



Surgery for Metastatic Melanoma: an Evolving Concept

Alessandro A. E. Testori¹ · Stephanie A. Blankenstein² · Alexander C. J. van Akkooi²

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Abstract

Purpose of Review This review describes the evolving role of surgery in stage III and IV melanoma.

Recent Findings Surgery has been the first option to cure melanoma patients at initial diagnosis of metastatic spread: a complete surgical excision of the disease either in stage III or IV has been the gold standard for decades. A positive sentinel node biopsy (SNB) has been followed by a complete lymph node dissection (CLND) since the early stages of modern surgical oncology. However, since two randomized trials have indicated that a CLND does not improve survival in patients with a positive SNB, a CLND is no longer considered mandatory. A therapeutic lymph node dissection (TLND) is still offered to patients with macroscopic nodal disease and in highly selected cases, patients with distant melanoma metastases can be treated surgically as well. Also the availability of adjuvant, and in the future possibly neoadjuvant, systemic therapy have shifted the landscape to less extensive surgery in metastatic melanoma.

Summary With the development of new systemic options, surgery in metastatic melanoma has become more and more part of a multidisciplinary treatment: surgical indications are moving from previous standards to a new role.

Keywords Melanoma surgery · Sentinel node biopsy · Lymph node dissection

Introduction

Surgery is an effective therapy for melanoma, but its indication is moving to a multidisciplinary pathway of treatments in combination with targeted and immunotherapies. This paper will go through the surgical indications and surgical technical procedures for the different clinical presentations for nodal, in-transit, and distant metastases, introducing the concepts of when to propose surgery versus locoregional or systemic therapy. Similar to the medical treatment approvals, decisions in the surgical field were driven by academic phase III trials: interestingly, no surgical trial has ever demonstrated that the comparison of a more “aggressive” surgical approach has

been found more effective compared with a more conservative indication in the treatment of locoregional disease.

Indications for Completion and Therapeutic Lymph Node Dissections

The original hypothesis developed by Morton and colleagues was based on the observation that patients with macroscopic nodal involvement had more involved lymph nodes and a worse prognosis. They hypothesized that early identification of limited microscopic disease by the sentinel node (SN) followed by completion lymph node dissection (CLND) for SN+ disease would prevent further spread and thus improve survival. The first prospective randomized controlled trial investigating this concept was the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I). The MSLT-I trial randomized patients between wide local excision (WLE) plus SN or WLE plus nodal observation (60:40). This trial failed to demonstrate a 5-year melanoma-specific survival benefit for the SN group (87.1% in the SN group vs. 86.6% in the observation group, $p = 0.58$) [1, 2, 3*]. Although the subgroup analysis seemed to indicate a potential benefit for the SN+ group, this subgroup analysis was however heavily criticized

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✉ Alessandro A. E. Testori
info@alessandrotestori.it; a.testori@smatteo.pv.it

¹ Dermatology, Fondazione IRCCS Policlinico San Matteo, v.le Golgi 19, 27100 Pavia, Italy

² Department of Surgical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands

[4, 5]. It might have been that not the SN but the CLND was the therapeutic part of the procedure and therefore the MSLT-I study did not have sufficient N+ patients to show any benefit, thus the MSLT-II and DeCoG-SLT trials were designed on that targeted SN+ disease. Both these trials randomized SN+ patients to either CLND or nodal observation by periodic ultrasound. Neither of these two studies demonstrated any survival benefit and since then have radically changed guidelines: sentinel node (SN)-positive patients are no longer proposed to undergo a routine CLND [6, 7••].

