Management of Regional Nodal Melanoma

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KEYWORDS

• Melanoma • Lymph nodes • Locoregional disease • Lymphadenectomy
• Nodal observation • Neoadjuvant/adjuvant therapy • Multidisciplinary care

KEY POINTS

- Complete nodal dissection is standard of care for clinically apparent nodal disease (with no evidence of distant metastases) along with consideration of adjuvant or neoadjuvant systemic therapy or enrollment in a clinical trial.
- Two prospective, randomized controlled trials show no significant benefit to performing a completion lymph node dissection (CLND) in sentinel lymph node–positive melanoma patients.
- Observation with ultrasound and clinical examination is an acceptable management strategy for sentinel lymph node biopsy–positive melanoma patients after consideration of patient-specific risks and benefits of forgoing CLND.
- The management strategy for regional nodal melanoma is evolving as ongoing investigations are being done with neoadjuvant and adjuvant therapies.

INTRODUCTION

Melanoma is the fifth most common cancer in the United States and one of the few with an increasing incidence. In fact, the rate of new melanoma diagnoses has been rising an average of 1.4% each year.[1] Although melanoma has historically been primarily a surgically treated disease due to poor systemic treatment options, recent advances in treatment with effective immunotherapy and targeted therapies have led to improvements in survival.[2–7] Along with these advances, the management of regional nodal melanoma has changed substantially.

The key management of clinical stage I and II melanoma remains primarily surgical in nature, with wide excision and sentinel lymph node biopsy (SLNB) for T1b or greater melanomas.[8] Nodal status continues to be the most informative prognostic factor for patients with clinically localized melanoma[9] and level I evidence demonstrates

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improved recurrence-free survival with SLNB than with nodal observation alone (no SLNB).[10] Following a positive-SLNB, completion lymph node dissection (CLND) had been the standard recommendation, but practice started to change, favoring observation and expectant management even before the data from 2 pivotal, prospective multi-institutional randomized controlled trials (RCTs) comparing CLND with observation demonstrated no statistical difference in survival endpoints at 3 years.[11–14]

With the changing landscape of melanoma management, including recent encouraging clinical trial results for neoadjuvant and adjuvant therapies for stage III melanoma,[15–17] it is imperative to have a good understanding of when and why to use a surgical approach to lymph node management.

EXTENT OF DISEASE

Regional nodal disease may present in patients as clinically occult, microscopic disease in the setting of a positive-SLNB, or as macroscopic disease in the setting of clinically evident, palpable or radiographic-detected lymph node(s). Given the high risk of distant metastatic disease in these patients,[18] it is essential that a thorough staging workup be done to evaluate for stage IV disease before making treatment decisions. In patients whose disease is limited to the nodal basins, their management differs based on whether they have microscopic or macroscopic disease.

Microscopic Disease

Until recently, the standard of care for patients found to have a positive-SLNB had been CLND of the involved nodal basin. This was based on the knowledge that about 15% to 20% of patients who undergo CLND will have additional nonsentinel lymph node (NSLN) disease, which is associated with poorer prognosis.[19–22] However, the clinical benefit of CLND had been increasingly questioned and there was evidence that CLND had been avoided in a high proportion of patients.[14,23–27] A recent meta-analysis of published retrospective studies and 2 RCTs looked at outcomes of observation versus CLND in the SLNB-positive population. Following a systematic review of the literature, 11 retrospective studies and 2 RCTs were found to have acceptable quality for inclusion in a meta-analysis. This included data from 8778 patients, 5895 of whom underwent CLND and 2883 who did not. Using event data and both locoregional and distant recurrences, meta-analysis showed no significant recurrence benefit for CLND compared with observation (risk ratio 0.91, 0.79–1.05; I^2 = 54%) (**Fig. 1**).[28] Additionally, there was no statically significant difference in survival between the 2 groups (risk ratio 0.85, 0.71–1.02, I^2 = 59%).[28]

When evaluating nodal recurrence rates, a higher incidence is expected in patients who undergo observation compared with CLND due to the known NSLN positivity rate found at the time of completion dissection.[19–21] Indeed, this was seen in the Multicenter Selective Lymphadenectomy II (MSLT-II) RCT with a rate of nodal recurrence 69% lower in the dissection group than in the observation group (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.24–0.41; P<.001), and just reached statistical significance in recurrence-free survival (RFS) (68% $\pm$ 1.7% in the CLND group and 63% $\pm$ 1.7% in the observation group; P = .05) with a median follow-up of 3.5 years.[11] In the Dermatologic Cooperative Group – Selective Lymphadenectomy (DeCOG-SLT) RCT, regional nodal recurrence was seen in 10.8% of patients who underwent CLND and 16.3% of those who were observed (not reported to be statistically different). Yet, the 5-year RFS rate was similar at 59.9% and 60.9%, respectively (HR 1.01, 90% CI 0.80–1.28; P = .94) with a median follow-up of 6 years. Interestingly, the DeCOG-SLT data now show that there may be less prognostic

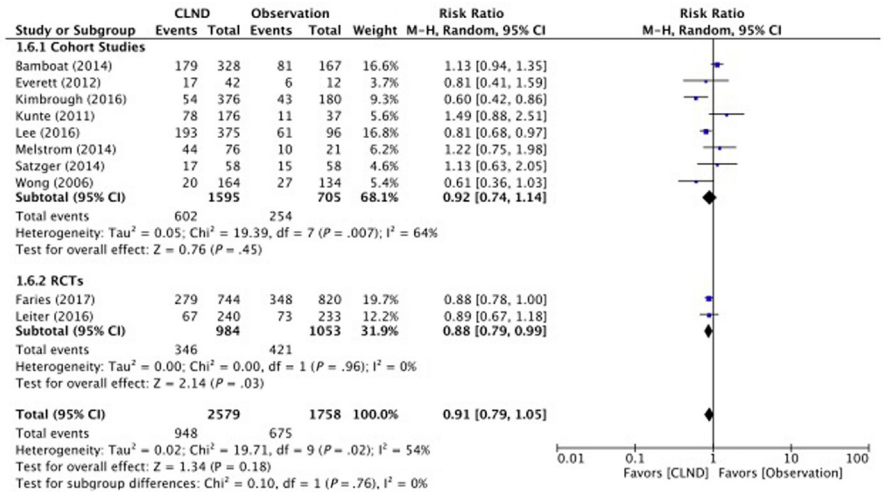

Fig. 1. Meta-analysis of recurrence after completion lymph node dissection or observation of patients with sentinel lymph node-positive melanoma. (*From* Angeles CV, Kang R, Shirai K, et al: Meta-analysis of completion lymph node dissection in sentinel lymph node-positive melanoma. Br J Surg 2019;106:672-81.)

significance to NSLN status than previously thought.[13] Both RCTs showed no differences in overall survival.

