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Changing Perceptions of Lymphadenectomy and Sentinel Lymph Node Biopsy in Melanoma

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1. Introduction

Lymph nodes (LN) represent the most frequent site of metastases for melanoma and the main purpose of lymphadenectomy (LND) is to provide loco-regional control of disease and accurate staging as well as to eventually cure patients with AJCC stage III melanoma. Currently, lymph node involvement is mostly diagnosed after sentinel lymph node biopsy (SLNB). However, although SLNB in melanoma patients at risk for lymph node metastasis is routinely performed almost everywhere, the role of completion lymphadenectomy (CLND) after positive SLNB remains controversial, as only 15-20% of the patients operated show additional lymph node metastases in the dissected basin. The MSLT-1 trial, which evaluated the impact of SLNB and immediate LND versus simple observation and LND after clinical evidence of metastases only, did not show any survival benefit between the two randomized groups of patients [1]. Moreover, other studies have shown that some of the patients with positive sentinel nodes seem at lower risk for additional lymph node metastasis, and will probably never develop additional non sentinel lymph node metastases. On the other hand, the final analysis of the MSLT-1 trial confirmed a longer disease free survival and a gain in survival only in the patients with positive nodes in the CLND group.

Until the results of the two ongoing prospective studies (MSLT-2 and MINITUB) investigating the role of CLND after SLNB positivity are available, radical lymphadenectomy should be considered the standard of care in patients with lymph node metastases, as suggested by the NCCN guidelines, which recommend lymphadenectomy in presence of positivity of SLNB or histological/cytological confirmed clinical lymph node metastases [2].

Despite this recommendation, adherence to clinical practice guidelines remains low among melanoma surgeons. In the USA, 50% of patients with positive SLNB do not undergo completion lymphadenectomy [3]. The still evident degree of confusion on the optimal surgical treatment of AJCC stage III melanoma has been confirmed by a recent international survey on lymphadenectomy in melanoma patients with positive sentinel nodes (SN), which showed an extremely heterogeneous approach to the extent of the completion lymph node dissection (CLND), especially for SN located in the neck or groin [4]. Aside from the indication and the levels of dissection, no agreement has yet been reached on the criteria to define lymphadenectomy as adequate and, even if the minimum number of lymph nodes that should be excised achieves a reasonable consensus, other quality assurance (QA) parameters for lymphadenectomy are far from being accepted.

In this context, a consensus process on indications, technical aspects and QA parameters for SLNB and, in particular, for lymphadenectomy is desirable among melanoma surgeons and pathologists. Providing new evidence-based results in these controversial fields might help to achieve better standards of treatment. The purpose of this chapter is to critically review the most recent literature on the lymph node surgical treatment in melanoma patients providing, wherever available, new evidence and contributing to standardize the current management of this tumor.

2. State of the art on SLNB and lymphadenectomy

2.1. Rationale for indication

Cutaneous melanoma presents an increasing annual incidence worldwide and despite several advances in understanding the molecular mechanism of tumour progression and the development of more selective therapeutic strategies, a significant proportion of patients remain incurable. Lymph nodes represent the most frequent site of metastases from melanoma and the main purposes of lymphadenectomy are to provide loco-regional control of disease, accurate staging as well as to eventually cure patients with AJCC stage III melanoma. A significant number of patients with localized melanoma harbor clinical occult metastases in the regional node basin, which, if left untreated, will lead to palpable metastatic nodes (macroscopic disease). In the past, the common approach to lymph node in melanoma patients ranged between two different strategies; observation followed by therapeutic lymph node dissection (TLND) when clinical disease became evident and elective lymph node dissection (ELND) at the time of treatment of the primary in absence of macroscopic disease. However, removing lymph node metastases before they become evident is potentially a better strategy to prevent local failure and could potentially prevent systemic failure in a significant portion of patients. The drawback of ELND is that 15 to 20% of patients only have microscopic disease in the regional lymph nodes; therefore, the majority of patients will have no benefit from elective surgery and will receive surgical overtreatment. Four randomized controlled trials (RCT) [5] and one meta-analysis [6] have compared these two treatment strategies with, none demonstrating a survival advantage. The negative result in survival of ELND can be explained

by the fact that more than 80% of patients in these trials will never develop lymph nodes metastases, making the studies underpowered to discover a statistical difference between the two groups. However, subgroup analysis from the WHO Melanoma Group Trial [7] showed a significant survival advantage in patients with clinically occult disease who underwent ELND compared to patients who underwent TLND for positive nodal recurrence (5-years survival 48.2 versus 26.6, P=0.04 respectively). These data suggest that there may be an improved survival in patients with occult disease, highlighting the importance of identification of early nodal disease. The difficulty in showing a survival advantage after ELND, unnecessary in 80% of patients and frequently associated with a high morbidity rate (including wound complications, lymphedema and pain), has made it, over the years, unappealing.

The controversy on performing ELND disappeared with the advent of SLNB, which deter‐ mined a consistent paradigm shift in melanoma patients at risk of lymph node metastasis. After the pioneering studies of Donald Morton, who first hypothesized the role of sentinel lymph node as the first lymph node receiving lymphatic drainage from the primary tumour, SLNB emerged as a minimal invasive staging procedure for determining the nodal status in patients with melanoma [8]. The intra-operative use of a combined technique based on blue dye and radiotracer has been demonstrated to be feasible and accurate for nodal staging of patients with melanoma [9]. A recent meta-analysis of 71 studies, which includes 25240 melanoma patients who underwent SLNB in the period 1998-2009, showed that SLNB is highly accurate in melanoma with a proportion of patients successfully mapped (a least one sentinel lymph node removed) of 98.1%, a rate which tends to increase with the year of publication and quality score of the studies, female sex, ulceration and age [10]. The same study reported a false negative rate of SLNB of 12.5% (i.e. the proportion of patients with nodal recurrence in un-dissected nodal basins after a negative SLNB over the total positive patients and the false negative patients), which is inversely associated with the proportion of patients successfully mapped. The ability of SLNB to predict the negative status of the lymph node basin is expressed by the post-test probability negative (PTPN, the ratio of patients with negative SNB who recurred to all patients with negative SLNB). The PTNB in this study is 3.4%, which represents the proportion of patients with negative SLNB who recur. This risk seems inversely related to the proportion of patients successfully mapped and positively associated with the length of follow-up, younger patient age, the proportion of females, the mean Breslow thickness and the proportion of ulcerated tumours. The overall data analysis showed that, after a negative SLNB, the chances of nodal recurrence can be estimated to be equal to or lower than 5% providing reassurance that SLNB is a feasible and reliable method for accurately predicting the lymph node status of melanoma patients and is now considered a reliable staging proce‐ dure for melanoma.

