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Do Not Forget About the Importance of Loco-Regional Therapy in Melanoma Management

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Immunotherapy agents have significantly changed the landscape of melanoma treatment over the past decade. Paradigm shifts in treatment require reanalysis of the treatment algorithms in melanoma. Despite surgical excision, certain high risk patients with desmoplastic melanoma remain at high risk for local recurrence and retrospective data suggests improvement in local control with adjuvant radiation therapy. Likewise, despite surgical excision and effective systemic therapy agents, patients with extracapsular extension and other high risk features are at substantial risk of nodal basin (regional) recurrence. Adjuvant radiation therapy has been demonstrated to reduce the local recurrence risk. Despite these benefits, adjuvant radiation therapy in melanoma remains controversial in part because its use has not been definitively demonstrated to improve overall or disease-free survival in a randomized prospective study.

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Introduction

The landscape in systemic therapy of melanoma is rapidly evolving. Since 2011, the FDA has approved 7 new therapies for the treatment of metastatic or unresectable melanoma, encompassing immunotherapies and targeted inhibitors. This emergence in new therapies has coincided with an increasing understanding and focus on immunotherapy as well as key genetic mutations in melanoma.

The mainstay of treatment for node-positive melanoma is wide local excision of the primary site with sentinel lymphadenectomy which may or may not be followed by complete lymphadenectomy.[1,2] However, the 5-year overall survival rate (OS5yr) after surgical excision for stage III disease is 77%.[3] The AJCC eighth edition staging breaks down stage III patients into more precise prognostic groups with stage IIIA 93% OS5yr, stage IIIB 83% OS5yr, stage IIIC 69% OS5yr, and stage IIID 32% OS5yr. Thus, adjuvant therapies are often used after surgical resection with the hope of preventing or delaying disease relapse especially in patients with stage IIIB and higher disease including patients with completely resected stage IV disease. Many of the same agents that have proven benefit in the metastatic setting have also shown a benefit in the adjuvant setting.

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Stage III melanoma can be divided broadly into 2 molecular groups: those with MAPK pathway mutations and those without. The MAPK or RAS-RAF-MEK-ERK signaling pathway is an important regulator of cellular growth and proliferation and has been implicated in many different tumors.[4-6] The main driver mutations in the MAPK pathway in melanoma are mutations in the BRAF and NRAS genes.

BRAF is a serine/threonine protein kinase and a member of the RAF family of kinases. The most common mutational event occurs at the V600 residue of the protein in exon 15. BRAF V600 mutations result in significantly increased activity of the protein, leading to constitutive activation of the MAPK cascade.[7] Studies evaluating BRAF V600 mutations in primary and metastatic tissues have reported rates of 40-50%.[8-12] BRAF V600E mutations comprise ~70% of detected BRAF mutations. BRAF V600K mutations are the second most common V600 mutation, making up ~20% of BRAF mutations. Other V600 mutations, such as in BRAF V600D and V600R, are rare.[13]

NRAS mutations are found in approximately 20% of cutaneous melanomas.[9-12] NRAS is part of the RAS family of genes (eg, KRAS, HRAS) encoding small GTPase proteins. Approximately 80% of NRAS mutations are in the Q61 residue of exon 2, with other frequently occurring mutations in the G12 and G13 residues of exon 1.[13] Studies have shown that BRAFV600 and NRAS mutations are largely mutually exclusive in untreated melanomas.[14,15]

In this review, we begin by discussing the currently available adjuvant therapy options after surgical excision for stage III disease. We will then explore the evidence for

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immunotherapy agents, and MAPK pathway inhibitors in stage III melanoma. Finally, we will discuss the available evidence for radiation therapy in the adjuvant setting.