Now that we have 2 RCTs that show no significant benefit to performing a CLND, SLNB-positive patients generally do not undergo immediate CLND. However, it is important for the surgeon to understand the patient demographics of those enrolled in these trials and the limitations of the studies. MSLT-II included patients with cutaneous melanoma of any site, of whom 18% had head and neck melanoma.[11] DeCOG-SLT only enrolled patients with truncal or extremity melanoma.[12] The median follow-up for MSLT-II and DeCOG-SLT was 3.5 years and 6.0 years, respectively. Most patients in both trials had only one positive sentinel lymph node (SLN) and a low volume of nodal metastases, with 66% of patients having <1 mm disease (**Table 1**). Therefore, the current data are limited by potentially underestimating the benefit of CLND in patients who have a larger tumor burden in the SLN. That said, CLND does not seem to influence the survival of those with higher tumor burden based on subgroup analyses. In the final analysis with 6-year median follow-up of DeCOG-SLT, the investigators performed a subgroup analysis of patients with $\leq$1 mm versus >1 mm SLN metastases and this distinction showed no effect of CLND on survival in either group.[13] In the MSLT-II trial, similar evaluation showed no difference as well.[11]

The question remains whether the patients who are ultimately found to have positive NSLN actually benefit from the immediate CLND. In the RCTs, only 16% to 18% of patients were found to have NSLN metastasis at the time of CLND. However, a much higher proportion of patients were found to have distant metastatic disease before or concurrent with local or regional recurrence, and therefore, CLND did not have a beneficial effect on total recurrence rates.[11–13] In addition, if a node-only recurrence is detected early (via close observation), as shown by both RCTs, delayed CLND provides the same survival benefit as immediate CLND.[11–13] Further study needs to be done to better prospectively identify a subset of SLNB-positive patients who may benefit from CLND.

Table 1
Select demographics and results of 2 randomized controlled trials comparing observation with completion lymph node dissection for patients with sentinel lymph node–positive melanoma

Characteristic	DeCOG-SLT[12,13]	MSLT-II[11]
# Patients, CLND/observation	240/233	744/820
Location of primary	Truncal and extremity only	Any site (18% head and neck)
Only 1 positive SLN	92%	81%
SLN micrometastasis $\leq$1 mm	66%	66%
Median follow-up, mo	72	43
Primary endpoint (CLND v OBS)	Distant metastasis-free survival (65% v 68%; $P = .87$)	Melanoma-specific survival (86% v 86%; $P = .42$)
Recurrence rate (CLND v OBS)	36% v 34%	38% v 42%

Abbreviations: CLND, completion lymph node dissection; DeCOG-SLT, Dermatologic Cooperative Group–Selective Lymphadenectomy; MSLT-II, Multicenter Selective Lymphadenectomy II; OBS, observation; SLN, sentinel lymph node.

What we do know is that completion node dissection gives us more thorough prognostic data. If a patient with a positive-SLNB, who has no evidence of additional disease on imaging, undergoes observation, then that patient likely will not be offered adjuvant therapy. However, if the same patient undergoes CLND and is found to have additional NSLN-positive disease, these data may lead to a recommendation of systemic therapy. Whether staging (and downstream decision making based on stage) are reasonable indications for performing a CLND continues to be debated.

Patients with a positive-SLNB should undergo a thorough discussion of their options and factors to consider when deciding between CLND and observation. This includes patient-specific clinicopathological findings that may increase the risk of additional disease (higher SLN tumor burden, head/neck primary, >2 mm thick primary melanoma, and number of SLNs involved),[29–32] the data from 2 RCTs showing no survival benefit of CLND, the morbidity of a lymph node dissection (discussed later in this article), the feasibility of observation, and patient preference (**Table 2**). The patients in both RCTs underwent rigorous surveillance with ultrasound and nodal examinations every 3 to 4 months for the first 2 years. This follow-up schedule must be discussed with the patient, and if not practical, one should consider CLND. Patients should also know that if nodal recurrence is detected with this observation schedule, delayed CLND is generally recommended given that the current data support CLND in the setting of lymph node–only recurrence. Nevertheless, there are several multidisciplinary discussions regarding the next phase of clinical trials, and neoadjuvant/adjuvant systemic therapy is increasingly being recommended. However, patients with stage IIIA disease have less than 20% risk of disease recurrence,[33] therefore observation without adjuvant therapy is generally recommended for this subset of patients.

The current data supporting the role of adjuvant therapy (immunotherapy and targeted therapies) for stage IIIB/C disease are based on trials that had required CLND for either SLNB-positive or clinically detected nodal disease (see section on Adjuvant Therapy, later in this article). This may be important when considering options with patients because eligibility criteria should be reviewed before treatment planning. Also, it is currently unknown what, if any, effect CLND had on the longer term endpoints of the trials.