SLNB status has been identified as the most important prognostic factor for overall survival in melanoma patients with no clinical evidence of metastatic disease [11] and has been included in the AJCC TNM staging system since the 6th edition in 2001 [12]. For this reason, a general consensus on performing SLNB in patients with intermediate thickness melanomas (Breslow 1-4mm)) [13] has been reached, as SLNB gives important prognostic information that can be used for planning follow-up protocols and adjuvant treatments [14]. Although the use of SLNB

in thick melanomas remains uncertain, the procedure is recommended in this sub-group of patients mainly for staging purposes and local control of disease [14]. For thin melanoma (≤1mm), the role of SLNB is more controversial. It is known that the risk of node positivity in thin melanoma patients is less than 5%, but we should consider that this group accounts for the majority of patients with melanoma (about 65%) and therefore a large number of patients with microscopic disease might be left under staged and possibly undertreated. A sufficient level of evidence exists to also consider SLNB in patients with thin melanoma, particularly in presence of ulceration and/or mitotic rate ≥1 (AJCC T1b melanomas) [15]. Several studies have investigated the optimal cut-off value to consider SLNB cost-effective in thin melanomas. In patients with Breslow ≤0.50 mm, SLNB positivity is very unlikely, with a reported incidence of positive nodes of 0% [16]. Between 0.51 and 0.99 mm, the risk tends to increase and in a subgroup of patients with thin melanoma of at least 0.76 mm in depth and 1 or more mitosis, a 12.5% incidence of SN metastases has been reported [17].

It has been calculated that only 50-60% of patients with positive SLNB underwent CLND in USA [3] and Europe [18]. This proportion is probably higher among surgeons normally dealing with melanoma, as reported by a recent survey [4]. In this study, mainly involving surgeons working in melanoma or surgical oncology units, 91.8% of responders recommend CLND in patients with positive SLNB. However, the role of CLND in the presence of positive SLNB, remains uncertain. The Multicenter Selective Lymphadenectomy (MSTL-1) trial was started in 1994 and evaluated over 8 years the outcome of 2001 patients with primary cutaneous melanoma randomly assigned to undergo wide excision and nodal observation (observation group) or wide excision and SLNB, with immediate lymphadenectomy in presence of nodal metastases detected on biopsy (biopsy group). The prognostic value of SLNB was overall confirmed in patients with intermediate-thickness (1.2 to 3.5 mm) melanoma; 10-years Melanoma-Specific survival was 85.1±1.5 in negative SLNB and 62.1± 4.8 in positive SLNB [1]. Moreover, the MSLT-1 confirms that, among other established prognostic factors (Breslow thickness and ulceration), SLNB status is the most powerful indicator for disease recurrence (HR=2.64) and death from melanoma (HR=2.40). Considering survival analysis of patients with intermediate-thickness melanomas, a better 10-year disease free survival was detected in the biopsy group (71.3±1.8% versus 64.7±2.3%, HR for recurrence and metastasis=0.76, P=0.01), even though no difference was detected in the 10-year melanoma-specific survival among the two arms (81.4±1.5 and 78.3±2.0%, P=0.18). Even if no impact on overall survival has been observed in the biopsy group, at this level of evidence the present data suggest performing CLND for all patients with positive SLNB, mainly for achieving better regional control [2, 14]. Furthermore, a complete LND with therapeutical intent is recommended in presence of clinically evident, cyto/histologically proven lymph node metastasis.

2.2. Surgical techniques

SLNB involves preoperative lymphoscintigraphy, obtained through the injection of human albumin nanocolloid labelled with technetium 99mTc. The injection is in the intradermal layer, close to the scar of the removed melanoma or to the tumor if still present, and followed by scintigraphic scans (early and late) in the likely locations of lymphatic drainage [9]. Once the

basin and location of the sentinel node has been identified, cutaneous projection area of each single node is marked on the skin. Immediately prior to surgery, the primary site is further injected intradermally with 0.5 to 1 mL of a vital dye (patent Blu), to increase the sensitivity of the method and to facilitate the finding of the lymph node (figure 1). SLNB is performed through a small skin incision, which should take into consideration the incision necessary for a subsequent radical lymphadenectomy [14]. Under the guidance of a radioisotope probe and following the blue lymphatic channels, the sentinel lymph node(s) is identified and removed (figure 1). Care should be taken not to disrupt or cauterize the lymph node capsule. Each SLN removed is checked ex vivo for radioactivity and the nodal basin is rescanned. Drains are seldom required and most patients are operated in one day-surgery regimen. The incidence of post-operative complications is relatively low, mainly related to wound (dehiscence/ infection or lymphatic collection), although limb lymphedema occurs not so un-frequently as generally supposed [19].
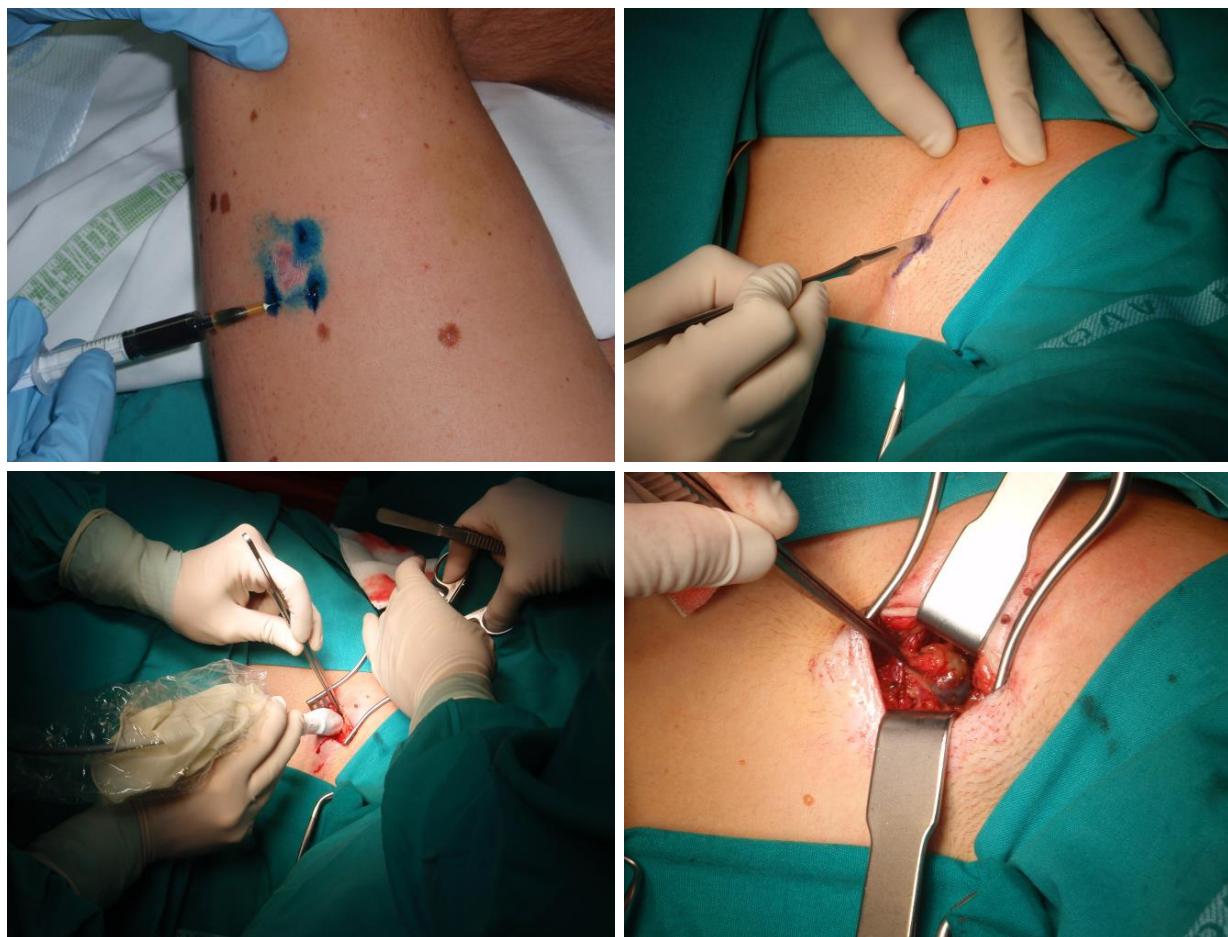

