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Management of Locoregional Melanoma

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KEYWORDS
• Melanoma • Locoregional melanoma • Surgically resectable melanoma • Targeted nodal resection
• Neoadjuvant therapy • Immunotherapy • Checkpoint inhibitors • Targeted therapy

KEY POINTS
- Surgical resection remains the cornerstone of locoregional melanoma management with wide local excision and adequate margins.
- Standard use of immunotherapy has resulted in a significant decline in the melanoma mortality rate for the first time in four decades.
- Neoadjuvant immunotherapy is standard of care for the management of advanced melanoma.
- De-escalation of nodal resection based on pathologic analysis of treatment response and clincial observation reduces the morbidity aassociated with nodal dissections without negatively impacting survival.
- Radiation therapy has a limited role in melanoma as it does not impact survival, limiting its use to palliative symptomatic management.

INTRODUCTION

For the first time in 4 decades, the melanoma mortality rate (MMR) significantly decreased from 2013 to 2017. The approval of innovative and effective immunotherapies by the Food and Drug Administration (FDA) has redefined the standard of care for melanoma treatment [1]. Surgical resection remains the cornerstone of locoregional melanoma management.

Traditional chemotherapy regimens have minimal benefit in melanoma treatment and are generally limited to use as salvage therapy [2]. Despite data demonstrating a reduction in locoregional recurrence with the use of radiotherapy, studies have consistently failed to demonstrate a survival impact [3–6].

Improved understanding of tumor biology, immunogenicity, and the tumor microenvironment has revolutionized our approach to cancer treatment. Immunotherapy agents modulate the innate antitumor response. Targeted therapies improve the identification and killing of neoplastic cells to induce a durable treatment response. Recent data have focused on the efficacy of these agents with respect to the timing of delivery and continue to demonstrate improved outcomes with the use of preoperative over postoperative systemic regimens. Regardless, the use of these transformative agents marks a paradigm shift in the management of locoregional melanoma.

Surgical excision remains essential for the management of local disease and bulky adenopathy. The extent and timing of surgical resection continues to evolve as clinicians strive to balance morbidity with clinical outcomes. De-escalation of surgery has improved wound

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healing complications, reduced the need for complex reconstruction, and has significantly improved quality of life for melanoma patients [7]. Optimal management of locoregional melanoma management considers the complex interplay between appropriate oncologic resection and the use of these novel, transformative agents to improve disease specific outcomes.

SECTION I: MANAGEMENT OF THE PRIMARY SITE

Surgical Management of the Primary Site

Surgery is the mainstay of management for primary melanoma. Wide local excision (WLE) with complete resection of the lesion down to fascia remains the standard of care [8]. Prospective, randomized clinical trials established appropriate margins for thin (<1 mm) and thick melanomas (>2 mm), with 1 cm and 2 cm margins, respectively [9,10], while the optimal margin size for 1 to 2 mm lesions remains an area of variability [7,11–14]. While these standards have been accepted for years, the ongoing randomized Melanoma Margins Trial II (MelMarT-II) aims to address the question of whether 2 cm margins are truly ever indicated [15].

Mohs micrographic surgery (MMS) is a specialized technique routinely used for nonmelanoma skin cancers. Some experts advocate for its role in invasive melanomas but the evidence supporting this is limited and largely discipline specific. MMS is primarily utilized in anatomically difficult sites, such as the nose, ear, and periorbital region [16,17]. The authors do not advocate MMS for invasive melanoma and prefer surgical resection with WLE as a standard.

Adjuncts to Surgery at the Primary Site

Topical agents and intralesional injectable therapies offer an alternative treatment for patients with localized metastatic melanoma [18]. These agents are especially useful in patients who are poor surgical candidates or in whom surgical resection would result in debilitating outcomes. Some clinicians utilize topical therapy for the initial management of melanoma in situ in locations such as the genitals or periocular region in specific circumstances.

