Adjuvant Therapy in High-Risk Stage III Cutaneous Melanoma

Christopher A. Barker, MD

Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

A 69-year-old man presents with a 2-month history of an enlarging right groin mass. Seven years before presentation, he underwent wide local excision and sentinel lymph node biopsy for a pT4bN0M0R0 cutaneous melanoma of the right upper leg, 32 mm thick, ulcerated, with lymphovascular space invasion. He has no other significant medical history.

On physical examination, he is 170.6 cm, 97.6 kg, with a body mass index of 33.5. A well-healed scar is present on the right upper leg, with no evidence of local or in-transit recurrence. In the right groin is a 5 × 5 cm firm, mobile mass, with no involvement of the overlying skin.

Fine needle aspiration of the mass reveals melanoma. Computed tomography of the head, chest, abdomen, pelvis, and lower extremity reveals a 6.1 × 4.5 × 7.1 cm lobulated mass in the subcutaneous tissues adjacent to surgical clips in the right groin (Fig. 1). No distant metastases or other sites of disease are noted.

He undergoes an uncomplicated therapeutic right inguinofemoral lymphadenectomy. A 5.7 × 5.5 × 4.0 cm ill-defined matted lymph node is noted in the surgical specimen. Fourteen other lymph nodes in the specimen do not harbor melanoma.

Fig. 1. Contrast-enhanced computed tomographic view in axial plane at level of palpable right groin lymphadenopathy.

Scroll down to read expert opinions

Conflict of interest: none.

Supported in part through the National Institutes of Health/National Cancer Institute Cancer Center Support Grant (P30 CA008748).
GRAY ZONE EXPERT OPINIONS

Radiation Therapy Followed by Ipilimumab Is Appropriate

I would not consider neoadjuvant therapy or an alternative definitive treatment before lymphadenectomy. After lymphadenectomy, elective irradiation will improve local control and I would likely offer it. I emphasize likely offer because it has not been associated with improved survival, and irradiation of the groin has been associated with more toxicity than similar radiation therapy (RT) of other sites (1). Assuming the patient (2) is willing to accept these realities, I would offer RT followed by immunomodulatory therapy.

I would prescribe 3000 cGy/5 fractions/2½ weeks intending to encompass the maximum extent of the mass according to imaging and surgical findings plus a several-centimeter margin designed to encompass the extracapsular spread of microscopic disease (the matted nature of the tumor tells me it is extracapsular) (3). To me, the “gray-est” issue is the current and future efficacy of immunomodulatory drugs. Adjuvant ipilimumab already has been shown to improve recurrence-free and overall survival in this setting (4). However, ipilimumab has inherent toxicity and, like adjuvant RT, is appropriate only for patients who understand the risk, are physically able to tolerate it and “want to do everything reasonable” to stay disease free. In the future, I can imagine the migration of anti-PD-1 drugs that are now being used to treat metastatic disease into this role, possibly in combination with ipilimumab. Whether their efficacy in preventing the recurrence that RT targets is good enough to obviate the rationale for RT is at the heart of this “gray zone.”

At present, my judgment is that elective RT followed by ipilimumab offers an appropriate balance between efficacy and toxicity. Killing residual tumor cells before drug therapy may shed more antigens for the immune system to detect (as a “bonus”); providing RT in a compact course allows the patient to move on to immunotherapy with little delay.

Jay S. Cooper, MD
Department of Radiation Oncology
Maimonides Medical Center
Brooklyn, New York

Encourage Enrollment in Clinical Trials of Neoadjuvant or Adjuvant Systemic Therapy, and Consider Adjuvant Radiation Therapy to Prevent Morbid Recurrence

Although I currently would not recommend neoadjuvant therapy off trial, this approach shows promise. In BRAF-mutated patients, neoadjuvant and adjuvant dabrafenib and trametinib significantly improved relapse-free survival compared with surgery followed by systemic therapy (1). For this obese patient with bulky disease (2), tumor shrinkage could decrease operative morbidity. I await the results of trials using neoadjuvant BRAF/MEK and/or checkpoint inhibitors (Table 1).

