National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Melanoma

Version 2.2016

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Panel Members
Melanoma

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NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

NCCN Guidelines for Patients® available at www.nccn.org

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NCCN Guidelines Version 2.2016 Updates
Melanoma

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Updates in Version 2.2016 of the NCCN Guidelines for Melanoma from Version 1.2016 include:

ME-4

- Adjuvant treatment: "*High-dose ipilimumab (category 2B)*" added as an option for Stage III (sentinel positive) and Stage III (clinically positive node[s]).
- Footnote s is new: "*Adjuvant ipilimumab is associated with improvement in recurrence-free survival. Its impact on overall survival has not been reported. The recommended dose of ipilimumab (10 mg/kg) was associated with adverse events which led to the discontinuation of treatment in 52% of patients. There was a 1% drug-related mortality rate.*"
- Footnote t is new: "*The clinical trial excluded patients with sentinel lymph node metastases ≤1 mm in size and who did not undergo CLND. The decision to use ipilimumab should be based on risk of recurrence balanced against the risk of treatment-related toxicity. It is unclear whether the decision should be based on CLND.*"

ME-5

- Primary Treatment for Stage III in-transit: "*Intralesional injection with talimogene laherparepvec (T-VEC) (category 1)*" added as an option with corresponding footnote z "*T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was most pronounced in Stage IIIB, IIIC and Stage IV-M1a disease and in patients who were treatment naive.*"

ME-8

- Treatment of Local, Satellite, and/or In-transit Recurrence: "*Intralesional injection with T-VEC (category 1)*" added as an option with corresponding footnote z.

ME-9

- Treatment of nodal recurrence with unresectable or systemic disease:
  - "Systemic therapy" is now listed as a "*preferred*" option.
  - Recommendation revised, "*Palliative* RT".
  - "*Intralesional injection with T-VEC*" added as an option with corresponding footnote z.
- Adjuvant Treatment for patients who have had a complete lymph node dissection and/or a complete resection of the nodal recurrence:
  - "*High-dose ipilimumab (category 2B)*" added as a treatment option with corresponding footnote s.
  - "Biochemotherapy" revised as follows "Biochemotherapy ~~for stages IIIB, IIIC~~."

ME-10

- Treatment for patients with disseminated (unresectable) distant metastatic disease:
  - "Systemic therapy" is now listed as a "preferred" option.
  - "*Intralesional injection with T-VEC"* added as an option for select patients with corresponding footnote ii "*T-VEC has shown a response rate (lasting ≥6 months) of 16% in highly selected patients with Stage IV-M1a disease (skin, subcutaneous, and/or remote nodes)*."

ME-E Systemic Therapy for Metastatic or Unresectable Disease

- For both first-line and second-line or subsequent targeted therapy, the recommended combination regimens are listed as "preferred" over single-agent therapy options.
- First-line Therapy: "*Vemurafenib/cobimetinib (category 1)*" added as a preferred treatment option.
- Second-line or Subsequent Therapy: "*Vemurafenib/cobimetinib*" added as a treatment option
- Footnote 3 revised: "Nivolumab/ipilimumab combination therapy is associated with improved relapse-free survival compared with single agent nivolumab or ipilimumab, at the expense of significantly increased toxicity. Compared to single agent therapy, the impact of nivolumab/ipilimumab combination therapy on overall survival is not known. The phase III trial of nivolumab*/ipilimumab* ~~alone~~ versus *either nivolumab or* ~~nivolumab/~~ipilimumab *monotherapy* ~~versus ipilimumab alone~~ was conducted in previously untreated patients with unresectable stage III or IV melanoma."
- Footnote 4 is new: "*In previously untreated patients with unresectable Stage IIIC or Stage IV disease, the combination of vemurafenib/cobimetinib was associated with improved PFS and response rate when compared to vemurafenib alone. The impact on overall survival compared to single agent vemurafenib is unknown.*"

Continued

ME-E Systemic Therapy for Metastatic or Unresectable Disease (continued)
- **New references added for vemurafenib/cobimetinib combination therapy.**

ME-F Management of Toxicities Asscociated with Immunotherapy and Targeted Therapy
Page 1 of 2
- **Immunotherapy: Under "Ipilimumab" the first bullet was revised, "For more information *and specific wording of the black box warning,* see the full prescribiing information (www.fda.gov)."**

Page 2 of 2
- **Targeted Therapy: Last bullet revised, "For more information on toxicities associated with dabrafenib *with or without* trametinib, or vemurafenib *with or without cobimetinib,* and for the management of these toxicities, see the full prescribing information (www.fda.gov).**