Topical therapy

Small studies in Europe and Australia investigated the use of topical agents for unresectable cutaneous and subcutaneous melanoma metastases. The most notable agents are diphencyprone (DPCP), imiquimod, and 5-fluorouracil. A small case series of 7 patients treated with DPCP produced a complete response (CR) in 4 patients and a partial response in 3 patients with weekly application [19]. Imiquimod induced disease regression in a small case series with application once or twice daily for several weeks [20,21]. A phase II study evaluated combined imiquimod and topical 5-fluorouracil in 5 patients with 45 metastatic melanoma lesions (30 cutaneous, 15 subcutaneous). A clinical response was noted in 98% of the lesions with a CR in 19 (42%), partial response in 25 (56%), and stable disease in the remaining lesion [21]. While not routinely used due to limited and variable data supporting efficacy, the mild side effect profile has allowed these agents to be considered when standard surgical resection is not an option.

Intralesional therapy

Intralesional therapy allows for direct delivery to the disease site. While Bacillus Calmette-Guerin (BCG), PV-10, and high-dose interleukin-2 were initial injectable therapies, all are largely of historical significance in modern care [22–26]. Talimogene laherparepvec (T-VEC) is a genetically oncolytic modified herpes simplex virus type 1 that is injected intralesionally and then selectively replicates within tumor cells. T-VEC produces granulocyte-macrophage colony–stimulating factor (GM-CSF) that enhances the systemic immune response when cells are lysed. The OPTiM trial compared the durable disease response rate (defined as continuous CR or partial response for at least 6 months) of intralesional T-VEC to subcutaneous GM-CSF in unresectable melanoma and found significant durable disease response when compared to GM-CSF alone ($P < .001$) [27,28]. Ongoing clinical trials are evaluating T-VEC in combination with novel immunotherapies. While there continues to be ongoing debate about the role of T-VEC, particularly regarding its systemic impact, the agent is primarily considered in patients with unresectable cutaneous disease and in those who are not surgical candidates.

Systemic Management of the Primary Site

While historically, surgery alone was used for primary lesions; recent studies have demonstrated that selected patients with high-risk features may benefit from adjuvant immunotherapy to reduce the risk of recurrence. Additional studies are needed to define the patient population who will benefit from such an approach and the melanoma community continues to work toward characterizing optimal treatment regimens for these high-risk patients [29]. Factors such as increasing age, anatomic site of the disease, absence of tumor-infiltrating lymphocytes (TILs), and differential expression of genes

associated with immune response have been shown to improve prognostication.

Agents used in melanoma target cytotoxic T-lymphocyte–associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1). Ipilimumab, a CTLA-4 antibody, prevents suppression of the immune response to promote continued T cell activation and proliferation that enhances the antitumor response. PD-1 interacts with programmed death-ligand 1 (PD-L1) expressed on melanoma cells and promotes T cell exhaustion. The mechanism of action of these therapies is illustrated in Fig. 1. Nivolumab and pembrolizumab are PD-1 antibodies that have demonstrated significantly improved relapse-free survival (RFS) in the treatment of patients with advanced melanoma [30]. Although systemic therapy is rarely used for primary melanomas, these drugs have demonstrated the greatest efficacy and are the backbone of immunotherapy [31].

Keynote-716 and CheckMate-76k evaluated the use of adjuvant immunotherapy in resected stage IIB or IIC melanoma at high risk for recurrence (defined as stage IIB or IIC). Keynote-716 compared adjuvant pembrolizumab, anti-PD-1, to placebo and found that disease recurrence and death were both significantly reduced in the treatment group. CheckMate-76k demonstrated reduced rate of locoregional recurrence with adjuvant nivolumab compared to placebo at 58% and 35%, respectively. This led to the approval of adjuvant pembrolizumab in patients with resected pathologic stage IIB/IIC melanoma by the FDA in 2021, and upon completion analysis of CheckMate-76k, nivolumab will likely follow suit [32–34].

Surgical resection remains the standard of care for localized melanoma with an impressive 99% 5-year survival rate for stage I or II localized disease [35]. However, there is a subset of high-risk patients who have a far lower rate of disease control. Recognition of patients at high risk of recurrence with localized disease that will benefit from adjuvant immunotherapy will help tailor a personalized approach to the treatment of this population.