Figure 1. Surgical technique of SLNB

Radical lymphadenectomy for melanoma involves the "en bloc" excision of lymph nodes with surrounding fat tissue. In the axilla, a radical lymphadenectomy should include dissection of levels I, II and III lymph nodes around the axillary vein [20]. A section of the pectoralis minor

muscle is suggested by some for a better access to level II lymph nodes or in presence of bulky level II and III nodes. Long thoracic and thoracodorsal nerves should be preserved and sectioned only if directly involved by the tumor. In case of metastasis to the inguinal lymph nodes, the standard approach involves the removal of the inguinal, external iliac and obturator lymph nodes [21]. In the classic description of inguinal dissection, a longitudinal or lazy-S-shaped skin incision is employed, extending a few centimeters cranially to the superior anterior iliac spine up to the apex of the femoral triangle (figure 2). The incision should include the SLNB scar. The cutaneous flaps are created medially and laterally, up to the pubic tubercle, the anterior margin of the gracilis and abductor muscles and up to the superior anterior iliac spine and Sartorius muscle, respectively. Deep dissection continues through the fascia lata, over the underlining muscles and femoral vessels. The saphena magna vein is generally sectioned at the apex of the femoral triangle and at the level of the saphenofemoral junction. In case of the risk of femoral vessel exposition after wound dehiscence, transposition of the sartorious muscle is warranted. Iliac and obturatory dissection is obtained through an extra-peritoneal approach. After sectioning of the oblique muscles and the inguinal ligament, the pelvic area is reached and the external iliac and obturatory lymph nodes removed, after identification of the urether and the obturator nerve.

For cervical lymph node metastastis, clear indications on the thoroughness of dissection are lacking and all the recommendations are supported by a low level of evidence and are obtained from opinions of experts in this field [22]. In case of clinically evident cervical lymph node metastasis, surgery is aimed at the removal of all five levels of lymph nodes (submandibular, jugular and supraclavicular), preserving sternocleidomastoid muscle, internal giugular vein and accessory spinal nerve (figure 3). Removal of the superficial part of the parotid is recommended only if clinically involved, because of the high risk of nerve damage observed.

Although general principles and technical details to perform adequate SLNB and LND are diffusely reported, surgeons in the clinical setting find many controversial aspects, regarding, in particular, the extent of given lymphadenectomy [22]. The question on what can be considered an adequate lymphadenectomy for metastatic melanoma is therefore largely un-answered. National guidelines are vague in defining this issue and simply suggest describing the anatomical limits of dissection [2]. This level of indeterminateness affects the attitude of melanoma surgeons in performing lymph node dissection [4]. A general agreement emerges in the presence of clinical evident lymph node metastatic disease, where a full regional lymphadenectomy is considered by most surgeons. More controversial is the thoroughness of lymphadenectomy in SLNB positive patients, in which, due to the significant risk, the approach is heterogeneous and controversial. For neck dissection, considering the risk of nerve damage as well as for the anatomic complexity, a consensus seems to emerge on performing CLND selectively and to remove the levels likely to be involved, depending on the site of the primary tumour, the site of the sentinel node and the lymphatic drainage highlighted at lymphoscin-tigraphy. Meanwhile, a superficial parotidectomy is associated only in presence of clinically evident metastasis [22]. For axilla, a general agreement exists on performing, in all cases, a three level dissection as the risk of lymphedema seems not affected by a more extensive lymphadenectomy. In fact, despite the risk of metastases of the third level is quite low [23],
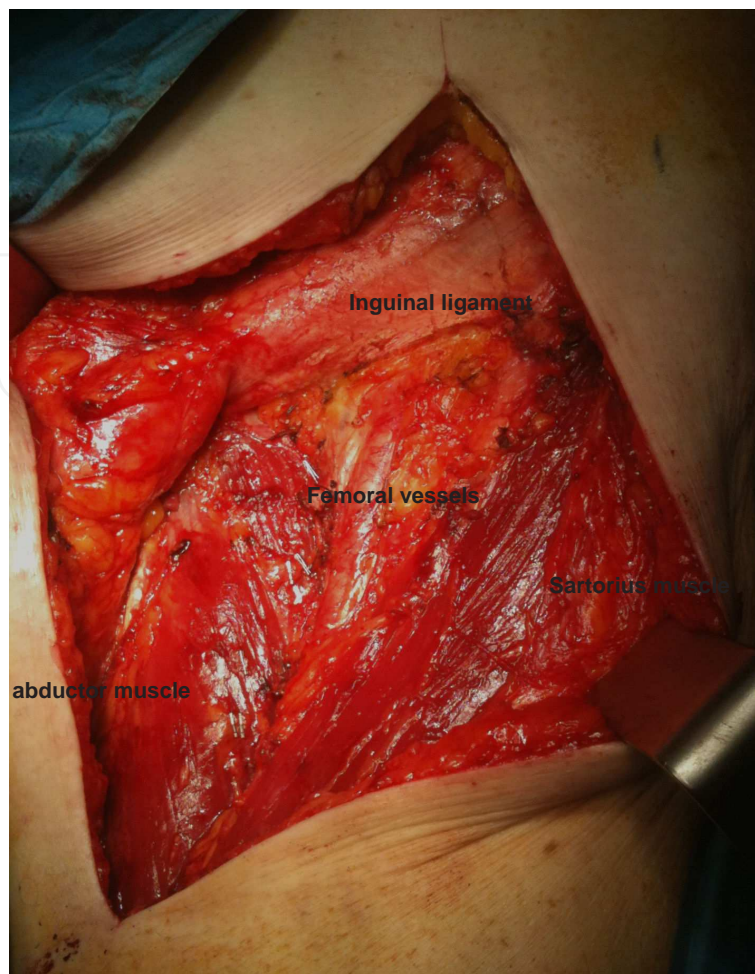
Figure 2. Intraoperative view of inguinal LND.