Ipilimumab

Ipilimumab is an immunotherapy that was approved by the FDA in 2011 as a monotherapy for unresectable or metastatic melanoma.[16,17] It is a monoclonal antibody that blocks CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), a protein receptor on the surface of T cells that normally inhibits inappropriate or prolonged activation of T cells. Ipilimumab is thus known as an immune checkpoint inhibitor as it acts by augmenting the natural immune mechanisms for eliminating cancer cells.

The drug has recently demonstrated benefit as an adjuvant therapy for resected stage III melanoma. In the phase III EORTC 18071 trial published in 2015,[18] ipilimumab was compared to placebo in patients who had undergone lymph node dissection (LND) for stage III disease. Patients received ipilimumab at 10 mg/kg, notably higher than the dose of 3 mg/kg approved for stage IV disease, every 3 weeks × 4, then every 3 months for up to 3 years. The trial ran from 2008 to 2011 and enrolled 951 patients: 475 patients in the ipilimumab arm, 476 in the placebo arm. At 3 years, the recurrence-free survival (RFS) was 40.8% in the ipilimumab group vs 30.3% in the placebo group (hazard ratio [HR] 0.76; 95% confidence interval [CI], 0.64-0.89; $P < 0.001$). The OS5yr was 65.4% with ipilimumab and 54.4% with placebo (HR 0.72; 95% CI, 0.58-0.88; $P = 0.001$). Adverse events led to discontinuation of the drug in 52% of the patients who started ipilimumab (n = 245/471), 54.1% of patients had grade 3/4 adverse events and 5 patients (1%) died due to drug-related adverse events. Ipilimumab's toxicity remains a concern as it has an array of significant immune-related side effects, particularly grade 3-4 colitis and hypophysitis which can lead to lifelong hormonal dysregulation.[18]

PD-1 Inhibitors

PD-1 or the programmed cell death protein 1 receptor is an inhibitory or immune checkpoint receptor present on activated T cells. PD-1 inhibitors are monoclonal antibodies against the PD-1 receptor. When the PD-1 receptor binds to its ligands, PDL-1 and PDL-2, often expressed by melanoma cells, this interaction causes suppression of activated T-cells and down-modulates the immune response. By preventing the interaction of the PD-1 receptor with its ligands, PD-1 inhibitors restore the antitumor immune response.[19] The PD-1 inhibitors with high level data in the adjuvant setting for melanoma are pembrolizumab and nivolumab.

In the pivotal phase III KEYNOTE-006 trial that was published in 2015,[20] pembrolizumab significantly improved OS, PFS, and overall response rate compared to ipilimumab for the treatment of unresectable advanced melanoma. The encouraging results from KEYNOTE-006 spawned studies of pembrolizumab as an adjuvant therapy in stage III disease. KEYNOTE-054 compared pembrolizumab 200 mg every 3 weeks for a year vs placebo after complete resection of high-risk stage III melanoma in 1019 patients.[21] Pembrolizumab was associated with a significantly longer RFS: at 1 year, the RFS was 75.4% in the pembrolizumab group vs 61.0% in the placebo group (HR 0.57; $P < 0.001$). Adverse events of grades 3+ were reported in 14.7% of patients in the pembrolizumab group vs 3.4 % in the placebo group.

A second landmark adjuvant study of PD-1 inhibition in stage III melanoma compared 906 patients treated with nivolumab 3 mg every 2 weeks vs ipilimumab 10 mg every 3 weeks ×4 doses and then every 4 weeks in patients with stage III-IV melanoma that had been removed by surgery.[22] Nivolumab was associated with a significantly longer RFS: at 1 year, the RFS was 70.5% in the nivolumab group vs 60.8% in the control group (HR 0.65; $P < 0.001$). Adverse events of grades 3+ were reported in 14.4% of patients in the nivolumab group vs 45.9% in the ipilimumab group.