Key Clinical Pearls for Management of the Primary Site

- Reduction in MMR for the first time in the past 4 decades supports the continued development of novel, effective immunotherapies.
- Surgical resection with WLE remains the primary treatment for localized melanoma, with excellent 5-year survival rates.
- Outcome analysis of the MelMarT-II trial will soon end the 1 or 2 cm margin resection debate in intermediate thick melanoma (1–2 mm).
- Primary tumor thickness and the presence of ulceration are poor prognostic indicators, among many others.
- Checkpoint inhibitors have demonstrated improved rates of recurrence and survival when used as adjuvant therapy in localized melanoma.
- Identification of high-risk features for the patient subgroup with increased risk of locoregional recurrence that may benefit from adjuvant immunotherapy is an area of continued interest. Tools such as gene expression profiling and other transformative scientific advances will aid our understanding of the disease.

SECTION II: REGIONAL DISEASE MANAGEMENT

The 2018, eighth edition of the American Joint Committee on Cancer staging system redefined the classification of regional disease. The characterization defines microsatellites as microscopic metastases found in the cutaneous or subcutaneous tissue adjacent to a primary melanoma but distinctly separated by normal dermis. Satellites and in-transit disease are located within 2 cm or greater than 2 cm from the primary tumor, respectively. In-transit disease occurs anywhere between the primary site and the regional lymph node basin as the name suggests. These types of non-nodal regional disease were combined for staging as studies revealed similar survival and prognosis [36].

Surgical Management of Non-Nodal Regional Disease

If feasible, complete surgical resection remains a primary consideration for resectable stage III/IV melanoma, though timing in relation to systemic therapy is rapidly evolving [14]. The extent of resection for recurrent melanoma with microscopically negative margins is sufficient as studies show no benefit with the larger margins that are typically used for primary lesions. Studies have reported long-term survival in 20% of cases despite recurrence [37–39].

Surgical Management of Nodal Disease

Sentinel lymph node (SLN) biopsy samples the first draining lymph nodes, or the sentinel nodes, from the nearest regional nodal basin, as this is the most likely location for microscopic metastasis. The identification of microscopic metastasis impacts clinical decision-making, as it may indicate the need for lymph node resection or adjuvant therapy. The American Society of Clinical Oncology (ASCO)-Society of Surgical