Table 2
Advantages and disadvantages of completion nodal dissection versus observation in patients with sentinel lymph node (SLN)-positive melanoma

Nodal Strategy	Advantages	Disadvantages
Complete Lymph Node Dissection (CLND)	Therapeutic • Reduced risk of nodal relapse Prognostic • Non-SLN status is a predictor of survival • Complete nodal staging	Patient satisfaction • Reduced quality of life • Increased morbidity, including pain, wound complications, lymphedema
Observation	Therapeutic • Equivalent survival (even in the setting of relapse with delayed CLND) Patient satisfaction • ~85% of patients are spared CLND	Therapeutic • Risk of nodal relapse Prognostic • Lack of complete nodal staging Patient satisfaction • Expectation for surveillance (every 4 mo examinations and ultrasonography)

Macroscopic Disease

Patients who present with clinically detected nodal disease or a high nodal disease burden found at the time of SLNB have a worse prognosis, with 5-year survival ranging from 69% (stage IIIC) to 32% (stage IIID) (American Joint Commission on Cancer, Eighth Edition).[34] Any patient with a clinically suspicious node should undergo fine-needle aspiration (FNA) or core needle biopsy, with ultrasound guidance if needed, to confirm presence of melanoma to inform the next steps in management. FNA has been shown to have high sensitivity and specificity for identifying melanoma in enlarged lymph nodes.[35] If FNA or core biopsy is nondiagnostic, excisional biopsy may be performed, being mindful of incision placement because of possible conversion to therapeutic lymph node dissection (TLND). In addition, radiological staging (computed tomography [CT], PET/CT, MRI) should be done before any surgical intervention to rule out distant metastatic disease that would make TLND less beneficial.

The data supporting deferral of CLND in the setting of microscopic disease found on SLNB should not be generalized to the patients who present with clinically palpable nodal disease. Currently there are no data to support abandoning nodal dissection in the clinically node-positive patients and thus, TLND is still considered standard of care. Nevertheless, in this era of rapid discoveries of new immunotherapeutics and targeted agents, it would be disadvantageous for patients to not consider neoadjuvant and adjuvant approaches or enrollment to clinical trials, along with surgical intervention. Patients with clinically detected nodal disease have a 70% chance of relapse with surgery alone.[33,36]

In the setting of bulky nodal disease, a neoadjuvant approach has multiple potential benefits. If a patient responds to neoadjuvant therapy, the decrease in disease burden could potentiate a safer dissection along nerves and vessels. One could also gain knowledge about the responsiveness of the tumor to the particular therapy, which is not possible in the adjuvant setting. Evaluation of responsiveness also gives insight into the appropriate approach with adjuvant therapy. The neoadjuvant approach allows preoperative monitoring of response clinically and radiographically, and postoperative assessment of pathologic response. Also, many patients with bulky nodal

disease may not have distant disease evident on imaging, yet they are high risk of harboring distant microscopic disease. These patients could benefit from systemic therapy sooner rather than later.

In patients harboring a susceptible *BRAF*-mutated tumor, one approach is using BRAF/MEK inhibitors upfront, which has a predictable, high response rate. BRAF/MEK inhibitor therapy also has an expected development of resistance in 6 to 9 months, therefore, planning surgery before this time may be essential. This approach may not only make lymph node dissection technically easier, but could improve RFS. A phase II randomized controlled trial in patients with high-risk, resectable stage III and IV BRAF-mutated melanoma showed improved event-free survival with 2 months of neoadjuvant and 10 months of adjuvant dabrafenib plus trametinib, compared with standard of care surgical resection followed by consideration of adjuvant interferon and/or radiation.[17]

A compelling theoretic benefit of using neoadjuvant immunotherapy lies in boosting one's immune system with checkpoint inhibitors while plenty of tumor antigen is present compared with the adjuvant setting when the tumor has been removed. In the neoadjuvant setting, more tumor antigens are ideally available to stimulate the immune system and prime a robust response. This was demonstrated in a randomized trial in which patients with locally/regionally advanced resectable melanoma were randomized to neoadjuvant ipilimumab 3 mg/kg or 10 mg/kg $\times$ 4 doses along with high-dose Inteferon-a2b (HDI), both of which were also administered following definitive surgery. Thirty-four percent of patients demonstrated a pathologic complete response (pCR). The tumor infiltrating lymphocytes (TIL) in the tumor microenvironment (TME) correlated with pCR, and the clonality of the TIL was found to be associated with improved relapse-free survival.[37] In addition, the tumor-associated clones in the blood correlated with amount of TILs and clonal diversity in the tumors, thereby demonstrating the influence of neoadjuvant systemic therapy on both the circulation and tumor microenvironment.

Recurrent Disease

In the setting of recurrent nodal disease, one should approach these patients similarly to the macroscopic, clinically node-positive patients. Nodal recurrence points toward a more aggressive biology with an increased risk of having additional distant disease[13,26] and extent of disease evaluation (re-staging) should be considered mandatory. If node-only recurrence is diagnosed, then CLND is reasonable, with consideration of adjuvant therapy due to the high risk of undetected distant micrometastatic disease. Another approach is neoadjuvant therapy for reasons discussed previously. This clinical scenario may become more frequent as practice changes away from CLND in this post MSLT-II and DeCOG-SLT era. Nevertheless, discussion at a multidisciplinary tumor board is recommended to consider these systemic options and clinical trials.

SURGICAL CONSIDERATIONS

CLND continues to be a necessary procedure in the surgical oncologist's armamentarium, albeit done less frequently in current practice. Patients with clinically apparent nodal disease, without any evidence of distant disease, have a 5-year survival of 30% to 50% after therapeutic lymphadenectomy[9,38,39] and there are no current data supporting better survival outcomes with nonsurgical therapy. Furthermore, there is still a role for palliative lymphadenectomy in the patient who is symptomatic and needs control of the regional nodal basin. A CLND entails a thorough dissection of the involved

nodal basin, whether that basin was determined by a positive SLN or a clinically positive node.

There is some controversy over what defines an optimal nodal dissection. There are limited retrospective data that attempt to define the ideal number of lymph nodes that need to be removed for an adequate dissection,[40–43] and therefore, there are no agreed on guidelines, although there have been some threshold node counts proposed as minimum counts (used as proxies for the extent of dissection). To ensure high-quality care of the patient, the surgeon's operative note should include the anatomic boundaries of the dissection. Specifics of lymphadenectomy related to particular nodal basins are discussed as follows.