surgical management of recurrent disease in the apex of axilla appears more difficult. More controversial is the approach to the groin, in particular for CLND after a positive SLNB, where two distinct lymphatic basin (inguinal and pelvic) are involved. Several national guidelines suggest combining pelvic dissection out of the inguinal, only in presence of radiological evidence of pelvic metastases, >3 positive inguinal nodes and metastases to the Cloquet's lymph node (so called sentinel lymph node of the pelvis). However, the evidence is low to sustain this surgical approach and a randomized controlled trial from the Australian and New Zealand Melanoma Trial Group comparing inguinal and pelvic CLND in SLNB-positive patients with negative PET/CT pelvic scan is about to start (EAGLE FM Study, ClinicalTrials.gov Identifier, NCT02166788) [24].

3. New evidence-based results

Referring to the most recent literature on SLNB and LND in melanoma patients, new evidence-based results are now available which can contribute to answer to (and find consensus on) the

three main questions still pending: 1) How can we make surgeons more confident with indications to SLNB and Lymphadenectomy (in SN positive patients)? 2) How can we get them convinced that completeness of lymphadenectomy is an important issue?, and 3) are new, more convincing, evidence-based referral values for the minimum number of lymph node to be excised now available?

3.1. Indication to lymphadenectomy in SLNB positive patients

The role of completion lymphadenectomy (CLND) after positive SLNB remains uncertain as additional non sentinel nodes (i.e. identified within lymph node dissection after SLNB) have been identified in 9 to 25% of patients. This rate is probably underestimated because, unlike the pathologic protocols normally applied for SLNB specimens, those for therapeutic lymphadenectomy are routinely limited to bisecting lymph nodes without any immunohistochemical stains. Aimed at investigating the prognostic and therapeutic impact of CLND in sentinel positive nodes two prospective trials have been undertaken: The Multicenter Selective Lymphadenectomy Trial-2 (MSTL-2) and the MiniTub trial. The MSTL-2 trial randomized patients with at least one positive SLN to observation or CLND. MSTL-2, whose patient accrual was completed in 2014, was designed to verify the incidence of nodal recurrence after removal of positive SLN(s) without CLND, the incidence and predictors of additional lymph nodes in the SLNB basin after CLND and the survival impact of CLND in SLNB positive patients. The MiniTub trial is a prospective registry investigating the outcome of patients with a T2-T3 primary melanoma and minimal SN tumour burden treated with CLND or nodal observation. While waiting for the results of these important studies, other important scientific reports have recently appeared in the literature, supporting the indication for CLND. For instance, the strength of the indication for CLND in these patients has been recently increased by the long-term results of the MSLT-1 trial [1, 25] Despite the lack of survival benefit of performing SLNB in the whole group, in a sub-group analysis, which excluded the SLNB negative patients, the node positive patients with intermediate thickness melanoma showed a 21% higher 10-year survival compared to patients who underwent lymphadenectomy for metastases discovered during follow-up. Of note is that the mean number of tumour involved nodes was significantly lower in the biopsy group with respect to the observation group (1.4 versus 3.3, P>0.001) [25]. The therapeutic effect of immediate CLND over lymphadenectomy at the time of clinically evident disease in patients with microscopic disease is confirmed by an interesting study which shows that immediate CLND is associated with a 10-year survival of 60% compared to delayed lymphadenectomy (around 45%), despite patients with early lymphadenectomy presenting worse adverse prognostic factors [26]. Moreover, a meta-analysis of non randomized studies encompassing 2633 patients, demonstrates, in patients with clinically undetectable lymph node metastasis, a 20% survival benefit after with SLNB followed by CLND [27].

Another argument in favour of the appropriateness of CLND comes from the important observation that patients with <11excised nodes were not adequately staged [28]. Furthermore, in case of sentinel node positivity, non sentinel lymph node status has an independent prognostic value in melanoma patients. The value of this observation is re-inforced by a meta-

analysis suggesting the use of this new and easily reproducible prognostic factor as risk stratification criteria for clinical trials investigating adjuvant therapies and its inclusion in the future edition of the AJCC staging system [29]. Thus, not performing CLND in a SL positive patient today means lack of knowledge about his staging work-up, depriving him of important clinical information.

Taken together, all this information strongly supports that an early diagnosis of lymph node metastases (SLNB) and the removal of the affected lymphatic basin (CLND) can more effectively cure melanoma patients. Likely, some immunological events within the SL environment precede melanoma sentinel spread, suggesting that melanoma is preparing the sentinel lymph nodes to receive metastatic melanoma cells [30]. Removing SLNs and non sentinel LNs at an early stage, when probably the loco-regional immunosuppressive changes are not fully active, could explain in part the different prognostic impact of sentinel and non sentinel metastatic lymph node and opens the door to future investigations on the mechanisms of tumor response and on the immunological role of sentinel lymph nodes in melanoma.