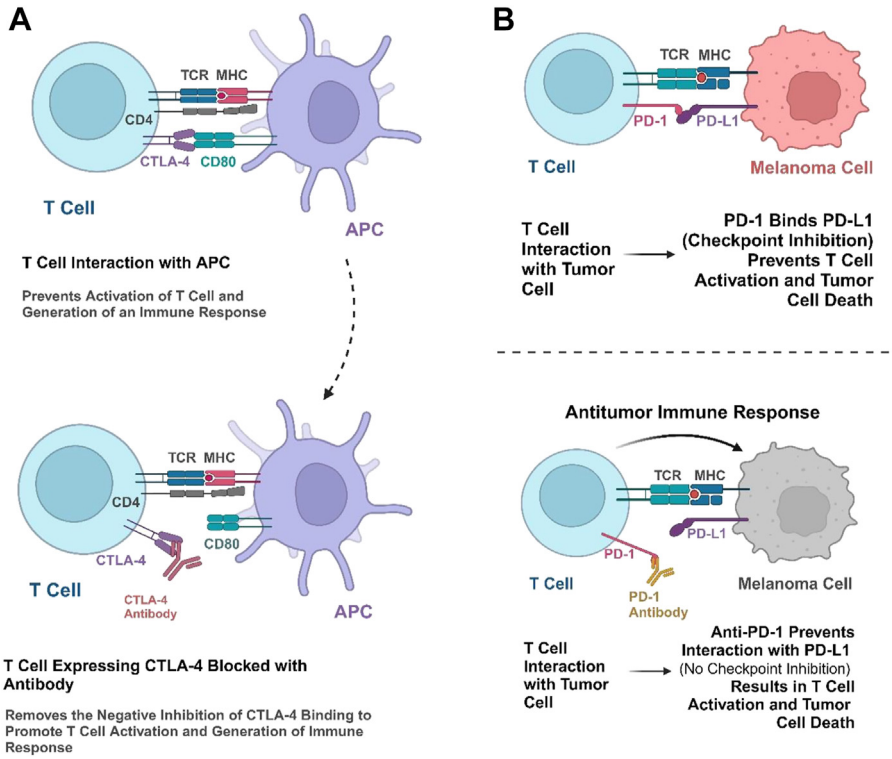

FIG. 1 Immune checkpoint inhibitor (ICI) mechanisms of action of key antibody treatments for melanoma including, anti-programmed cell death protein-1 (anti-PD-1) and anti-cytotoxic t-lymphocyte-associated protein-4 (anti-CTLA-4) agents. (**A**) T cell interaction with antigen-presenting cells (APCs) in the lymph node and peripheral blood require multiple signals from interaction of the T cell receptor (TCR) from CD4+ T cells with the major histocompatibility complex (MHC) present on APCs. Additionally, binding of CD80 on APCs to cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) are critical signals for activation or inhibition, if present, of the immune checkpoint to prevent overactivation of an immune response. (*Above*) T cell interaction with an APC that prevents T cell activation and generation of an immune response. (*Below*) Presence of a CTLA-4 antibody that binds the CTLA-4 receptor on T cells prevents binding to CD80 on APCs and thus removes the negative inhibition and promotes T cell activation and generation of an immune response. (**B**) T cells directly interact with melanoma cells via TCR and MHC binding as well as the programmed cell death protein-1 (PD-1) on T cells to its ligand PD-L1 on melanoma cells. These interactions are key checkpoints that inhibit activation of the T cell and prevent generation of an immune response (as depicted on the *upper half* of *B*). (*Below*) Generation of an antitumor immune response that activates T cells to kill melanoma cells is produced by preventing PD-1 from binding PD-L1 with a PD-1 antibody. (Figure created with BioRender.com.)

Oncology guidelines for SLN biopsy were updated in 2018 to include stratification by primary site thickness, as risk of nodal involvement is known to increase with tumor thickness [13]. Table 1 shows the consensus recommendations for SLN biopsy based on this panel.

The Multicenter Selective Lymphadenectomy I (MSLT-I) trial established that SLN biopsy accurately predicts the presence of microscopic lymph node metastases and supports the use of SLN biopsy to improve prognostication and identify patients that may require additional surgical or systemic treatment [40]. Positive SLN biopsy indicates the presence of microscopic metastatic nodal disease for which complete lymph node dissection (CLND) was previously the standard of care. The morbidity of CLND and lack of clear survival benefit led to the pursuit of data clarifying its role. The MSLT-II and the German Dermatologic Cooperative Group (DeCOG-SLT) trials compared survival in patients with a positive SLN biopsy who underwent CLND against nodal basin observation alone. Both

TABLE 1
American Society of Clinical Oncology-Society of Surgical Oncology Sentinel Lymph Node Biopsy Practice Guidelines for Invasive Melanoma Stratified By Primary Disease Thickness

ASCO-SSO Sentinel Lymph Node Biopsy Practice Guidelines for Invasive Melanoma				
	T Stage	Breslow Thickness	Presence of Ulceration	Recommendation
Thin melanoma	T1a	(<0.8 mm)	Non-ulcerated	*SLN Biopsy not recommended*.
	T1b	(<0.8 mm)	With ulceration	Discuss risks and benefits of SLN biopsy with patient for consideration. No firm recommendation.
		(0.8–1 mm)	Non-ulcerated	
Intermediate thick melanoma	T2a	> 1.0–2.0 mm	Non-ulcerated	*Perform SLN biopsy*.
	T2b		With ulceration	
	T3a	> 2.0–4.0 mm	Non-ulcerated	
	T3b		With ulceration	
Thick melanoma	T4a	> 4.0 mm	Non-ulcerated	Discuss risks and benefits of SLN biopsy with patient for consideration. May improve staging and potentially disease control. No firm recommendation.
	T4b	> 4.0 mm	With ulceration	

Abbreviations: ASCO, American Society of Clinical Oncology; SLN, sentinel lymph node; SSO, Society of Surgical Oncology; T, primary tumor.

studies found that there was no benefit to routine CLND. There was no difference in either study regarding distant metastasis-free survival (DMFS) or melanoma-specific survival between study arms [41,42]. These findings support active nodal observation in patients with SLN biopsy-only proven disease. It is important to note that patients who cannot (or choose not to) undergo nodal surveillance should be recommended to undergo completion lymphadenectomy. In the setting of clinically detected disease or recurrence during observation, therapeutic lymph node dissection (TLND) remains the standard of care.