Though the groin involves the greatest radiation therapy (RT) toxicity risk, because of gross extracapsular extension (3), I would recommend RT, followed by adjuvant systemic therapy. Whether systemic advances will obviate nodal RT or make RT more important to prevent late recurrences, RT is not expected to improve overall survival (3). Therefore, RT is best justified if the quality-of-life detriment from recurrence is of greater concern than RT toxicity. I support SWOG (Southwest Oncology Group) 1404, which randomizes patients to ipilimumab (preferred) or interferon versus pembrolizumab. EORTC (European Organisation

References


http://dx.doi.org/10.1016/j.ijrobp.2016.12.031

Conflicts of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 98, No. 1, pp. 13-17, 2017
0360-3016/S - see front matter © 2017 Elsevier Inc. All rights reserved.
for Research and Treatment of Cancer) 18071 revealed adjuvant ipilimumab, 10 mg/kg, improved overall survival for patients with stage III cancer (4). However, severe immunologic toxicities were frequent, and the results of ECOG (Eastern Cooperative Oncology Group) 1609 will clarify whether 3 mg/kg is preferable.

I would simulate with the scar wired and the hip slightly flexed, abducted and externally rotated to mitigate groin dermatitis. My clinical target volume would include the operative bed delineated by the scar as well as the external iliac nodes starting from the inferior sacroiliac joint, extending caudally along the inguinal nodes to 2 cm below the saphenous-femoral junction. The literature suggests a slightly increased toxicity risk but no oncologic benefit with hypofractionation, so I therefore favor 48 Gy in 20 fractions (3). If I could not need organ-at-risk dose constraints with a multi-field 3-dimensional plan, I would consider using intensity modulated radiation therapy (IMRT) (5). Of note, ovarian dose must be minimized in pre-menopausal women. Although bolus was often applied in the phase III trial reported by Henderson et al. (3), the risk of scar recurrence is relatively low so to minimize toxicity I do not recommend its routine use. With IMRT, the skin dose should be adequate regardless of whether bolus is present.

Christopher J. Anker, MD
Division of Radiation Oncology
University of Vermont Cancer Center
Burlington, Vermont

Conflict of interest: none.
**Consider Adjuvant Intensity Modulated Radiation Therapy to the Lymph Node Basin, Especially If the Melanoma Is BRAF Wild Type**

This patient has operable stage III disease (1), and the standard of care remains lymphadenectomy at this point in time. Although neoadjuvant therapy is attractive owing to the competing risks of regional and metastatic disease, this should only be considered as part of a clinical trial at this point in time. Testing the BRAF mutational status should be done, given that it is an independent prognostic factor in resected stage III disease (2), and this may guide adjuvant therapy, trials, and follow-up protocols.

Given the bulky, ill-defined, and matted disease (suggestive of gross extracapsular nodal extension), this patient is at very high risk of both regional and distant relapse. Adjuvant radiation therapy should be considered, given the randomized evidence that it will have almost half the risk of in-field relapse compared with observation (3). However, given that adjuvant radiation therapy has no impact on disease-free or overall survival, consideration to systemic therapy should also be given. Given that randomized, published data are limited for routine adjuvant systemic therapy and/or immunotherapy, enrolling on a clinical trial, when available, should be encouraged until such point that the data from adjuvant trials become available.

The ideal sequencing of radiation therapy and systemic therapy and/or immunotherapy is not known and should be evaluated in future trials. However, given that isolated nodal recurrence rarely occurs in BRAF-mutated melanoma, the rationale for early radiation therapy in this group would seem less significant. Radiation therapy would be delivered via an intensity modulated radiation therapy technique, using a dose of 48 Gy in 20 fractions over 4 weeks. Bolus should be used to a region 2 cm around any surgical scars or drain sites to ensure full dose on the skin surface to reduce the rate of in-field, dermal recurrence. There is no consensus with respect to the target volume for adjuvant radiation therapy for the inguinalfemoral nodal basin. Extrapolating from the 2-dimensional volumes in the adjuvant melanoma randomized trial, the clinical target volume in this case would include at-risk lymph nodes and deep femoral, inguinal, obturator, internal, and external iliac nodes, as well as the surgical bed and a 3-cm margin around the scar (below the level of the inguinal ligament). A planning target volume margin of a 7-mm isotropic expansion on the clinical target volume would be used, clipped to skin to aid dose calculation (4).

Matthew Foote, BSc, MBBS (Hons), FRANZCR  
Department of Radiation Oncology  
Princess Alexandra Hospital  
Woolloongabba, Queensland  
Australia

Conflict of interest: none.