3.2. Adequacy of lymphadenectomy and quality control

Although the extent of each LND is still argued, it has recently been demonstrated in melanoma patients that the so-called lymph node ratio (i.e. the number of positive lymph nodes over the total number of excised lymph nodes) is associated with survival [31-33]. Patients with low ratio present better prognosis independently of the number of the positive nodes, indirectly confirming the prognostic value of the number of lymph node removed during surgery. Moreover, a recent multicentric Italian study showed, in the largest caseload so far available, that patients who had a higher number of excised lymph nodes after lymphadenectomy have a better prognosis, independently of AJCC T stage, ulceration, LN tumor burden and N stage [28] (figure 3). A clear and univocal explanation of this data is not available. The association between the number of lymph nodes and prognosis can find different explanations; 1) more lymph nodes means a better immunological control of melanoma, 2) a more accurate patient staging of patients 3) a therapeutic role of more extensive surgery. The latter lends support to the hypothesis that a thorough lymphadenectomy might have a therapeutic effect in melanoma patients with lymph node metastases, in particular in those who underwent CLND for a positive SLNB with intermediate thickness primary tumour.

Once the need of a CLND in melanoma patients with lymph node metastases is accepted and the anatomical extent of a given procedure is established, how can we provide surgeons with parameters and referral values for QA? Unfortunately, shared parameters for QA of lymph node dissections for melanoma are still lacking, with the exception of the minimum number of retrieved lymph nodes, for which a general consensus seems to exist for its simplicity, reproducibility and comparability [4]. However, the benchmark values of this quality parameter (minimum number of lymph nodes for each dissected field) and the method to obtain these benchmark values are still matter of study. The minimum number values proposed in the literature are quite heterogeneous, reflecting the different method adopted for proposing it (table 1).
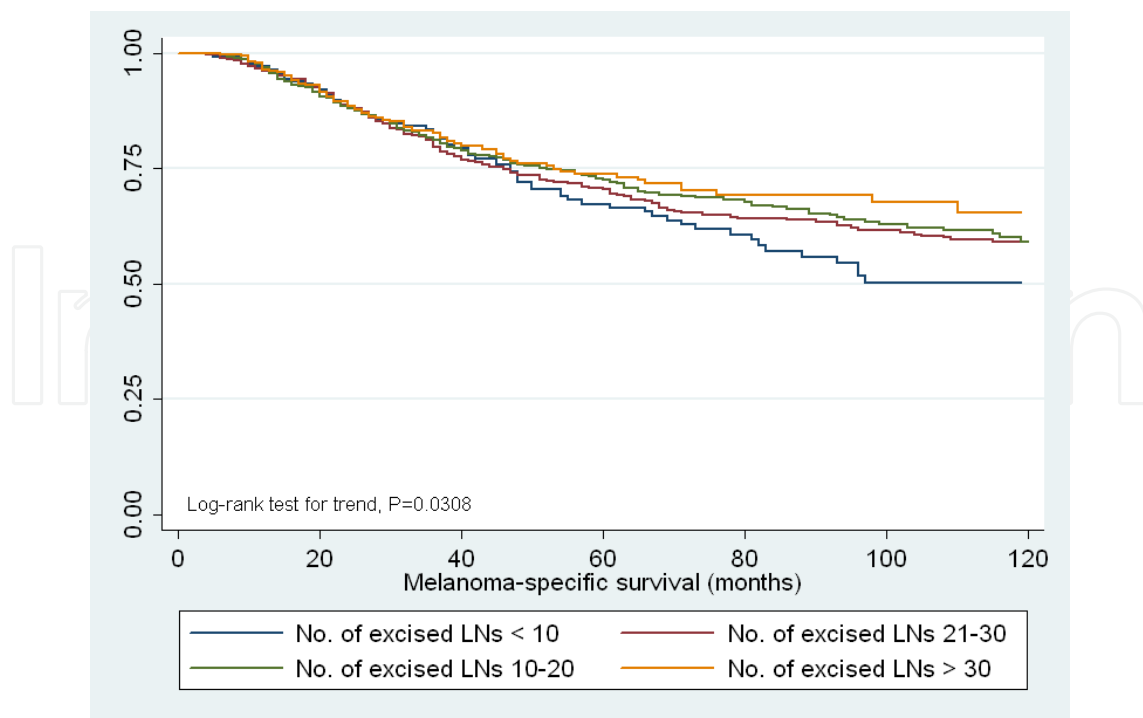
Figure 3. Patient survival according to the number of excised lymph nodes categorized as follow: ≤ 10 LNs, 11-20 LNs, 21-30 LNs and > 30 LNs. From IMI (Italian Melanoma Intergroup) caseload.

Reference	Method	Axilla	Neck		Groin	
			≤3 levels	≥4 levels	Inguinal	Inguinal and pelvic
Balch et al. [34]	Expert opinion	10	20	20	5	5
MSLT-2 [1]	Expert opinion	15	30		6	6
Eggermont et al [35]	Expert opinion	10	15	15	5	5
Galliot-Repkat et al. [36]	Survival analysis	10	10	10	10	10
Xing et al. [33]	Survival analysis	8	15		6	6
Billimoira et al. [37]	Expert opinion	10	15	15	5	5
Spillane et al. [38, 39]	10th percentile	10	6	20	7	14
Rossi et al. [40]	10th percentile	12	7	14	6	13
Rossi et al. [28]	Survival analysis	11	14		9	12

(above the table:) **Minimum number of excised lymph nodes**

Table 1. Minimum number values of excised lymph node for single lymphatic basin.