Local Management of Regional Cutaneous Disease

Local therapy remains a tool in the clinician's armamentarium for the management of patients with unresectable melanoma as listed in Box 1. While a clinical trial or standard systemic therapy regimen remains the initial lines of therapy, if advanced disease is limited to an extremity, the use of hyperthermic isolated limb perfusion (HILP) or isolated limb infusion (ILI) may still be considered.

Both approaches involve focused delivery of chemotherapy to a limb that has been "isolated" from the systemic circulation. HILP involves surgical isolation of the vasculature to the affected extremity for insertion of cannulas to deliver chemotherapy, whereas ILI limits systemic spread through the use of a tourniquet. In both cases, melphalan remains the primary drug of choice. In HILP, the drug is circulated in a hyperthermic environment through an oxygenated extracorporeal circuit. This technique has demonstrated impressive CR rates of 50% to 75% [43–45]. In contrast, ILI improved the toxicity seen in HILP by using percutaneous catheters and a tourniquet. The circuit is nonoxygenated, and the temperature range is lower than that used for HILP, which significantly reduces morbidity. While not as effective as HILP, response rates make it a preferred technique of HILP in consideration of its reduced complication profile [46,47].

BOX 1
Local Therapies for the Management of Unresectable Locoregional Melanoma in Patients Without Distant Metastases.

Local therapies used for unresectable melanoma include:

- Hyperthermic isolated limb perfusion
- Isolated limb infusion
- Intralesional therapy
- Electrochemotherapy
- Radiation therapy

Systemic Management of Regional Disease

Immunotherapy has altered the treatment paradigm in patients with advanced melanoma. Checkpoint inhibition and targeted agents have provided clinicians and patients with options and results that have never been seen previously in melanoma. The key clinical trials that led to these changes in the treatment algorithm of melanoma are summarized in this section briefly.

The European Organization for Research and Treatment of Cancer (EORTC) 18,071 trial demonstrated significantly improved RFS with adjuvant ipilimumab (anti-CTLA-4) compared to placebo [48] and EORTC 1325 trial demonstrated longer RFS and higher DMFS in patients that received adjuvant pembrolizumab (anti-PD-1) [49].

CheckMate 238 compared adjuvant ipilimumab to nivolumab (anti-PD-1) and concluded that adjuvant nivolumab increased RFS with lower adverse events. Nivolumab received FDA approval for treatment in this patient population upon study completion [50]. However, current standard of care in most patients with advanced melanoma is combination therapy using ipilimumab and nivolumab, as this revealed a 53% response rate and significantly improved survival [51].

Targeted therapy

Targeted therapy is utilized in patients with a BRAF mutation to prevent constitutive activation of this pathway with BRAF inhibitors. The COMBI-AD trial compared adjuvant combination dabrafenib (BRAF inhibitor) and trametinib (mitogen-activated protein kinase kinase [MEK] inhibitor) to placebo in patients with resected stage III melanoma and demonstrated an impressive 3-year RFS of 58% compared to 39% ($P < .001$). Overall survival and DMFS at 3 years were higher in the treatment arm, which led to FDA approval for combination therapy in the adjuvant stage III setting [52,53].

Treatment with adjuvant pembrolizumab or BRAF-MEK targeted therapy (dabrafenib-trametinib) reduces the risk of recurrence by 43% and 53%, respectively, in stage III disease compared to surgical resection alone [49,54]. In addition, atezolizumab, an anti-PD-L1 agent, demonstrated improved PFS when used with vemurafenib and cobimetinib compared to targeted therapy alone [55]. Ongoing clinical trials are investigating other approaches to treatment with different targets as well as adoptive cell therapy, engineered chimeric antigen receptor T cells, and TILs in the treatment of melanoma.