MAPK Pathway Inhibitors

Dabrafenib is a BRAF V600 inhibitor that was approved for use in metastatic disease in 2013, after it was shown to significantly improve PFS over dacarbazine in patients with previously untreated metastatic disease and BRAFV600E mutations.[23] Trametinib is a MEK1/MEK2 inhibitor that was initially approved in 2013 for patients with metastatic disease and a BRAF V600 mutation, and who had previously been treated with a BRAF inhibitor.[24] MEK1/MEK2 are serine-threonine protein kinases that are involved in signaling downstream from the RAF proteins in the MAPK cascade.[13] Dual agent MAPK-pathway inhibition has been shown to be superior to single agent inhibition in metastatic melanoma.[25]

Dual agent MAPK-pathway inhibition as an adjuvant therapy in patients with resected V600E/K mutated stage III melanoma was tested in the phase III COMBI-AD trial of 870 patients randomly assigned to dabrafenib 150 mg twice daily plus trametinib 2 mg once daily vs a double placebo.[26] At a median follow-up of 2.8 years, the 3-year RFS was 58% for MAPK inhibitors and 39% for placebo (HR 0.47; $P < 0.001$). The 3-year OS was 86% for MAPK inhibitors and 77% for placebo (HR 0.57; $P < 0.001$). Adverse events of grades 3+ were reported in 36% of patients in the nivolumab group vs 10% in the placebo group.

Other Immunotherapy Strategies

Interferon had a nearly 20-year era of eminence as the major immunotherapy option in melanoma, however its use was plagued by a high toxicity profile and marginal benefits. Because of the striking outcomes and better toxicity profiles of newer agents, interferon has been abandoned as an adjuvant in all but rare circumstances. Similarly, other immunotherapy strategies such as biochemotherapy and IL-2 infusion are no longer investigated actively or used clinically.

Radiation Therapy

Systemic recurrences after surgical therapy are the dominant form of recurrence; however, several important large retrospective series have demonstrated a group of patients at high risk for regional recurrence after lymphadenectomy. In 2000 researchers from Roswell Park reviewed 338 patients undergoing complete lymphadenectomy for melanoma with a mean follow-up of 54 months.[27] Seventy-five percent of patients underwent therapeutic nodal dissection for clinically involved nodes and 25% had elective nodal dissection. No patients in their series had adjuvant radiation therapy. The overall rate of nodal basin recurrence was 30% at 10 years with a mean time to nodal basin recurrence of 12 months. The site of nodal involvement was prognostic with 43%, 28%, and 23% nodal basin recurrence at 10 years with cervical, axillary, and inguinal involvement, respectively (P = 0.008). Extracapsular extension (ECE) led to a 10-year nodal basin failure rate of 63% vs 23% without ECE ($P < 0.0001$). Patients undergoing a therapeutic dissection for clinically involved nodes had a 36% failure rate in the nodal basin at 10 years, compared to 16% for patients found to have involved nodes after elective dissection (P = 0.002). Lymph nodes larger than 6 cm led to a failure rate of 80% compared to 42% for nodes 3-6 cm and 24% for nodes less than 3 cm ($P < 0.001$). The number of lymph nodes involved also predicted for nodal basin failure with 25%, 46%, and 63% failure rates at 10 years for 1-3, 4-10, and >10 nodes involved (P = 0.0001). Based on these data, criteria for determining patients at high risk for regional recurrence were proposed: cervical involvement, ECE, >3 positive lymph nodes, clinically involved nodes, or any node larger than 3 cm.

Many retrospective studies evaluating patients who received adjuvant RT after LND to these nodal basins have shown a significant benefit of adjuvant RT vs observation alone on preventing loco-regional recurrence.[28-32] The largest of these retrospective studies was a pooled analysis by Agrawal et al of 615 patients treated at 2 tertiary cancer centers.[33] All patients had high-risk nodal disease in cervical, axillary, or inguinal nodal basins. A total of 509 patients underwent LND followed by adjuvant RT while 106 patients underwent LND followed by observation. The patients in the RT arm received 30 Gy in 5 fractions (6 Gy/fraction). This pooled analysis showed a significant improvement in both loco-regional control and disease-specific survival (DSS) in the adjuvant RT arm vs the observation arm at 5-year follow-up. The 5-year regional control rate was 89.8% in the adjuvant RT arm vs 59.4% in the observation arm ($P < 0.0001$). The 5-year DSS was 51% in the adjuvant RT arm vs 30% in the observation arm ($P < 0.0001$). Importantly, however, there was a significantly increased rate of treatment-related toxicity, specifically lymphedema, in the RT arm (20% vs 13% at 5 years; $P < 0.004$).