The most recently proposed cut-offs to deem a lymph-node dissection adequate are evidence-based (obtained by the 10th percentile/survival method) and come from two independent

caseloads: one from Australia [38, 39] and the other from Italy [28, 40]. As reported in table 1, the results are similar and should prompt surgeons (and pathologists) to adopt them as referral standards to measure their own performance, making a through revision of the procedure necessary when the reported numbers are below these thresholds. Another interesting evidence-based observation in this field comes from an already cited study which, besides a correlation between the absolute number of excised lymph nodes and survival, shows that, an adequate sub-staging of AJCC stage III melanoma patients is not possible below the cut-offs reported in the table [28] (figure 4).
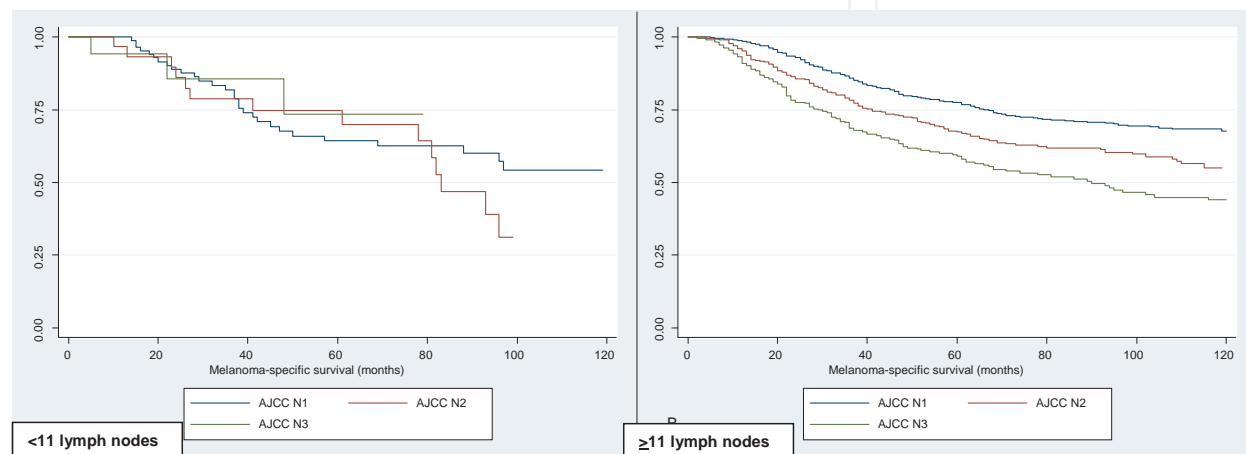

Figure 4. Loss of prognostic significance of AJCC TNM N substages according to the number of lymph nodes (< or > 11). From IMI (Italian Melanoma Intergroup) caseload.

The implementation of QA programs at institutional/multi-institutional levels needs to define other parameters for monitoring quality and the relative benchmark values. Beyond the minimum number of lymph nodes, complication rates and local recurrence rates have been suggested as QA parameters for lymphadenectomy in a recent national consensus [22]. In the near future, standardization and implementation of effective QA programs for major surgical procedures in melanoma should increase patients' standard of care as well as the likelihood of reliable results from clinical trials testing new treatments in the adjuvant setting.

4. Perspectives

4.1. Improving patient selection for SLNB and CLND

Almost 80% of patients who undergo SLNB do not harbor node metastases. Having no benefit from the procedure, they are considered to receive a surgical over-treatment. Moreover, SLNB represents a surgical procedure associated with a defined morbidity rate (10%) [41] and significant cost for the health care system [42]. For these reasons, a series of clinical pathological

variables associated with SLN status has been widely studied in the literature, but the statistical predictive power of each single factor on SLNB positivity remains poorly defined (table 2).

Breslow thickness
Ulceration
Mitotic rate
Lymphovascular invasion
Clarke level IV
Young age

Table 2. Factors associated with risk of metastases in sentinel nodes

The development of statistical predictive models which analyse independent variables seems able to spare an unnecessary SLNB in between 18 to 30% of cases with an estimated error rate (i.e. patient with sentinel negative prediction even if they are sentinel positive at pathological examination) of 0.5-2.1% [43]. However, these tools need to be tested and validated in prospective studies and eventually implemented in the clinical setting. On the other hand, new markers of biologic behaviour can overcome and define the metastatic phenotype in primary melanoma and quantify the true risk of nodal metastases, but additional studies are needed to identify a subgroup of patients (in particular for thin melanomas) with defined clinical-pathological parameters at risk of SL positivity.

Identification of clinical and pathological parameters predictive of non sentinel nodes positivity represents a crucial point to improve selection of patient candidates for CLND, as it is possible to spare un-necessary CLND in a defined quota of patients [44]. Several predictors of additional non-sentinel positive LNs have been identified, including those associated with primary tumor (i.e., melanoma thickness) or sentinel nodes (i.e. metastatic burden) [45, 46]. For instance, in patients with thin melanoma, the risk of additional lymph nodes in CLND is calculated 0.1% suggesting that the potential benefit of lymph node dissection after SLNB in this group should be balanced with the morbidity of CLND [47]. Histo-pathological parameters reflecting the pattern and amount of melanoma involvement in the SNs and the related risk-assessment systems able to predict the risk of additional non sentinel lymph node metastases in CLND are reported (table 3).

As well as for predictors of SL positivity, these parameters need to be validated prospectively, and the ongoing research on new biological markers might predict the pathological status of the additional nodes, even more precisely in the near future.

4.2. Lowering the false negative rate of SLNB

The false negative rate (FNR) of SLNB probably represents the most important drawback for this procedure. The values reported in literature are wide ranging between 8.6 and 21% [10]. The main reason for this variability resides in the different methods to calculate this proportion after SLNB. In the past, many authors have erroneously considered the FNR as the ratio between the FN cases and the truly negative plus the truly positive instead the of truly positive

Systems	Parameters
Rotterdam system [48]	dimension of tumour deposit
Starz classification [49]	tumor penetrative depth
Hannover Scoring System (Hannover-II) [50]	dimension of the greatest deposit, tumor penetrative depth involvement of the capsula
Non-Sentinel Node Risk Score (N-SNORE) [51]	sex regression, proportion of harvested SNs maximum size perinodal lymphatic invasion
Rotterdam-Dewar Combined criteria (RDC) [52]	dimension of tumour deposit microanatomic location