This is also based on advances in adjuvant treatment of N+ melanoma, with both immune checkpoint blockade and BRAF/MEK inhibitors. The first adjuvant therapy showing a clear recurrence-free survival (RFS) and overall survival (OS) benefit was high-dose ipilimumab (10 mg/kg), which was compared with placebo in the EORTC18071 trial, but was accompanied with high rates of severe toxicity [8, 9]. Subsequently, ipilimumab was bypassed by more recent results of anti-PD-1 agents nivolumab and pembrolizumab. In the Checkmate 238 study, nivolumab showed a significant benefit of 10% in RFS at 12 months over high-dose ipilimumab, with much lower severe adverse event rates (14.4 vs. 45.9%) [10]. The EORTC 1325 randomized patients to either pembrolizumab or placebo, with 1-year RFS rates of 75.4 vs. 61.0% respectively [11•]. In BRAF-mutated patients, also adjuvant BRAF and MEK inhibitors dabrafenib and trametinib are available, since the COMBI-AD study showed a significant RFS benefit with a 3-year RFS of 59% (95% CI, 55 to 64%) in the dabrafenib and trametinib arm and 40% (95% CI, 35 to 45%) in the placebo arm (HR, 0.53; 95% CI, 0.42 to 0.67) [12, 13].

Other reasons that have been proposed to continue the practice of early CLND include local control, staging, larger SN tumor burden (> 1 mm) and head and neck location. Although CLND does improve local control, it is still unnecessary in over 80% of patients (as shown above) and these patients do get exposed to the possible complications (lymphedema was observed in 24.1% of patients in the CLND group and in 6.3% in the observation group of the MSLT-II trial, $p < 0.001$) [6]. One could also argue that additional information on staging is missed when no CLND is performed, but studies by Verver et al. and Madu et al. showed that although in 11.6% of patients additional positive non sentinel nodes were found at CLND, upstaging in AJCC stage was seen in only 5.9% and 5.8% respectively [14, 15]. In patients with a SN tumor burden of > 1 mm, chances of distant metastases by hematogenous spread are substantial, demonstrated by the forest plot subgroup analysis in appendix of MSLT-II, favoring observation over CLND in this group. Rather than adjuvant surgery, choosing adjuvant systemic therapy for SN tumor burden > 1 mm should be preferred. In the MSLT-II trial, a trend favoring CLND was seen in the subgroup of head and neck localization. However, this represents only a very small subgroup

of the total study population with melanomas in this localization, causing a very large confidence interval due to this group being heavily underpowered and the result was also not statistically significant [6].

In other words, the alternative reasons for proposing to continue the routine practice of CLND for SN+ disease seem weak. Rather than adjuvant surgery, high-risk SN+ disease should be offered adjuvant systemic therapy. However, if patients develop a locoregional recurrence, then a delayed CLND would be appropriate to perhaps salvage cure and for optimal local control.

A therapeutic lymph node dissection (TLND) is still proposed to patients developing macroscopic (palpable or imaging detected) nodal metastases. In this population, however, chances of distant progression are substantial and perhaps the probability to offer a real benefit by LND is low [16]. TLND on macroscopic N+ patients is standard of care for the great majority of countries: in the future, it could be proposed to do a selective nodal excision of clinically evident positive nodes followed by adjuvant systemic therapy. Certainly, in the near future, neoadjuvant approaches will bring higher efficacy and lower morbidity than extensive surgery alone.

Both neoadjuvant immunotherapy and BRAF-directed therapy have shown promising results. In two studies, BRAF mutant patients were treated with neoadjuvant dabrafenib and trametinib, in both studies achieving high complete pathologic response rates (49% and 58%) [17, 18]. All patients were also treated with adjuvant therapy, to complete a total of 1 year of treatment, which might be necessary to achieve a durable survival effect. Also, multiple trials have been conducted with neoadjuvant immunotherapy. Combination therapy with ipilimumab 3 mg/kg and nivolumab 1 mg/kg showed pathologic response rates up to 80%, but at a cost of severe immune-related toxicity (grade 3/4 adverse in 90% of patients) [19, 20]. Fortunately, the Opacin-neo study identified the less toxic, but similarly effective schedule of ipilimumab 1 mg/kg and nivolumab 3 mg/kg (overall response rate 77%; grade 3/4 toxicity 20%) [21•]. An extension cohort of this trial, the PRADO study, is currently investigating whether surgery can be less extensive after neoadjuvant treatment. Only the marked index node is removed and in patients with a pathologic complete response no TLND is performed. TLND is still performed in case of a pathologic partial response or no pathologic response and, in patients without a response, adjuvant therapy is added to the TLND [22].