Updates in Version 1.2016 of the NCCN Guidelines for Melanoma from Version 3.2015 include:

Global Changes
- **The footnote describing when and how to perform mutational analysis has been revised. (ME-6, ME-7, ME-8, ME-9)**

ME-1
- **Footnote c revised: "While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate *benign from malignant neoplasms, or* melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary *cutaneous* melanomas (before or following SLNB) is not recommended outside of a clinical *study* (trial). ~~Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended or patients who are otherwise NED.~~"**
- **Footnote d is new: "*In the absence of metastatic disease, BRAF testing of the primary cutaneous melanoma is not recommended.*"**
- **Footnote f revised: "~~Given lower reported rates of SLN positivity in pure desmoplastic melanoma, it is important that an experienced dermatopathologist examine the entire lesion before making the decision to perform a SLNB.~~ *There is uncertainty regarding the diagnostic criteria for, the probability of a positive sentinel node in, and the prognostic significance of the sentinel node in pure desmoplastic melanoma. Multidisciplinary consultation including a dermatopathologist is recommended for determining staging and treatment options.* ~~(Busam KJ. Desmoplastic Melanoma. Clin Lab Med 2011;31:321-330.)~~**

ME-2
- **"Clinical Stage" revised: "Stage IA, *IB* (≤0.75 mm thick, *any features)* ~~no ulceration, mitotic rate 0 per mm²); Stage IB (≤0.75 mm thick with ulceration, and/or mitotic rate ≥1 per mm²~~."**
- **Footnote j revised: "SLNB is an important staging tool,~~ but the impact of SLNB on overall survival is unclear~~ *but has not been shown to improve disease-specific survival among all patients. Subset analysis of prospectively collected data suggest that SLNB is associated with improvement in distant metastasis-free survival among patients with melanomas 1.2–3.5 mm thick, compared to patients with melanomas of similar thickness who are initially observed and subsequently develop clinical nodal metastases.*"**

ME-3
- **"Clinical Stage" revised: "Stage IB~~, Stage II~~ (0.76–1.0 mm thick with ulceration or mitotic rate ≥1 per mm²) or *Stage II* (>1 mm thick, any ~~characteristic~~ *feature*, N0)."**

Continued

ME-4

- **Stage III (sentinel node positive)**
  - **Primary Treatment: Recommendation revised, "*Discuss and offer* complete lymph node dissection."**
  - **Adjuvant Treatment: Interferon alfa changed from category 2B to category 2A.**
- **Stage III (clinically positive node[s])**
  - **Workup: Bullet revised, "FNA preferred, if feasible, or *core, incisional, or excisional biopsy* ~~lymph node biopsy~~."**
  - **Primary Treatment: Recommendation revised, "...complete *therapeutic* lymph node dissection."**
  - **Adjuvant Treatment:**
    - **Interferon alfa changed from category 2B to category 2A.**
    - **Biochemotherapy (category 2B) added as an option.**
    - **Recommendation revised, "...Consider RT to nodal basin in selected *high-risk* patients based on location... " (Also for ME-9)**
- **Footnote s is new: "*For a list of biochemotherapy regimens, See Other Systemic Therapies (ME-E 2 of 5).*"**
- **Footnote q revised: "~~The impact of complete lymph node dissection in patients with stage III (sentinel node positive) patients is unknown. This will be clarified when results of MSLT-II are published.~~ *CLND contributes to staging. Its impact on regional disease control and overall survival is the focus of ongoing clinical trials. Factors which predict non-sentinel lymph node positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor.* See Principles of Complete Lymph Node Dissection (ME-C)."**
- **Footnote r revised: "Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); ~~its impact on overall survival remains unclear (category 2B)~~ *but there is no impact on overall survival*." (Also for ME-9)**
- **Footnote t revised: "Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has ~~no impact on~~ *shown no improvement* in relapse-free or overall survival.~~, and~~ Its benefits must be weighed against *potential toxicities* ~~the increased probability of long-term skin and regional toxicities and potential reduced quality of life~~."**

ME-5

- **Fourth column: After "Primary Treatment" the statement "If free of disease" was divided into two pathways "If free of disease *by surgery*" and "*If free of disease by other treatments*". For the latter, "Clinical trial" or "Observation" are recommended as adjuvant treatment options.**

ME-6

- **Footnote y revised: "...Obtain tissue for genetic analysis from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy or if the ~~tissue~~ *mutation status* is relevant to eligibility for participation in a clinical trial."**