Cervical Lymphadenectomy

Melanoma located on the head and neck and the upper trunk can metastasize to the cervical lymph node basins. A modified neck dissection should be performed that includes levels II, III, IV, and V, and spares the spinal accessory nerve, the sternocleidomastoid muscle, and the internal jugular vein. If there are clinically positive or microscopically positive lymph nodes in the parotid gland, a superficial parotidectomy along with modified neck dissection on that side should be completed.[44] There has been discussion about doing a more selective node dissection with fewer anatomic regions in patients with only microscopic disease, yet there are no supporting data for this. Given the results of MSLT-II, observation of these patients is reasonable. If immediate CLND is elected, then a modified radical dissection should be performed. Patients who have disease with direct extension into a surrounding structure may require a radical neck dissection. According to expert opinion and retrospective data, the minimal number of nodes to be removed during a $\geq$4 level cervical neck dissection is 15 to 20 nodes.[40,41,45] However, the National Comprehensive Cancer Network (NCCN) guidelines do not recommend a specific number of nodes to be removed given the low level of supporting evidence.[46]

Axillary Lymphadenectomy

A complete axillary nodal dissection includes levels I, II, and III. This had been the standard of care for patients who were found to have axillary nodal disease. Now just as level III dissection was questioned for treatment of breast cancer (and current standard of care is dissection of levels I and II[47,48]), the utility in melanoma has been questioned. Level III disease is only found in 1.5% to 3.0% of patients with microscopic (positive-SLNB) axillary lymph node metastasis.[49,50] Many of these patients will not undergo CLND given the changing practice toward observation, and if they do elect CLND, it would be reasonable to dissect level III and remove any hard or enlarged nodes en bloc, or to complete a level III dissection if there is any concern for adenopathy on preoperative cross-sectional imaging. In a recent study, 17% of patients with clinically positive axillary lymph node melanoma metastases were found to have pathologic positive level III lymph nodes compared with 0% of SLNB-positive (microscopic disease) patients.[51] Therefore, CLND in these patients with recurrent disease should include levels I to III. Expert opinion suggests the minimum excised lymph nodes in a 3-level axillary lymphadenectomy should be at least 10 to 12.[40,41,45]

Inguinalfemoral (Superficial) and Ilioinguinal (Deep) Lymphadenectomy

In patients with microscopic positive-SLNB of the superficial inguinal nodal basin who elect CLND, an inguinalfemoral dissection is recommended. Many surgeons will excise the Cloquet node, which is the first deep pelvic node located under the inguinal ligament and posterior and medial to the external iliac vein. If the Cloquet node is

found to be positive intraoperatively (clinically or frozen section), a deep dissection could be performed due to increased risk of positive deep lymph nodes. Over the past 10 to 15 years, most surgeons have shifted away from testing the Cloquet node in this setting based on data showing that the risk of having a positive pelvic lymph node is only 12%[52] and the difference in recurrence and survival of patients undergoing superficial versus superficial and deep dissections for SNLB-positive disease is not significant.[53,54] On the other hand, the risk of having pelvic nodal disease in the setting of palpable superficial inguinal nodal disease is 40% to 55%.[54,55] Current recommendation is to consider pelvic dissection in patients with suspicious iliac and/or obturator nodes on cross-sectional imaging (pelvic CT or PET/CT), palpable inguinalfemoral nodes, or $\geq$3 involved inguinal femoral nodes. These criteria all point to high-risk disease with poor survival, thereby bringing to question the benefit of doing a pelvic node dissection. In this evolving time with advances in systemic therapy, we may see more benefit with pelvic dissection than historical figures due to contemporary treatment planning with neoadjuvant or adjuvant therapy. Suggested minimum number of nodes to excise in a superficial (inguinal) dissection is 5 to 7, and in a superficial and deep (ilioinguinal) dissection, it is 13 to 14.[40,41,45,56]

Morbidity of Lymphadenectomy

When considering the option of lymphadenectomy as part of melanoma management, the risks and benefits need to be clearly discussed with the patient. Even before data from MSLT-II and DeCOG-SLT were available, only 50% of SLNB-positive patients actually underwent the previous standard of care CLND.[14] This is likely due to decision making based on the negative impact lymphadenectomy has on quality of life, which includes decreased mobility, pain, psychological distress, and chronic lymphedema.[11,57–59] On the other hand, the complications of bulky adenopathy should not be dismissed. Patients who present with late disease or who do not respond to systemic therapy may experience neuropathy, vascular congestion, compression of the airway (if in the cervical nodal basin), pain, and lymphedema. In these patients, the benefits of lymphadenectomy usually outweigh the risks; however, each patient's personal and disease characteristics will influence this balance. Both increased age and obesity have been shown to increase the complication rate.[60,61] Also, the severity of the morbidity is somewhat dependent on the specific nodal basin.

Modified radical neck dissection has a reported morbidity rate of approximately 10%.[62,63] The risks to the neurovascular structures are dependent on the extent of surgery and whether the parotid is involved. An even more selective approach to dissection has been considered to further reduce morbidities while maintaining similar recurrence and survival rates.[64]

Reported morbidity for axillary nodal dissection ranges from 20% to 50%.[62,63,65,66] Common complications include seroma, lymphocele, wound infection, axillary web syndrome (also known as cording), and loss of sensation due to injury to the intercostobrachial nerve. Chronic lymphedema is a major concern for patients, as it affects one's health-related quality of life.[59] In the breast cancer literature, postoperative lymphedema after axillary dissection has been reported as high as 13% to 50%,[67,68] yet rates appear to be much lower in the melanoma population (5%).[62,69]

Inguinal lymphadenectomy has a much higher incidence of overall morbidity and chronic lymphedema. This has been studied more thoroughly and multiple studies have shown overall morbidity of approximately 50% to 60% with complications including wound infection, wound dehiscence, prolonged seroma, skin flap necrosis, lymphedema, and deep vein thrombosis.[70,71] In the Sunbelt Melanoma Trial, 32% of patients who had an inguinal lymphadenectomy developed some lymphedema.[62]

