experience (increasing patient numbers) after learning curve. Another one[8] found that incidence of annual complications inversely correlated with the cumulative number of SLNBs performed during this period.

Stoffels et al[47] compared morbidity of SLNB performed under TLA (tumescent local anaesthesia) or GA (general anaesthesia). No major complications like lymphoedema or vascular injuries or nerve damage occurred. There was no operative death. Twenty- two of 300 (7.3%) patients had one minor complication. The rate of complications was 6.2% (13/211) in the TLA group and 10.1% (9 / 89) in the GA group. The operating times between the TLA group and the GA group were comparable.

Roaten et al[8] detected that use of closed-suction drainage was associated with a higher incidence of wound-specific complications (13.2% vs 2.2%, $p < 0.001$), whereas some authors not found association with the use of drain tubes[38]. The retrospective nature of this study makes it impossible to discern whether there is a real causal relationship between closed-suction drainage and complications. It may be that the use of closed-suction drains is a surrogate for another variable related to complications from SLNB, such as the extent of dissection.

Rødgaard et al[42] compared the risk of postoperative complications when lymphoscintigraphy was performed 24 hours prior to SLNB with delayed static imaging and with early dinamic imaging, when it was performed on the same day. Surgical morbidity was nearly the same in both procedures.

Regarding geographic variations in surgical procedure, a meta-analysis[20] found no statistically significant difference for complication rates across the different continents. Europe had the highest percentage of reported complications at 12.0% (95% CI: 8.3-16.4), followed by USA with 10.9% (95% CI: 1.9-26.0) and Australasia had the fewest at 5.4% (95% CI: 0.1-17.7). There was only one study from Asia; therefore, it was not included in the pooled proportion analysis.

Conclusions

SLNB was introduced as a minimally invasive procedure to provide valuable information regarding the regional spread of melanoma. It was initially regarded as a means of avoiding unnecessary ELND, which are associated with significant morbidity. However, not all publications associated with SLNB make reference to complications or morbidity.

The role of SLNB is becoming increasingly controversial in patients with melanoma, because MSTL-2[50] concluded that there is no final proof that SLNB influences their overall survival. This limited therapeutic benefit makes the need for a highly accurate technique with no significant side effects.

Our study supports historical data that SLNB is a low-risk procedure. The key findings of this analysis about patients who underwent SLNB in a single AMS unit include a low average complication rate of 22.1% (being the most commonly reported minor and early post-operative complications) and absence of intra or post-surgical mortality, life-threatening local complications and differences among surgical specialities. Readmission was required only in 2.6% of cases, mostly due to infection-related cases circumstances that needed intravenous antibiotics. The location of primary melanoma and lymph node basin were significantly related to higher risk of post-operative complications.

Similar to other authors[17], we consider that further multi-centre and prospective studies with accurate and uniform definitions of complications are needed to collect comparable data Also, the standard way to report the timing of complications is required, in order to allow analysis of early and the timing of reported complications needs to be more commonly reported to enable the study of early and late morbidity. The solution could be to counsel patients before the procedure, and to aid surgeons in assessing their practice.

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