Key Clinical Pearls for Management of Regional Disease

- Surgical resection is the optimal treatment whenever possible, in the absence of distant metastasis.
- SLN biopsy indications were updated and recommend performing this procedure in patients with intermediate thick melanoma (1.0–2.0 mm) to improve recurrence and guide adjuvant treatment.
- The DeCOG-SLT study and the MSLT-II trial showed that nodal basin observation is safe and CLND can be omitted in patients with positive SLN biopsy only.
- The standard of care involves a total of 12 months of systemic therapy with immunotherapy, leading to significantly improved outcomes.
- The use of combination targeted therapies for patients with BRAF mutations has demonstrated the greatest benefit in this population.

SECTION III: MANAGEMENT OF ADVANCED DISEASE

Neoadjuvant therapy has demonstrated impressive treatment effects in the management of melanoma and is favored whenever clinically possible. In addition to improved outcomes over purely adjuvant therapy, neoadjuvant therapy enables evaluation of the pathologic response to treatment in the surgical specimen. The initial treatment response also improves the prediction of sustained benefit, facilitating individualized treatment regimens.

Tailored Surgical Management of Advanced Disease

While at present, TLND remains the standard of care for patients with clinically node-positive disease; many patients with clinically node-positive disease experienced objective benefit from neoadjuvant therapy and had no evidence of disease on pathologic analysis at lymphadenectomy. This inspired the PRADO trial for resectable stage III melanoma to potentially reduce unnecessary lymphadenectomy. This trial included patients with clinical disease from the concurrent OpaCIN-neo trial. They received 2 cycles of ipilimumab and nivolumab and had a fiducial marker placed in the "index lymph node" (ILN), defined as the largest node with pathologically confirmed metastatic disease, prior to treatment. The ILN was surgically resected after 6 weeks, and pathologic analysis identified the presence and degree of response that determined the next steps.

Pathologic response was broadly defined as major pathologic response (MPR), partial pathologic response

(pPR), and pathologic nonresponse (pNR). MPR includes pathologic CR (pCR) and near-pCR, defined as $\leq$ 10% viable tumor, and these patients did not receive additional treatment. Patients with pPR had greater than 10 to $\leq$50% viable tumor, and those with pNR had greater than 50% viable tumor on analysis. Patients with pPR or pNR underwent TLND, but only pNR patients received adjuvant immunotherapy and synchronous radiotherapy [56]. Early results indicate that the ILN appears to accurately predict pathologic response and may omit the need for TLND in this subgroup. An analysis of long-term outcomes may lead to further de-escalation of lymph node dissection. The study may justify the application of targeted nodal resection and permit personalization of treatment using pathologic response.

Local Management of Advanced Disease

The National Comprehensive Cancer Network guidelines do not recommend adjuvant radiation following resection of regional disease, but it may be considered in patients at high risk for recurrence. A prior study characterized the rate of nodal basin recurrence following TLND or elective lymph node dissection among patients who had not had adjuvant radiation. Findings demonstrated that at 10 years 30% of patients had nodal basin recurrence with a mean time to recurrence of 12 months [57]. This study established the risk factors for regional recurrence but did not impact treatment. The Trans-Tasman Radiation Oncology Group (TROG) 2.01 study is the only prospective phase III trial that evaluated adjuvant radiation therapy following lymph node dissection in patients with high-risk nodal disease and revealed improved rates of local recurrence without a survival impact [58]. The role of radiation therapy remains extremely limited in the treatment of melanoma. Possible synergistic effects of radiation therapy and immunotherapy remain an area of investigation with multiple ongoing trials evaluating this combination therapy.

Systemic Management of Advanced Disease

The Southwest Oncology Group (SWOG) S1801 trial has established neoadjuvant single-agent immunotherapy as the new standard of care in stage III melanoma. This trial compared neoadjuvant pembrolizumab followed by surgical resection and adjuvant treatment with the same agent to surgical resection and adjuvant treatment with pembrolizumab in patients with clinically detected regional disease and revealed a 2-year event free survival of 72% in the neoadjuvant arm compared to 49% in the adjuvant arm ($P = .004$) [59]. This groundbreaking trial cemented the role of neoadjuvant therapy in patients with clinically detected nodal disease or other resectable recurrences.