To decrease this morbidity, other than considering alternatives to surgery (observation for SLN-positive disease and neoadjuvant systemic therapy for clinical positive disease), some techniques include preserving the saphenous vein, sparing the muscle fascia, sartorius transposition, and videoscopic minimally invasive techniques. Videoscopic inguinal lymphadenectomy has been shown to reduce wound complications while maintaining comparable oncological outcomes.[72]

ADJUVANT RADIATION

The use of adjuvant radiation (RT) for nodal disease could be considered in patients who are high risk for nodal relapse. The one prospective randomized trial (ANZMTG 01.02/TROG 02.01) that investigated adjuvant nodal RT versus observation after lymphadenectomy limited the trial to these high-risk patients, which they defined as any 1 of the following factors:

1. Involvement of $\geq$1 parotid nodes, $\geq$2 cervical or axillary nodes, or $\geq$3 inguinal nodes
2. Extranodal extension
3. Maximum diameter of the largest metastatic lymph node $\geq$3 cm for a cervical node or $\geq$4 cm for an axillary or inguinal node.[73,74]

The long-term data (median follow-up 73 months) showed a significant decrease in the risk of nodal relapse in the RT group (adjusted HR 0.52; 95% CI 0.31–0.88; P = .023), whereas there was no difference in overall survival or relapse-free survival (HR 1.27; 95% CI 0.89–1.79; P = .21, and HR 0.89; 0.65–1.22; P = .51, respectively.) Radiation does not come without side effects. In this study, 74% of patients experienced grade 2 to 4 toxic effects from radiotherapy (mostly pain and fibrosis of the skin or subcutaneous tissue) and 20% had grade 3 to 4 toxic effects. Limb assessments were performed over a period of 5 years and there was a significant increase in lower extremity lymphedema in the adjuvant radiotherapy group compared with observation (mean volume ratio 15.0% vs 7.7% [95% CI 1.5–13.1], P = .014). A nonsignificant difference was seen in the upper extremity (difference 3.4% [95% CI –3.0–9.3]; P = .25).

Notably, this trial was completed when the only adjuvant therapy available was interferon. Therefore, now that we have newer, more promising immunotherapies and targeted therapies, it is important to consider systemic therapy (which has a better chance to improve survival) as a first-line adjuvant therapy. The role of radiation therapy remains ill-defined despite the RCT data. Also, now that patients with melanoma have longer survival, the long-term effects of radiation may cause more harm than good.

ADJUVANT SYSTEMIC THERAPY

There is ongoing debate about which patients with regional nodal disease should or should not get adjuvant systemic therapy. Data from prospective trials with immune checkpoint inhibitor therapy show that there are consistently higher toxicity rates in the adjuvant compared with metastatic setting.[75,76] Therefore, one could speculate that waiting to treat with immunotherapy until there is a recurrence could result in an immune response to the tumor and less reactivity to self-antigens, or autoimmune side effects. Also, all of the stage III adjuvant trials to date have required CLND before adjuvant therapy, and now since MSLT-II and DeCOG-SLT, many of the positive-SLNB patients will not have a CLND but will be referred for adjuvant therapy. These practice changes are outside of the tested treatment protocols. Regional recurrences are increased in patients who do not have a CLND, yet if they do recur, they undergo

salvage surgery and adjuvant therapy. Consequently, typical practice for stage IIIA patients with <1 mm tumor deposit in the SLNB is observation without adjuvant therapy. Patients with stage IIIA with ≥1 mm tumor deposit or IIIB/C will be referred for discussion of adjuvant therapy or clinical trial.

Ipilimumab (IPI), a CTLA-4 inhibitor, was the first new-age immunotherapy agent approved in the adjuvant setting. This was based on the results from the European Organization for Research and Treatment of Cancer (EORTC) 18,071 trial that evaluated high-dose IPI (10 mg/kg) versus observation in patients with high-risk, resectable stage III disease. There was improvement in overall survival (65.4% vs 54.4%) and RFS (26.1 vs 17.1 months) in the IPI group.[75] It is important, however, to note that many patients could not tolerate the high dose of IPI due to toxicity and more than half of the patients discontinued the drug, resulting in diminished enthusiasm for this adjuvant treatment.

The first PD-1 inhibitor approved in the adjuvant setting was nivolumab (NIVO). The CheckMate 238 trial evaluated high-dose IPI compared with NIVO in patients with resectable stage IIIB, IIIC, and IV melanoma. Patients who received NIVO had a significantly longer RFS than IPI at 1 year (71% vs 61%) and a lower rate of grade 3 or 4 adverse events (14% NIVO vs 46% IPI).[16] An update presented at the American Society of Surgical Oncology annual meeting in 2018 showed continued success with the 2-year RFS rates (63% NIVO vs 50% IPI.) No overall survival data are available, however, due to the superiority of NIVO along with its lower toxicity profile compared with IPI, oncologists prefer NIVO in the adjuvant setting.

Pembrolizumab (PEMBRO), a PD-1 inhibitor, was compared with placebo in the KEYNOTE-054/EORTC1345 study that looked at patients with completely resected stage III disease, including IIIA. PEMBRO was associated with a significantly longer RFS than placebo in the intention-to-treat group (75% vs 61%) and grade 3 or higher toxicities were found in 15% of patients.[76] Although it is too soon to have survival data, many patients and providers prefer PEMBRO in the adjuvant setting because of the every 3-week schedule compared with the every 2-week schedule for NIVO, and there is a lower toxicity profile compared with IPI.

Given that in 2 phase 3 trials (COMBI-d and COMBI-v) patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations had an improvement in overall survival with the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib,[5,77] this regimen was tested as an adjuvant therapy versus placebo for completely resected stage IIIA (lymph node metastases >1 mm), IIIB, or IIIC cutaneous melanoma in the COMBI-AD trial. Patients who received the combination therapy had an improved relapse-free survival and overall survival at 3 years (RFS: 58% combo vs 39% placebo, HR 0.47; 95% CI 0.39–0.58; $P<.001$, and overall survival: 86% combo vs 77% placebo, HR 0.57; 95% CI, 0.42–0.79; $P = .0006$).[15] It is recommended that all patients with stage III melanoma undergo BRAF tumor testing and for patients who have a BRAF mutation, oral dabrafenib/trametinib is a viable option in the adjuvant setting. As discussed previously, this is also a good option to use in the neoadjuvant setting for palpable or bulky nodal disease to decrease the extent of the surgical resection.