Lymph Node Dissection Techniques (Axillary, Inguinal-Iliac-Obturator, Popliteal, Epitrochlear)

Lymph node dissections are the most specific surgical procedures in melanoma patients. The basins most frequently involved are the neck, the axilla, and the groin. Few patients experience the possibility of unusual metastatic deposits in the

popliteal fossa or in the epitroclear or other “in-transit” regions. The goals to be reached by a surgical oncologist approaching the spread of melanoma to locoregional sites are to be radical, firstly, and secondly to be as less invasive as possible. The two goals are not incompatible: a scientific discussion is ongoing on the definition of what can be considered the standard of care for these patients.

The classic surgical procedure indicates to perform a lymph node dissection of the 5 levels of nodes of the neck, of the 3 levels of the axilla and of the superficial inguino-femoral and deep ilio-obturator nodes [23]. In the neck dissection, the parotid gland is only included into the specimen when a primary melanoma originates from the face or the scalp between the orbital and the mastoid regions. But not all surgeons proceed with the dissection of the five levels of nodes if the metastatic ones are very far, like performing the conservation of the submental mandibular (level I) nodes when the metastases lie in the posterior triangle (V level) nodes.

The same concept can be proposed in the groin dissection: the ilio-obturator nodes are not excised by all surgeons in patients with macroscopic nodal metastases, since multiple studies showed that combined superficial and deep groin LND does not increase the prognosis of patients compared with superficial groin LND alone, in patients without risk factors. These risk factors include positive deep pelvic nodes on imaging; high number of positive inguinal nodes; and extracapsular extension and high lymph node ratio (LNR) [24–27]. LNR is defined as the proportion of tumor-positive lymph nodes in the total of removed and examined lymph nodes. This was studied and found to be a prognostic factor in patients included in the EORTC 18871, 18952, and 18991 [28]. The currently accruing EAGLE trial randomizes patients without positive pelvic nodes on PET/CT between inguinal or ilio-inguinal lymphadenectomy [29]. The question is if this trial will be able to show any impact now that these patients will be offered adjuvant systemic therapy.

So, a more extensive groin LND does not seem to influence prognosis in most patients, but it does increase the morbidity of the operation. This is mainly true for the short postoperative term, especially if the approach is through an open surgical procedure, as using a robotic assisted approach the recovery is faster. However, lymphedema represents the most common long-term morbidity of this procedure, and it is identical whether a dissection is limited to the groin or extended to the pelvis [27]. Data on robotic assisted surgery suggests that it reduces the rate of long-term postoperative lymphedema. On the contrary, avoiding the pelvic dissection may compromise a precocious diagnosis of possible enlargement of pelvic nodes and a delayed recognition of bulky nodes can result in a more difficult surgical approach. The reduction of node levels of excision from the axilla (i.e., 2 of the 3 levels) has never been found as a concrete proposal as no difference in the (low) lymphedema rate has been described as a result of such an indication.

Surgery of Locoregional Recurrences and In-transit Metastases

Local Recurrence/Satellitosis

Historically, a satellite lesion was defined as a skin involvement within 2 cm from the primary tumor. The most recent classifications are putting all together microsattelites, satellites, and in-transit, since characterized by similar poor prognosis, in a unique form of involved melanoma lymphatic spread into the surrounding lymphatic channels (stage III), and should be treated similarly when lesions are clinically visible [30–32].