ME-7

- **Followup for Stage IIB-IV NED**
  - **Third bullet revised: "Consider chest x-ray, CT, *brain MRI* and/or PET/CT scans..."**
  - **Recommendation removed: "Consider brain MRI annually (category 2B)"**
- **Footnote aa revised: "The frequency of follow-up and intensity of cross-sectional imaging should be based on the conditional probability of recurrence at any point in time after initial treatment. *Follow-up recommendations listed here are for surveillance for recurrence in patients with no evidence of disease.*"**

Continued

ME-8

- **Local, satellite and/or in-transit recurrence**
  - **Workup: First bullet revised, "~~FNA or biopsy~~ *FNA preferred, if feasible, or core, incisional, or excisional biopsy.*"**
  - **Fourth column after "Treatment of Recurrence" the statement "If free of disease" was divided into two pathways "If free of disease *by surgery*" and "*If free of disease by other treatments*". For the latter, "Clinical trial" or "Observation" were recommended as adjuvant treatment options.**

ME-9

- **Nodal recurrence:**
  - **Workup**
    - **First bullet revised: "~~FNA (preferred) or lymph node biopsy~~ *FNA preferred, if feasible, or core, incisional, or excisional biopsy.*" Corresponding new footnote dd added: "*Biopsy preferred if recurrence is unresectable.*"**
    - **Bullet removed: "Pelvic CT if inguinofemoral nodes clinically positive."**
  - **Adjuvant Treatment:**
    - **Interferon alfa changed from category 2B to category 2A.**
    - **Biochemotherapy for stages IIIB, IIIC (category 2B) added as an option.**

ME-10

- **Distant metastatic disease**
  - **Workup**
    - **First bullet revised: "~~FNA (preferred) or lymph node biopsy~~ *FNA preferred, if initial resection is planned. Biopsy (core, excisional or incisional) preferred if initial therapy is to be systemic*."**
  - **For disseminated (unresectable) disease with brain metastases, recommendation revised: "Consider *palliative* resection and/or..."**

ME-A Principles of Biopsy and Principles of Pathology

- **Footnote 3 revised: "While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate *benign from malignant neoplasms, or* melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary *cutaneous* melanomas (before or following SLNB) is not recommended outside of a clinical *study* (trial). ~~Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended or patients who are otherwise NED.~~"**
- **Footnote "4" is new: "*In the absence of metastatic disease, BRAF testing of the primary cutaneous melanoma is not recommended.*"**

ME-C Principles of Complete Lymph Node Dissection

- **Second bullet revised: "In the groin, consider elective iliac and obturator lymph node dissection if clinically positive ~~superficial~~ *inguinofemoral* nodes or ≥3 ~~superficial~~ *inguinofemoral* nodes are positive (category 2B)."**

Continued

ME-D Principles of Radiation Therapy for Melanoma
Page 1 of 3

- **"Regional disease" recommendation revised: "Adjuvant treatment in selected patients following resection of clinically appreciable nodes (category 2B) if ~~LDH <1.5 x upper limit of normal AND~~..."**
- **Footnote 1 revised: "Interactions between radiation therapy and systemic therapies (eg, *BRAF* inhibitors, ~~and~~ interferon alfa-2b*, immunotherapies, and checkpoint inhibitors*) need to be very carefully considered as there is potential for increased toxicity."**
- **Footnote 3 revised: "Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has ~~no impact on~~ *shown no improvement* in relapse-free or overall survival. Its benefits must be weighed against potential *toxicities* ~~the increased probability of long-term skin and regional toxicities and potential reduced quality of life~~."**
- **Footnote 4 revised: "Adjuvant whole brain radiation following resected melanoma brain metastasis is controversial and should be considered on an individual patient basis. ~~An ongoing randomized clinical trial (ANZMTG 01-07, ACTRN12607000512426, NCT01503827) is currently investigating adjuvant whole brain radiation (Fogarty G, Morton RL, Vardy J, et al. Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial. BMC Cancer. 2011;11:142.)~~."**

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- **Primary Disease: New reference added "*Hedblad MA, Mallbris L. Grenz ray treatment of lentigo maligna and early lentigo maligna melanoma. J Am Acad Dermatol 2012;67:60-68.*"**

ME-E Systemic Therapy For Metastatic or Unresectable Disease
Page 1 of 5

- **This section was reorganized and extensively revised including:**
  - **The "Metastatic or unresectable disease" treatment pathways for "*BRAF* V600 wild type" and "*BRAF* V600 mutant" were combined into one algorithm.**
  - **Nivolumab/ipilimumab was added to the list of options for "First-line therapy" and "Second-line or subsequent therapy".**

ME-E Systemic Therapy For Metastatic or Unresectable Disease
Page 1 of 5 (continued)