NEOADJUVANT TRIALS

To date there have been several small neoadjuvant systemic trials that included patients with clinical stage III melanoma. These trials had small sample sizes with various designs and endpoints, but all had early promising results with 19% to 58% pathologic complete response (pCR) rate and improved relapse-free survival.[17,37,78–82] Neoadjuvant dabrafenib plus trametinib followed by surgery and additional same adjuvant therapy has been shown to have 49% to 58% pCR and 20 to 23 months of relapse-

Table 3
Ongoing neoadjuvant clinical trials in stage III melanoma

Treatment Regimen	Patient Population	Phase	Study Outcomes	Trial Name Study ID
Neoadjuvant nivolumab ± ipilimumab or relatlimab and adjuvant nivolumab	Clinical stage III or oligometastatic stage IV	II	1° pathR 2° immunoR, objective response, RFS, OS, adverse effects	NCT02519322
Adjuvant vs neoadjuvant (plus adjuvant) pembrolizumab	Clinically detectable, resectable stage III-IV	II	1° Event-free survival 2° OS, disease control, pathR, RECIST, iRECIST	NCT03698019
Neoadjuvant and adjuvant dabrafenib and trametinib (single arm)	Resectable, clinical stage IIIB/C	II	1° RFS 2° OS, pCR, adverse events	Combi-Neo NCT02231775
Neoadjuvant dabrafenib, trametinib and/or pembrolizumab	BRAF V600 mutated resectable stage IIIB/C	II	1° PathR 2° RECIST, RFS, OS, postop complications, adverse events, operability, tumor/blood markers	NeoTrio NCT02858921
Neoadjuvant vemurarfenib, cobimetinib ± vemurafenib and atezolizumab	High-risk resectable stage III	II	1° pCR, RFS 2° Adverse events, change in PET/CT uptake	NeoACTIVATE NCT03554083
ipilimumab (3 or 10 mg/kg) and high-dose interferon α2b bracketing surgery	Resectable stage IIIB/C and IV	I	1° Adverse events 2° PathR, RadR, PFS, OS	NCT01608594[a]

Abbreviations: CT, computed tomography; immunoR, immunologic response; iRECIST, immune-related RECIST; OS, overall survival; PathR, pathologic response; pCR, pathologic complete response; PFS, progression free survival; RadR, radiological response; RECIST, response evaluation criteria in solid tumors; RFS, recurrence-free survival.

[a] Completed accrual, awaiting results.

free survival.[17,79] Also, there are encouraging early results from 2 trials of combination neoadjuvant checkpoint blockade with NIVO and IPI followed by adjuvant therapy with 45% to 57% pCR and greater than 80% relapse-free survival.[80,81] These and other results from early-phase trials have led to the current enthusiasm to investigate the clinical impact of neoadjuvant therapy in patients with clinical stage III melanoma.

There are multiple ongoing neoadjuvant melanoma trials for patients with resectable stage III melanoma, which are summarized in **Table 3**. These trials are investigating various immunotherapy and targeted therapeutic regimens and examining several clinical and pathologic outcomes, as well as adverse events. The neoadjuvant trial NCT01608594 looking at the combination of IPI and high-dose interferon α2b before and after surgery in resectable stage IIIB/C and IV melanoma has completed recruitment. The melanoma community eagerly awaits the results from these trials that are destined to be practice changing. Nonetheless, because many have both neoadjuvant and adjuvant in their design, deciding which approach is more beneficial will be challenging.

SUMMARY

The management of regional nodal melanoma has evolved and is continuing to evolve in an era of new discoveries and controversies. It is an exciting time with new data to support doing fewer lymph node dissections for microscopic nodal disease,[11,12] while creating a vigor to investigate which of these patients may actually benefit from dissection. At the same time, the extent of effective treatment options is expanding with both targeted and immunotherapies, affecting the decision making around the surgical management of melanoma, specifically related to the role of CLND.

For patients with microscopic, SLNB-positive melanoma (stage IIIA) with <1 mm of nodal disease, observation is recommended. For patients with SLNB-positive >1 mm nodal disease or stage IIIB, observation is reasonable as long as the patient understands the possibility of nodal relapse and later consideration of CLND. Patients with clinically evident nodal disease should be discussed at multidisciplinary tumor boards and be considered for neoadjuvant and/or adjuvant therapy and clinical trials; however, lymphadenectomy is still standard of care and should be performed. Salvage lymphadenectomy should be considered in patients who require regional control as long as the patient has been considered for systemic options and understands the risks and benefits of the procedure. The morbidity of lymphadenectomy is a significant factor in patient and surgeon decision making because of potential negative impacts on quality of life, including decreased mobility, pain, psychological distress, and chronic lymphedema, and therefore should always be discussed with the patient. The use of radiation should be limited to patients with high risk of nodal relapse who either failed systemic therapy or who are otherwise not candidates for systemic options as first-line adjuvant treatment given the increased morbidity without significant survival benefit.

There will continue to be evolution of the surgical management of nodal melanoma. Robust investigations are needed to inform continued high quality of care and improvement in outcomes for patients with melanoma.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Anichini A, Maccalli C, Mortarini R, et al. Melanoma cells and normal melanocytes share antigens recognized by HLA-A2-restricted cytotoxic T cell clones from melanoma patients. J Exp Med 1993;177:989–98.

2. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.
3. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–26.
4. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
5. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521–32.
6. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122–33.
7. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006–17.
8. Wong SL, Faries MB, Kennedy EB, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. J Clin Oncol 2018;36:399–413.
9. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 2001;19:3622–34.
10. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014;370:599–609.
11. Faries MB, Thompson JF, Cochran AJ, et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med 2017;376:2211–22.
12. Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol 2016;17:757–67.
13. Leiter U, Stadler R, Mauch C, et al. Final analysis of DeCOG-SLT Trial: no survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. J Clin Oncol 2019;37(32):3000–8.
14. Bilimoria KY, Balch CM, Bentrem DJ, et al. Complete lymph node dissection for sentinel node-positive melanoma: assessment of practice patterns in the United States. Ann Surg Oncol 2008;15:1566–76.
15. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017;377:1813–23.
16. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–35.
17. Amaria RN, Prieto PA, Tetzlaff MT, et al. Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. Lancet Oncol 2018;19:181–93.
18. Romano E, Scordo M, Dusza SW, et al. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol 2010;28:3042–7.
19. Sabel MS, Griffith K, Sondak VK, et al. Predictors of nonsentinel lymph node positivity in patients with a positive sentinel node for melanoma. J Am Coll Surg 2005;201:37–47.
20. Lee JH, Essner R, Torisu-Itakura H, et al. Factors predictive of tumor-positive nonsentinel lymph nodes after tumor-positive sentinel lymph node dissection for melanoma. J Clin Oncol 2004;22:3677–84.

21. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. Ann Surg 2005;242:302–11 [discussion: 311–3].
22. Pasquali S, Mocellin S, Mozzillo N, et al. Nonsentinel lymph node status in patients with cutaneous melanoma: results from a multi-institution prognostic study. J Clin Oncol 2014;32:935–41.
23. Wong SL, Morton DL, Thompson JF, et al. Melanoma patients with positive sentinel nodes who did not undergo completion lymphadenectomy: a multi-institutional study. Ann Surg Oncol 2006;13:809–16.
24. Smith VA, Cunningham JE, Lentsch EJ. Completion node dissection in patients with sentinel node-positive melanoma of the head and neck. Otolaryngol Head Neck Surg 2012;146:591–9.
25. Mosquera C, Vora HS, Vohra N, et al. Population-based analysis of completion lymphadenectomy in intermediate-thickness melanoma. Ann Surg Oncol 2017; 24(1):127–34.
26. Bamboat ZM, Konstantinidis IT, Kuk D, et al. Observation after a positive sentinel lymph node biopsy in patients with melanoma. Ann Surg Oncol 2014;21:3117–23.
27. Satzger I, Meier A, Zapf A, et al. Is there a therapeutic benefit of complete lymph node dissection in melanoma patients with low tumor burden in the sentinel node? Melanoma Res 2014;24:454–61.
28. Angeles CV, Kang R, Shirai K, et al. Meta-analysis of completion lymph node dissection in sentinel lymph node-positive melanoma. Br J Surg 2019;106: 672–81.
29. Kibrite A, Milot H, Douville P, et al. Predictive factors for sentinel lymph nodes and non-sentinel lymph nodes metastatic involvement: a database study of 1,041 melanoma patients. Am J Surg 2016;211:89–94.
30. Gershenwald JE, Andtbacka RH, Prieto VG, et al. Microscopic tumor burden in sentinel lymph nodes predicts synchronous nonsentinel lymph node involvement in patients with melanoma. J Clin Oncol 2008;26:4296–303.
31. Murali R, Desilva C, Thompson JF, et al. Non-Sentinel Node Risk Score (N-SNORE): a scoring system for accurately stratifying risk of non-sentinel node positivity in patients with cutaneous melanoma with positive sentinel lymph nodes. J Clin Oncol 2010;28:4441–9.
32. Rossi CR, Mocellin S, Campana LG, et al. Prediction of non-sentinel node status in patients with melanoma and positive sentinel node biopsy: an italian melanoma intergroup (IMI) study. Ann Surg Oncol 2018;25:271–9.
33. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:472–92.
34. Gershenwald JE, Scolyer RA, Hess KR. Melanoma of the Skin. In: Amin MB, et al, editors. AJCC Cancer Staging Manual. 8th edition. Springer; 2017;47:563-585.
35. Hall BJ, Schmidt RL, Sharma RR, et al. Fine-needle aspiration cytology for the diagnosis of metastatic melanoma: systematic review and meta-analysis. Am J Clin Pathol 2013;140:635–42.
36. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206.
37. Tarhini A, Lin Y, Lin H, et al. Neoadjuvant ipilimumab (3 mg/kg or 10 mg/kg) and high dose IFN-alpha2b in locally/regionally advanced melanoma: safety, efficacy and impact on T-cell repertoire. J Immunother Cancer 2018;6:112.