In-transit Metastases

In-transit metastases (ITM), i.e., cutaneous or subcutaneous melanoma lesions between the primary tumor and the regional lymph node basin, constitute a significant challenge. Resectable in-transit recurrences should be treated surgically with clear margins (no wide excisional margins are proven beneficial), but amputation is not indicated and does not improve survival. In case of a recurring in-transit lesion, re-excision is possible as long as it is technically feasible. With multiple lesions, carbon dioxide laser ablation can be used, but the recurrence rate is very high and this technique is limited to lesions smaller than 1 cm in diameter. Other local/locoregional modalities including radiotherapy, cryotherapy, intralesional injections, hyperthermic isolated limb perfusion (ILP), and electrochemotherapy may be used in specific situations [33–36].

ILP with melphalan and preferably with tumor necrosis factor (TNF) α is a technique widely used in case of multiple in-transit metastases of the extremity [37]. Many studies have demonstrated high efficacy of this procedure for local control of in-transit metastases [38–45]. The technical variation of this procedure is the isolated limb infusion (ILI) as originally proposed by Australian investigators [46]. Both techniques (ILP and ILI) can be repeated in selected cases [43].

Electrochemotherapy (ECT) is a treatment modality for cutaneous and subcutaneous metastases of numerous tumors, including melanoma. ECT increases antitumoral efficacy by combining chemotherapy with electroporation, which increases cell membrane permeability and hence drug uptake. ECT can be proposed in case of in-transit or distant cutaneous or soft tissue metastases, both on the body trunk or on limbs. It has shown a high success rate after a single session, obtaining valid local control with minimum damage to healthy tissue. Other advantages are the lack of protein denaturation, so that tumor antigens are not destroyed and may elicit an immune response; the excellent safety profile and favorable cost/benefit ratio [47–51]. The appearance of widespread cutaneous and subcutaneous tumor nodules is a distressing

situation for many patients with advanced melanoma, causing an unfavorable impact on the quality of life, which has been shown to improve in patients treated with ECT [52].

Another, more recently developed, locoregional treatment is oncolytic viral immunotherapy with talimogene laherparepvec (T-VEC). This modified herpes simplex virus is administered intralesionally and has shown promising results. In the OPTIM registration trial, an overall response rate (ORR) of 26% was reported and in a more selected patient population an even higher ORR was seen [53]. Two groups have described real world data on the use of T-VEC, with ORR of 56.5–88.5% with 43.5–61.5% of patients achieving a complete response. In the study reported by Franke et al., only early metastatic melanoma patients (stage IIIB/C-IVM1a) were treated and similarly in the study by Perez et al., the majority of the patients (81.5%) had unresectable stage III disease [54, 55]. So this appears to be an effective treatment, especially in patients with multiple and/or recurrent ITM. Also, this treatment is well tolerated and can be used in frail patients.

For patients with unresectable stage III, also new systemic options are available, but no studies have been conducted to compare the different traditional locoregional therapies to intralesional therapy or systemic therapy. Immunotherapy and targeted therapy have clearly shown to be effective in advanced disease, but the same is true for locoregional treatments in ITM. The difficult decision is which approach to choose first. It is important to discuss the different options with the patients: for ITM, you may offer both local therapies or systemic, while in distant disseminated disease only systemic therapies can be offered. If you have already treated a patient with in-transit disease with systemic therapies, these are no longer available in case of distant progression.

Surgery for Distant Metastases

Stage IV metastatic melanoma, as for other tumors, is the phase of the disease with distant metastases. Melanoma metastasizes most frequently to the liver, lung, brain, small bowel, and bones. Unfortunately, survival in this stage of the disease is very low, but has improved over the last decade due to new systemic therapies. With immune checkpoint inhibitors and targeted therapy, long-term favorable results can be reached in up to 30–40% of patients. However, a mean OS of a few months will be found in the non-responding patients [56–58]. One study described by Howard et al. compared surgery or surgery combined with systemic therapy to systemic therapy alone and showed a survival benefit in the surgery group. However, this study was conducted in 2012, in the era before systemic immunotherapy and BRAF/MEK inhibitors were available [59].