There has only been 1 prospective phase III trial investigating the use of adjuvant RT vs observation after LND in patients with high-risk nodal disease—the TROG 02.01 study, conducted by the Australian and New Zealand Melanoma Trials group.[34] In this trial, 217 patients with nodal disease who met the high-risk criteria described above and were not ineligible for other reasons were randomized to either adjuvant RT or observation after LND. The study included 109 patients in the adjuvant RT arm and108 patients in the observation arm. A dose of 48 Gy in 20 fractions (2.4 Gy/fraction) was administered in the adjuvant RT arm within 12 weeks of LND. The authors found a significant difference in the 3-year rate of local recurrence between the 2 groups: 19% in the adjuvant RT group vs 31% in the observation group (20 vs 34 relapses; HR 0.56; 95% CI, 0.32-0.98; P = 0.041). However, there was no difference in RFS between the adjuvant RT and observation groups (70 vs 73 events; HR 0.91; 95% CI, 0.65-1.6; P = 0.56). Interestingly, there was a statistically insignificant trend toward worse OS in the adjuvant RT group (59 vs 47 deaths; HR 1.37; 95% CI, 0.94-2.01; P = 0.12). In the final analysis of the study, which extended the mean follow-up to 73 months (Henderson LancOnc 2015), adjuvant RT reduced the risk of local recurrence by 52% (HR 0.52; 95% CI, 0.31-0.88; P = 0.023), but had no impact on survival (HR 1.13; 95% CI, 0.82-1.55; P =0.21). Additionally, the rate of regional symptoms was significantly higher in the adjuvant RT arm (P = 0.035). Grade 2-4 RT toxicity was found in head and neck (33%), axilla (41%-44%), and groin (38%-67%).[35]

The significant improvement in DSS with adjuvant RT in the pooled retrospective analysis by Agrawal et al was not replicated in the TROG 02.01 prospective study, but as a relatively small study was not powered to assess endpoints like RFS or OS. As such, the use of adjuvant RT remains controversial and it is not offered at all cancer centers. Nevertheless, its benefits on loco-regional control are important, and it remains a valuable option for some patients with high-risk nodal disease. The benefits of adjuvant RT must be weighed against its side effects, particularly lymphedema, but also acute dermatitis, risk of wound infection, pain, cost, and other more rare side effects. Studies have shown that conventional regimens (~2 Gy/fraction and 2.4 Gy/fraction as in the TROG 02.01 study) and hypo-fractionated regimens (higher doses per fraction, as in the Agrawal et al study) appear equivalent in effectiveness and equally tolerated.[36-38]

The use of adjuvant radiation therapy after LND for stage III disease remains controversial and not performed ubiquitously. In the current NCCN Guidelines on Melanoma it is a stage 2B recommendation,[39] that is this recommendation lacks uniform consensus and it is based on lower-level vs high-level evidence. Furthermore, the guidelines recommend *consideration* of adjuvant RT after LND only if specific high-risk criteria are met. These high-risk criteria vary depending on the nodal station involved, that is parotid, cervical, axillary, or inguinal stations. The criteria include LDH <1.5× upper limit of normal AND extranodal tumor extension AND/OR: parotid: ≥1 involved node, any size of involvement, cervical: ≥2 involved nodes, and/or ≥3 cm tumor within a node, axillary: ≥2 involved nodes and/or ≥4 cm tumor within a node, inguinal: ≥3 involved nodes and/or ≥4 cm tumor within a node. Figure 1 is a suggested algorithm for which patients may have a favorable risk:benefit for adjuvant nodal radiation therapy. There is not