38. Spillane AJ, Pasquali S, Haydu LE, et al. Patterns of recurrence and survival after lymphadenectomy in melanoma patients: clarifying the effects of timing of surgery and lymph node tumor burden. Ann Surg Oncol 2014;21:292–9.
39. Khosrotehrani K, van der Ploeg AP, Siskind V, et al. Nomograms to predict recurrence and survival in stage IIIB and IIIC melanoma after therapeutic lymphadenectomy. Eur J Cancer 2014;50:1301–9.
40. Rossi CR, Mozzillo N, Maurichi A, et al. Number of excised lymph nodes as a quality assurance measure for lymphadenectomy in melanoma. JAMA Surg 2014;149:700–6.
41. Spillane AJ, Cheung BL, Stretch JR, et al. Proposed quality standards for regional lymph node dissections in patients with melanoma. Ann Surg 2009;249:473–80.
42. Xing Y, Badgwell BD, Ross MI, et al. Lymph node ratio predicts disease-specific survival in melanoma patients. Cancer 2009;115:2505–13.
43. Galliot-Repkat C, Cailliod R, Trost O, et al. The prognostic impact of the extent of lymph node dissection in patients with stage III melanoma. Eur J Surg Oncol 2006;32:790–4.
44. Pathak I, O'Brien CJ, Petersen-Schaeffer K, et al. Do nodal metastases from cutaneous melanoma of the head and neck follow a clinically predictable pattern? Head Neck 2001;23:785–90.
45. Bilimoria KY, Raval MV, Bentrem DJ, et al. National assessment of melanoma care using formally developed quality indicators. J Clin Oncol 2009;27:5445–51.
46. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:367–402.
47. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. Cancer 1992;69:2496–501.
48. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer 1992;28A:1415–8.
49. Tsutsumida A, Takahashi A, Namikawa K, et al. Frequency of level II and III axillary nodes metastases in patients with positive sentinel lymph nodes in melanoma: a multi-institutional study in Japan. Int J Clin Oncol 2016;21:796–800.
50. Nessim C, Law C, McConnell Y, et al. How often do level III nodes bear melanoma metastases and does it affect patient outcomes? Ann Surg Oncol 2013;20:2056–64.
51. Mahvi DA, Fairweather M, Yoon CH, et al. Utility of level III axillary node dissection in melanoma patients with palpable axillary lymph node disease. Ann Surg Oncol 2019;26:2846–54.
52. Chu CK, Delman KA, Carlson GW, et al. Inguinopelvic lymphadenectomy following positive inguinal sentinel lymph node biopsy in melanoma: true frequency of synchronous pelvic metastases. Ann Surg Oncol 2011;18:3309–15.
53. Verver D, Madu MF, Oude Ophuis CMC, et al. Optimal extent of completion lymphadenectomy for patients with melanoma and a positive sentinel node in the groin. Br J Surg 2018;105:96–105.
54. Egger ME, Brown RE, Roach BA, et al. Addition of an iliac/obturator lymph node dissection does not improve nodal recurrence or survival in melanoma. J Am Coll Surg 2014;219:101–8.
55. Glover AR, Allan CP, Wilkinson MJ, et al. Outcomes of routine ilioinguinal lymph node dissection for palpable inguinal melanoma nodal metastasis. Br J Surg 2014;101:811–9.

56. Spillane AJ, Haydu L, McMillan W, et al. Quality assurance parameters and predictors of outcome for ilioinguinal and inguinal dissection in a contemporary melanoma patient population. Ann Surg Oncol 2011;18:2521–8.
57. Theodore JE, Frankel AJ, Thomas JM, et al. Assessment of morbidity following regional nodal dissection in the axilla and groin for metastatic melanoma. ANZ J Surg 2017;87:44–8.
58. Hyngstrom JR, Chiang YJ, Cromwell KD, et al. Prospective assessment of lymphedema incidence and lymphedema-associated symptoms following lymph node surgery for melanoma. Melanoma Res 2013;23:290–7.
59. Gjorup CA, Groenvold M, Hendel HW, et al. Health-related quality of life in melanoma patients: Impact of melanoma-related limb lymphoedema. Eur J Cancer 2017;85:122–32.
60. Friedman JF, Sunkara B, Jehnsen JS, et al. Risk factors associated with lymphedema after lymph node dissection in melanoma patients. Am J Surg 2015;210: 1178–84 [discussion: 1184].
61. Urist MM, Maddox WA, Kennedy JE, et al. Patient risk factors and surgical morbidity after regional lymphadenectomy in 204 melanoma patients. Cancer 1983;51:2152–6.
62. McMasters KM, Noyes RD, Reintgen DS, et al. Lessons learned from the sunbelt melanoma trial. J Surg Oncol 2004;86:212–23.
63. Guggenheim MM, Hug U, Jung FJ, et al. Morbidity and recurrence after completion lymph node dissection following sentinel lymph node biopsy in cutaneous malignant melanoma. Ann Surg 2008;247:687–93.
64. Geltzeiler M, Monroe M, Givi B, et al. Regional control of head and neck melanoma with selective neck dissection. JAMA Otolaryngol Head Neck Surg 2014; 140:1014–8.
65. van Akkooi AC, Bouwhuis MG, van Geel AN, et al. Morbidity and prognosis after therapeutic lymph node dissections for malignant melanoma. Eur J Surg Oncol 2007;33:102–8.
66. Karakousis CP, Hena MA, Emrich LJ, et al. Axillary node dissection in malignant melanoma: results and complications. Surgery 1990;108:10–7.
67. Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol 2007;25:3657–63.
68. Taylor KO. Morbidity associated with axillary surgery for breast cancer. ANZ J Surg 2004;74:314–7.
69. Postlewait LM, Farley CR, Seamens AM, et al. Morbidity and outcomes following axillary lymphadenectomy for melanoma: weighing the risk of surgery in the era of MSLT-II. Ann Surg Oncol 2018;25:465–70.
70. Henderson MA, Gyorki D, Burmeister BH, et al. Inguinal and ilio-inguinal lymphadenectomy in management of palpable melanoma lymph node metastasis: a long-term prospective evaluation of morbidity and quality of life. Ann Surg Oncol 2019;26(13):4663–72.
71. Sabel MS, Griffith KA, Arora A, et al. Inguinal node dissection for melanoma in the era of sentinel lymph node biopsy. Surgery 2007;141:728–35.
72. Martin BM, Etra JW, Russell MC, et al. Oncologic outcomes of patients undergoing videoscopic inguinal lymphadenectomy for metastatic melanoma. J Am Coll Surg 2014;218:620–6.
73. Henderson MA, Burmeister BH, Ainslie J, et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further

lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. Lancet Oncol 2015;16: 1049–60.
74. Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol 2012;13: 589–97.
75. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:522–30.
76. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378:1789–801.
77. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877–88.
78. Amaria RN, Menzies AM, Burton EM, et al. Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium. Lancet Oncol 2019;20:e378–89.
79. Long GV, Saw RPM, Lo S, et al. Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB-C, BRAF(V600) mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial. Lancet Oncol 2019;20:961–71.
80. Amaria RN, Reddy SM, Tawbi HA, et al. Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. Nat Med 2018;24:1649–54.
81. Rozeman EA, Menzies AM, van Akkooi ACJ, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. Lancet Oncol 2019;20:948–60.
82. Huang AC, Orlowski RJ, Xu X, et al. A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma. Nat Med 2019;25:454–61.