The NADINA trial, which is currently underway, compares adjuvant single-agent nivolumab with neoadjuvant ipilimumab-nivolumab and includes tailored care pathways that de-escalate further interventions based on pathologic response similar to those from the PRADO trial [60]. Results of the NADINA trial and future studies will characterize the indications for neoadjuvant therapy, improve durable response to treatment, and continue to redefine surgical management as demonstrated in the PRADO trial.

Key Clinical Pearls for Management of Advanced Locoregional Disease

- Targeted nodal resection using pathologic response as demonstrated in the PRADO trial is safe and its results support the continued de-escalation of unnecessary nodal resections.
- Radiation therapy has not impacted survival, but it can be discussed to use for disease control of the nodal basin as demonstrated in TROG 2.01.
- SWOG 1801 has established neoadjuvant pembrolizumab as standard treatment for regional metastatic disease.
- The NADINA trial will further expand indications and options for neoadjuvant immunotherapy in melanoma management.

SUMMARY

Immunotherapy has revolutionized the management of locoregional melanoma. Twelve months of systemic immunotherapy is the standard of care in stage III/IV melanoma. Neoadjuvant immunotherapy with pembrolizumab is the standard of care for stage III melanoma following results of the SWOG 1801 trial.

Clinical, pathologic, and histologic features with poor prognosis have helped define high risk that benefit from adjuvant therapy. Gene expression has been implemented to identify biologic markers of prognosis and response. These transformative scientific findings have contributed to the improved understanding and treatment of melanoma and will continue to drastically change management and improve survival with reduction in recurrence.

KEY CLINICAL CONCEPTS OF LOCOREGIONAL MELANOMA MANAGEMENT

- Surgical resection remains the cornerstone of locoregional melanoma management.

- De-escalation of primary site margin size is safe, and the results of the MelMarT-II trial will soon end the margin debate of 1 or 2 cm for intermediate thick melanoma.
- De-escalation of lymph node resections in favor of observation of the nodal basin is also safe and decreases lymphedema. CLND is hardly indicated, and TLND is seemingly less beneficial.
- Targeted nodal resection allows for evaluation of pathologic response that determines treatment response and survival. It informs treatment decision-making to improve rates of recurrence and survival.
- Radiation therapy has a limited role in the management of locoregional melanoma, and it is most effective for palliative symptom management of unresectable lesions.
- The standard of care includes 12 months of adjuvant immunotherapy following complete surgical resection of stage III melanoma.
- Neoadjuvant therapy is standard practice in clinical stage III melanoma from results of SWOG S1801. The ongoing NADINA trial will define more neoadjuvant treatment regimens and define indications in management.

CLINICS CARE POINTS

- Surgical resection remains the cornerstone of locoregional melanoma management as it confers the best chance of survival and reduces the risk of recurrence.
- Narrow margins and less radical resections improve cosmesis, quality of life, and clinical outcomes listed above.
- Mel-MarTII will define the margin size for surgical resection that remains without clear consensus in practice guidelines around the world.
- Recommendations for indication to perform SLNB have changed, with a fewer SLNB performed overall.
- Studies have reported significantly decreased performance of lymph node dissections, such as CLND, TLND, eLND, due to lack of oncologic benefit. This subsequently resulted in decreased surgical morbidity from complications and decreased incidence of lymphedema.
- The PRADO Trial established the safety of targeted nodal dissection in the management of melanoma and to provide evidence that this node can predict pathology to determine the need for lymph node resection.
- High-risk stage IIB/IIC melanoma patients, especially those with multiple risk factors, are at an increased risk of recurrence.
- Neoadjuvant immunotherapy is standard of care for advanced melanoma (Stage III, IV), and the indications continue to rise with the number of new combination therapies.
- Chemotherapy is largely ineffective and limited to salvage therapy; while Radiation Therapy is primary used for symptomatic management, due to the consistent inability to impact survival it is rarely utilized.
- Gene expression tests and in vitro cell growth promote discovery of tumor neo-antigens that serve as biomarkers of disease and potentially may be able to predict response to therapy. Thus, allowing for individualization of treatment regimens.

DISCLOSURE

The authors have no relevant disclosures.

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