Table 3. Risk assessment systems of Non-SLN involvement

plus false negative and, only recently, a standard definition has been adopted [53]. However, a recent meta-analysis shows a FNR of 12.5% [10]. This means that considering melanoma patients harbouring node metastases, approximately one out of ten of these patients has a negative SLNB. Furthermore, FNR tends to increase with the duration of follow-up and the quality of the study and is inversely correlated with the identification rate. Reasons for FNR after SLNB can involve different specialists at different steps of the SLNB procedure; lympho-schintigraphy evaluation (nuclear medicine physician), lymph node detection during surgery (surgeon) and node's pathological examination (pathologist) [54]. The number of peri-tumoral injection seems to influence the outcome of lymphoscintigraphy but controlled studies are needed to confirm the real impact on FNR [9]. Failure in lymphoscintigraphy interpretation has been demonstrated to lead to in one third of false negative results after SLNB [54]. One third of cases, a FN result is explained by the failure of surgery to remove all the nodes identified at pre-operative lymphoscintigraphy, especially in neck and groin lymphatic basin. It should be noted that the ratio of marked on lymphoscintigraphy and excised sentinel lymph nodes is equal in only 38% of patients who underwent SLNB and that 20% of patients have fewer lymph nodes removed then those marked during lymphoscintigraphy [55]. FNR after SLNB seems higher in head and neck melanomas, confirming a greater complexity of SLNB in this body district, mainly for the proximity of primary tumor and lymphatic basin, the complexity of lymphatic drainage of neck and the higher risk of complications [56]. Moreover, a lack of standardization exists between centres on the threshold beyond which radioactivity of residual lymph nodes should indicate their excision. The 10 % rule (i.e., SN defined as all the lymph nodes with >10% radioactivity of the hottest SN removed) was proposed as standardization criteria and it was demonstrated to be able to reduce the rate of missing positive nodes, but a clear consensus on this is still lacking and further research is needed in this field [57, 58].

Pathologists can also contribute to FNR. In fact, the most appropriate pathologic protocol for SN examinations is still a matter of discussion. The number of sections to be stained and the optimal distance between them can significantly influence the metastases detection in SNs.

Two main protocols have been popularized which seems to reach an acceptable compromise between diagnostic accuracy and costs [59, 60]. Although some evidence suggests that ultra-staging with polymerase chain reaction (PCR) of SNs represents an appealing prognostic tool and seems to improve melanoma cell detection in SNs, the clinical and prognostic value of molecular biology-based detection of melanoma cells in SNs needs to be further verified and supported by additional investigation in this field [61]

4.3. Videoscopic approach to lymphadenectomy

Fear of complication often influences surgeons' and patients' decision on whether or not to perform a lymphadenectomy in melanoma patients. Thus, to reduce morbidity is an important issue for surgical oncologists and for this purpose video-assisted surgery has recently been proposed for lymph node dissection. Considering the principal lymphatic basins, groin is indubitably associated with the greater incidence of wound complications. Wound infection, dehiscence/necrosis and seroma/lymphocele after traditional lymphadenectomy ranges between 15-55, 7-53 and 2-46%, respectively [62]. Videoscopic lymphadenectomy (VL) of the groin appears to be a promising tool in lowering the incidence of wound complication. Inguinal and iliac-obturator VL consists of two different surgical times. The inguinal part is performed using three trocars, placed at a variable distance from the apex of the femoral triangle (figure 5).
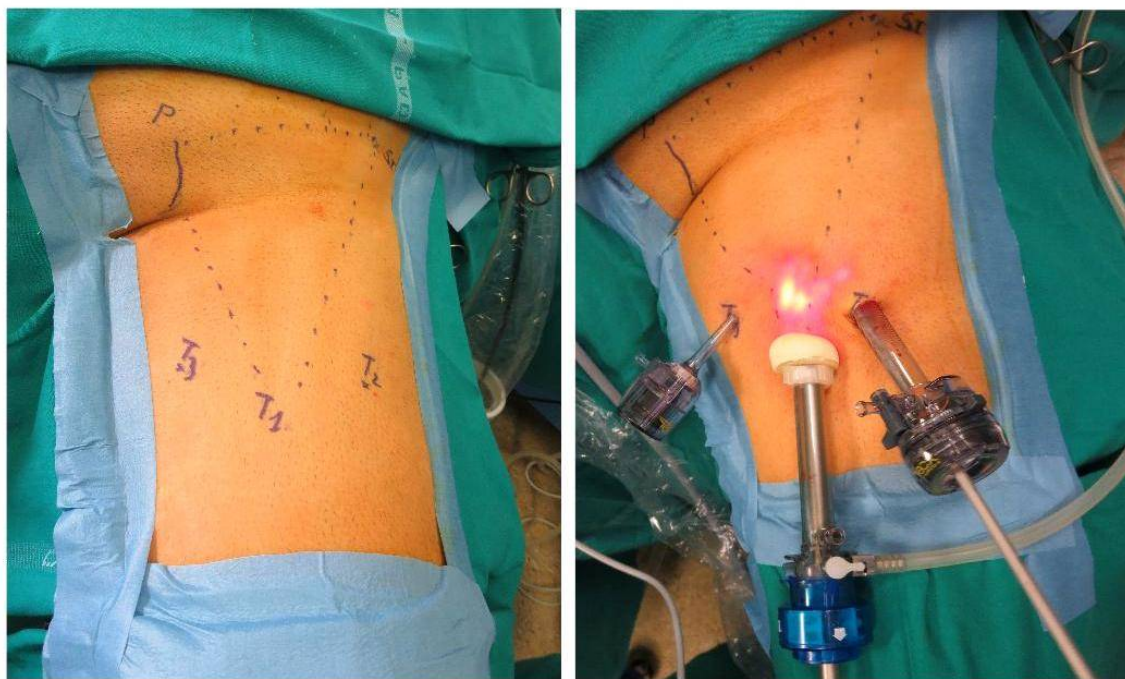

Figure 5. Trocar position for inguinal lymphadenectomy VL.

The working space is obtained after a skin incision and blunt dissection of the area under the Camper fascia. The creation of a working space using high pressure CO_2 levels (25 mm/Hg) at the beginning of the procedure make dissection easier. The saphenous vein is generally

sectioned with endostaplers or endoclips. Removal of the surgical specimen is performed using endobag.