Since visible distant metastases may only be a tip of the iceberg and micrometastases are very likely to be present,

currently systemic therapy is preferred in most patients. However, in some patients, surgery may play a role within the treatment, after discussion in a multidisciplinary board. For example in patients who develop oligometastases after a long follow-up (>2–3 years from stage I, II, or III), surgery followed by adjuvant therapy could be proposed [60]. Sosman et al. showed in a prospective trial that in selected patients surgery was feasible, with a median RFS of 5 months (95% CI 3–7 months), median OS of 21 months (95% CI 16–34 months), and the possibility to repeat surgery in relapsed patients [61]. Additionally, a new role for surgery may have arisen especially in patients with a good response to systemic therapy. Bello et al. found that surgery after immunotherapy was beneficial in a selected population of patients who had a measurable response and could undergo complete resection [62]. Similarly, Puza et al. showed that patients with an oligoprogressive disease and a mixed response after immunotherapy may benefit from surgery [63].

If surgery is performed, the most typical resections are of single, easily accessible cutaneous, and subcutaneous nodules, but also visceral lesions can be excised. The most important goal to be reached is that the tumor is completely excised, i.e., R0 (the term “radical” cannot be formally proposed in IV stage melanoma patients) and that the quality of life of the patient is not deeply compromised for a long period (in relation to the average life expectancy of less than 1 year if the drugs now available might not be effective).

Palliation can also be an indication to perform surgery, but this is a case by case discussion. Often, the decision is based on clinical dilemmas such as pain, bleeding, or bowel obstruction, but this is less involved in a general strategic discussion on which approach is indicated first.

The modern approach is to expose patients to systemic therapy first and in case of a complete response, no surgery is required. In case of progressive disease mostly characterized by multiple lesions, surgery is not of benefit and patients may require subsequent second-line systemic therapy. Only in the case of stable or partial response and (residual) oligometastatic disease or oligoprogression surgery may be of benefit.

Conclusions

Surgery was often the only option for advanced melanoma patients in the twentieth century, but the discovery of new systemic immunotherapy and targeted therapy has shifted the landscape. Surgery is now more and more a part of a multidisciplinary treatment in patients with stage III and IV melanoma.

The role of the sentinel node (SN) and completion lymph node dissection (CLND) has evolved. SN should be considered standard of care for staging, but neither SN nor immediate

CLND for SN+ disease improves survival. SN+ disease with > 1-mm SN tumor burden should be offered adjuvant systemic therapy rather than adjuvant surgery. If patients recur during or soon after adjuvant systemic therapy, and recurrence is solely confined locoregionally, then these are the appropriate patients that might benefit from a, delayed, CLND.

In patients with palpable lymph node metastases, LND is still standard of care, but this will probably evolve into a less invasive approach as positive results of neoadjuvant trials in this population are arising.

In stage IV disease, the evolving treatment modalities are identifying a new population of patients who could benefit from a surgical indication: patients in partial response (PR) or oligoprogressive after a systemic treatment who could be rendered R0 with a relatively minimal invasive surgical approach.

To conclude, the indication for surgery is evolving in melanoma patients. From the milestone of available treatments in all stages, it is becoming a piece of a mosaic where none is essential but all are required to design the best strategy to offer to cure melanoma patients.

Compliance with Ethical Standards

Conflict of Interest Alessandro A.E. Testori declares that he has no conflict of interest.

Stephanie A. Blankenstein declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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63. • Puza CJ, Bressler ES, Terando AM, Howard JH, Brown MC, Hanks B, et al. The emerging role of surgery for patients with advanced melanoma treated with immunotherapy. *J Surg Res*. 2019;236:209–15. **This study is exemplary for the evolving role of surgery in stage IV melanoma in the era of new systemic therapies. Patients with remaining lesions of a partial response or mixed response/oligoprogression might benefit from surgery.**

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