**References**


http://dx.doi.org/10.1016/j.jrobp.2016.12.029
that have an impact on survival, treatments are moving toward earlier stages. One interesting aspect of neoadjuvant treatments is the possibility to study tumor tissue after therapy. At this point, however, neoadjuvant approaches are conceivable only in the setting of clinical trials. For example, there is currently a study using neoadjuvant injections of talimogene laherparepvec (T-VEC), a genetically modified herpesvirus for direct intralesional tumor injection before other therapeutic procedures (eg, surgical excision) are performed. Other controlled clinical trials using targeted therapy or checkpoint inhibitors have shown very interesting preliminary data.

In this particular case (1), in our institution a total surgical excision of the tumor mass of the right groin would be attempted in the sense of a complete lymph node dissection, especially in a patient with no further manifestations of metastases.

Eggermont et al (2) recently demonstrated that ipilimumab at a dosage of 10 mg/kg body weight used as an adjuvant therapy for high-risk stage III melanoma significantly improves survival in comparison with placebo. Other important approaches, including the use of anti-PD-1 antibodies and kinase inhibitors, have been tested in clinical trials. However, no data are yet available regarding these other agents. An adjuvant use of pegylated interferon, as it can be applied in the case of micrometastases, is not indicated regarding the considerable tumor mass of the inguinal right in this patient.

On the basis of the current available data, the adjuvant administration of ipilimumab after lymphadenectomy or inclusion of the patient in a clinical trial should be discussed with the patient.

Fabrice Kaufmann, MD
Simone M. Goldinger, MD
Department of Dermatology
University Hospital
Zurich, Switzerland

Conflict of interest: none.

References


http://dx.doi.org/10.1016/j.ijrobp.2017.01.245

Adjuvant and Neoadjuvant Therapy in High-Risk Stage III Cutaneous Melanoma

This patient (1) is at high risk for recurrence, even if treated with the best available adjuvant therapies.

Fig. 1. (A) Pretreatment computed tomographic (CT) view from a 41-year-old patient with metastatic axillary nodal melanoma, BRAF V600E mutant. (B) Repeated CT after 6 months of dabrafenib and trametinib, demonstrating a radiologic partial response. Axillary lymphadenectomy was performed at this time. (C) Pathologic analysis of the resected tumor specimen revealed no viable tumor in any of 30 axillary lymph nodes (melan-A immunohistochemistry, ×50 magnification). Photomicrograph courtesy of Jane L. Messina, MD, Moffitt Cancer Center.
For melanoma patients presenting with palpable nodes >2 to 3 cm, we use upfront systemic therapy before or possibly even instead of lymphadenectomy. If a BRAF V600 mutation is identified, we treat with BRAF and MEK inhibitors for 6 months, followed by re-evaluation for lymphadenectomy. The response rate in this neoadjuvant setting is extremely high (2). But because response to targeted therapy is often transient, we advocate lymphadenectomy routinely whenever technically possible (Fig. 1). After lymphadenectomy, we do not resume additional systemic therapy. For those without a BRAF mutation, we consider “upfront” immunotherapy using an anti-PD1–based approach, but we operate only selectively for persistent or progressive disease rather than routinely, as for neoadjuvant BRAF/MEK inhibition in BRAF mutant cases.

Our preferred off-protocol option remains high-dose interferon, based on randomized trials and meta-analyses (3). Pegylated interferon is an appropriate alternative. We remain concerned about toxicity associated with adjuvant ipilimumab at the approved dose, and we do not advocate its use outside of a clinical trial. Ongoing adjuvant trials will determine whether a new standard of care is on the horizon for stage III melanoma.

Conflict of interest: Dr Sondak is a compensated consultant for Array, Genentech, Merck, Pfizer, Polynoma, and Provectus. Dr Khushalani is a compensated consultant for AstraZeneca, Bristol Myers Squibb, Castle Biosciences, EMD Serono, and Genentech; he has received research funding from Amgen, Bristol Myers Squibb, Glaxo Smith-line, Merck, Novartis, and the National Comprehensive Cancer Network (general research support from Pfizer, Roche, and Spectrum).

References


http://dx.doi.org/10.1016/j.ijrobp.2017.02.224