For iliac and obturator VL (figure 6), the access is extraperitoneal with the first trocar being placed infraumbilical and two trocars between the umbilicus and the pubic symphysis.
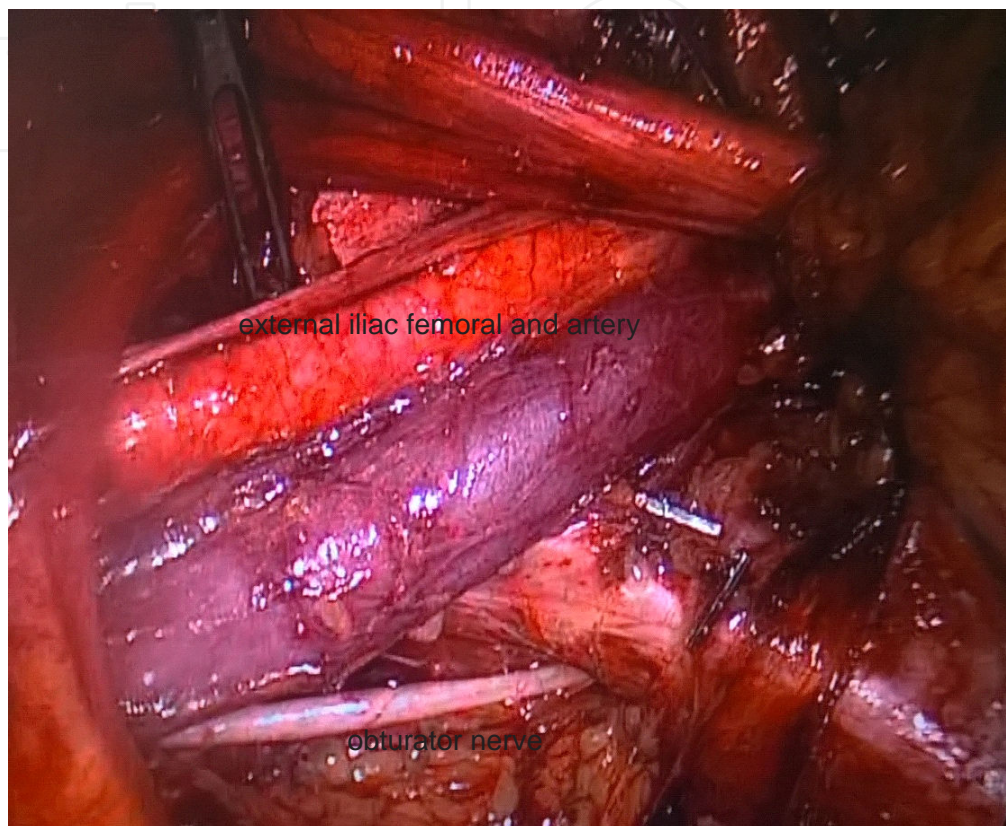

Figure 6. Intraoperative view of iliac and obturator VL

The greatest advantage of VL is probably the virtual elimination of inguinal incision and (in case of iliac lymphadenectomy) the avoidance of the parietal abdominal muscles section. This potentially leads to a significant reduction of the post-operative wound related morbidity and pain. In one uncontrolled comparative study, the incidence of complications (infection and wound dehiscence) was significantly lower after VL (47.5% versus 80%, P=0.002) [63]. In another comparative study, although the incidence of infection and wound dehiscence was not statistically different after VL compared to open lymphadenectomy, in the open group wound infections appear more serious, requiring hospital readmission and intravenous antibiotics in five of the eight patients (62 %) [64]. Although the experiences are limited and the level of evidence is low, VL for melanoma is technically feasible, seems associated with a lower post-operative morbidity profile with comparable oncological outcomes (i.e. number of excised lymph nodes, loco-regional recurrence) (table 4). Before VL becomes suitable for routine clinical practice, the lower post-operative morbidity and safe oncological profile shown in retrospective and prospective series needs to be investigated within prospective RCTs.

	Videoscopic Lymphadenectomy	Procedures (N)	Conversion rate (%)	Wound complication rate (%)	Lymph node excised (N)	Local recurrence rate (%)
Trias M, et al [65]	Iliac	12	0	16.7	10.2	Not reported
Schneider C, et al [66]	Iliac	31	0	9.7	4.6	9.7
Abbott AM, et al [64]	Inguinal	13	7.7	1.8	13	Not reported
Martin BM, et al [63]	Inguinal	40	10	15	12.6	2.5
Sommariva, et al. [unpublished data]	Inguinal and Iliac	24	16.5	4	20.4	0

Table 4. Summary of results on videoscopic groin lymphadenectomy for melanoma

5. Conclusion

Even in the present exciting era of discovering new drugs to cure patients with advanced melanoma, surgery still represents the most performed and effective treatment for this potentially lethal disease. Nevertheless, the effort to solve many controversies related to this important subject has been so far insufficient and the ongoing clinical practice guidelines often lack clear indications for an adequate clinical approach, in particular dealing with patients at high risk for or with lymph node metastasis. While waiting for the conclusion of the ongoing controlled clinical trials (MLST-2 and MiniTub), surgeons should look for new evidence based results strengthening support for indication of SLNB and lymph node dissection, completeness of the latter and QA parameters on which the surgical performance should be measured.

Indication to SLNB is accepted almost everywhere as a staging procedure. Moreover, a recent meta-analysis of retrospective studies and the last report on the long-term results of the MLST-1 controlled trial reinforce its curative value in patients with positive nodes who undergo immediate CLND. In perspective, a more precise patient selection, based on valida-tion new statistical tools and/or identification of new molecular markers, and lowering its false negative rate might improve its efficiency and make this procedure even more appealing.

At present, LND represents the most controversial subject in the surgical treatment of mela-noma, particularly in SN positive patients. Its indication can be further warranted by, besides the long-term results of the MLST-1, the demonstration of its essential role as staging proce-dure. A recent study shows that below the threshold of 11 excised lymph nodes an accurate sub-staging is impossible, and another one demonstrates that the status of the additional lymph nodes is an independent prognostic factor in stage III melanoma patients. These evidence-based results also prompt for their inclusion in the surgical QA process (the former), and in the forthcoming melanoma staging system (the latter). Even if the extension of each lymphadenectomy is still a matter of discussion, further evidence has been recently added to the need of its completeness, such as the demonstration that the lymph node ratio and the

absolute number of excised lymph nodes are independently associated with survival. As for other solid tumours in which LND has an impact on staging and survival, melanoma surgeons are in search of simple and reproducible parameters to deem the procedure adequate. The minimum number of lymph nodes to be excised seems to meet this requirement, and the reproducible numbers provided as benchmark values by the 10th percentile method, for each type of LND, are likely to make this parameter the most reliable. Looking at the future, statistical tools and molecular markers for a better patient selection, randomized trials for devising the LND extent, and the mini-invasive surgical approach to reduce the fear of complication and improve patients' quality of life, will probably fulfil the present lack of knowledge and make surgical treatment of melanoma more standardized and cost-effective. Nevertheless, since now surgeons can be helped by the new evidence-based results in the difficult process of building consensus on some important issues in melanoma surgery.

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