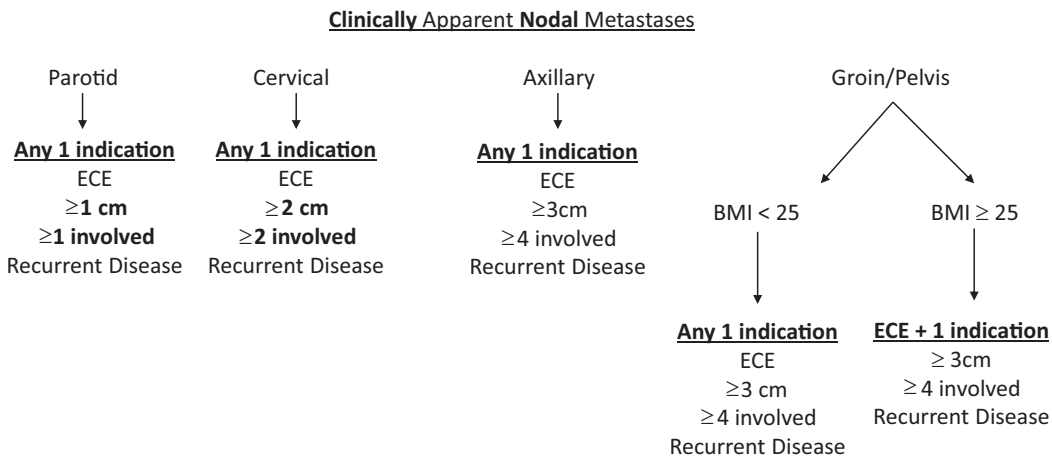

Figure 1 Adjuvant nodal basin radiation therapy treatment algorithm.

sufficient data to give a recommendation on the utility of adjuvant radiation therapy after dissection of epitrochlear or popliteal lymph node regions.

Adjuvant Radiation Therapy in the Immunotherapy Era

The widespread use of adjuvant PD-1 inhibitors has begun only within the last year, and therefore comparisons of regional recurrence rates in patients treated with these immunotherapy agents are limited. The EORTC has published an early look at regional control in their 2 adjuvant therapy studies (1325: pembrolizumab vs placebo and 18071: ipilimumab vs placebo).[18,21] The 5-year rate of locoregional only recurrence with ipilimumab in EORTC 18071 was 21% and 25% in the placebo arm (NSS) and total 5-year rate of locoregional recurrence of 24% and 31% in the ipilimumab and placebo groups, respectively. Five-year data are not yet available in the pembrolizumab vs placebo study, but at 1.5 years it appears that the number of locoregional recurrences is slightly decreased compared with the ipilimumab and placebo arms of the EORTC 18071 study. Even at a potentially decreased rate of locoregional recurrences with adjuvant PD-1 inhibitors, there is still likely to be a subgroup of patients at such high risk of isolated regional recurrence that adjuvant radiation therapy is likely to be of benefit. Identifying those patients at high risk based on pathologic features and radiogenomic signatures should be focus of future research in this area.

Conclusions

In this review, we have discussed the currently approved systemic treatment options for stage III disease, provided an overview of the evidence for identifying patients at high risk of regional nodal recurrence, and discussed the evidence for use of adjuvant radiation therapy in selected high risk patients. With greater understanding of the molecular profiles of patients with stage III disease, the future of treating node-positive disease may be directed towards a more targeted and personalized approach. Combinatorial or sequential treatment strategies that employ targeted inhibitors, immunotherapy, radiation therapy, or other options based on patients' specific risk profiles may be particularly beneficial. This is an exciting time in melanoma research, and the results of the trials described here will provide essential insights on the path toward giving patients a more robust survival outlook after diagnosis of node-positive disease.

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