- **Footnote 3 is new: "*Nivolumab/ipilimumab combination therapy is associated with improved relapse-free survival compared with single agent nivolumab or ipilimumab, at the expense of significantly increased toxicity. Compared to single agent therapy, the impact of nivolumab/ipilimumab combination therapy on overall survival is not known. The phase III trial of nivolumab alone versus nivolumab/ipilimumab versus ipilimumab alone was conducted in previously untreated patients with unresectable stage III or IV melanoma.*"**
- **Footnote 4 is new: "Consider second-line agents if not used first-line and not of the same class.**

Page 2 of 5

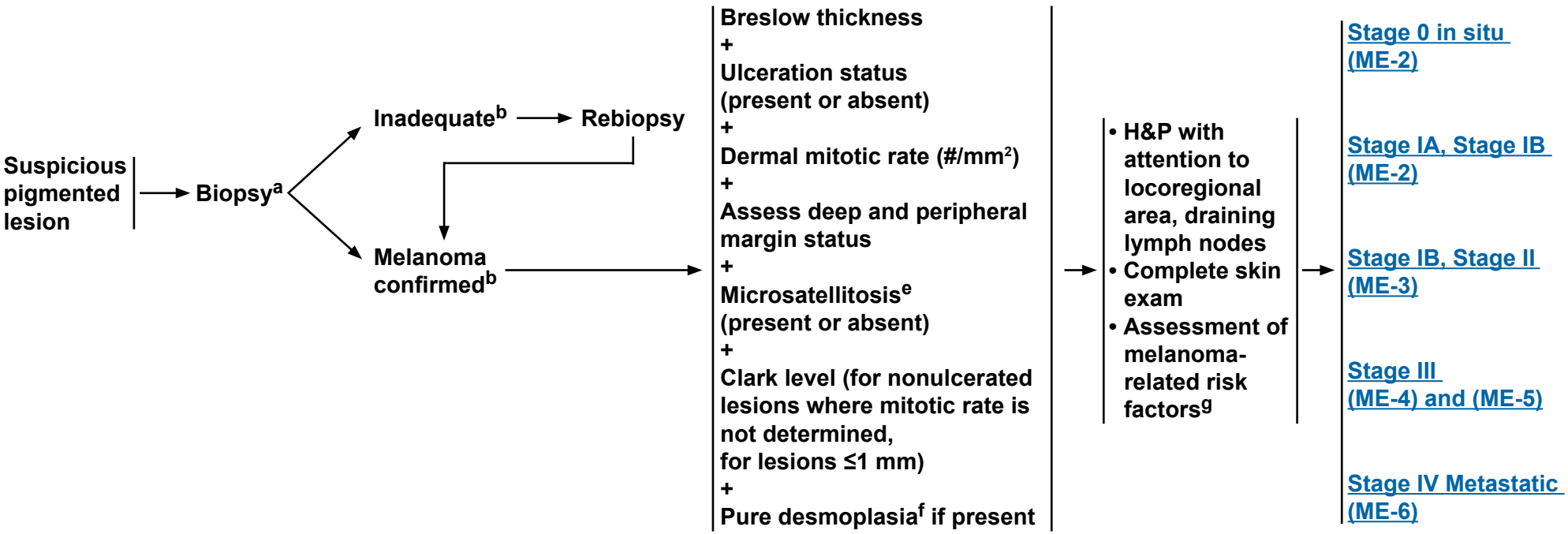
- **Page title changed from "Systemic Therapy for Metastatic or Unresectable Disease" to "*Other Systemic Therapies*".**
- **Subheading title changed: "Cytotoxic Regimens *for Metastatic Disease.*"**
- **Subheading title changed: "Biochemotherapy *for Metastatic Disease.*"**
  - **This section was extensively revised.**
- **New section added: "*Biochemotherapy for Adjuvant Treatment of High Risk Disease.*"**
  - **"*Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b (category 2B)*" added as the recommended regimen.**
- **Footnote 1 regarding cytotoxic regimens and biochemotherapy is new: "*In general, options for front-line therapy for metastatic melanoma include immunotherapy or targeted therapy.*"**

Page 3 of 5, Page 4 of 5 and Page 5 of 5

- **The reference section was extensively revised to reflect the changes in the algorithm.**

ME-F Management of Toxicities Associated with Immunotherapy and Targeted Therapy

- **This section was previously entitled "Principles of Immunotherapy and Targeted Therapy."**
- **This section was reorganized and extensively revised.**



[a] See Principles of Biopsy and Pathology (ME-A).

[b] If diagnostic biopsy is inadequate for treatment decisions, rebiopsy may be appropriate.

[c] While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside of a clinical study (trial).

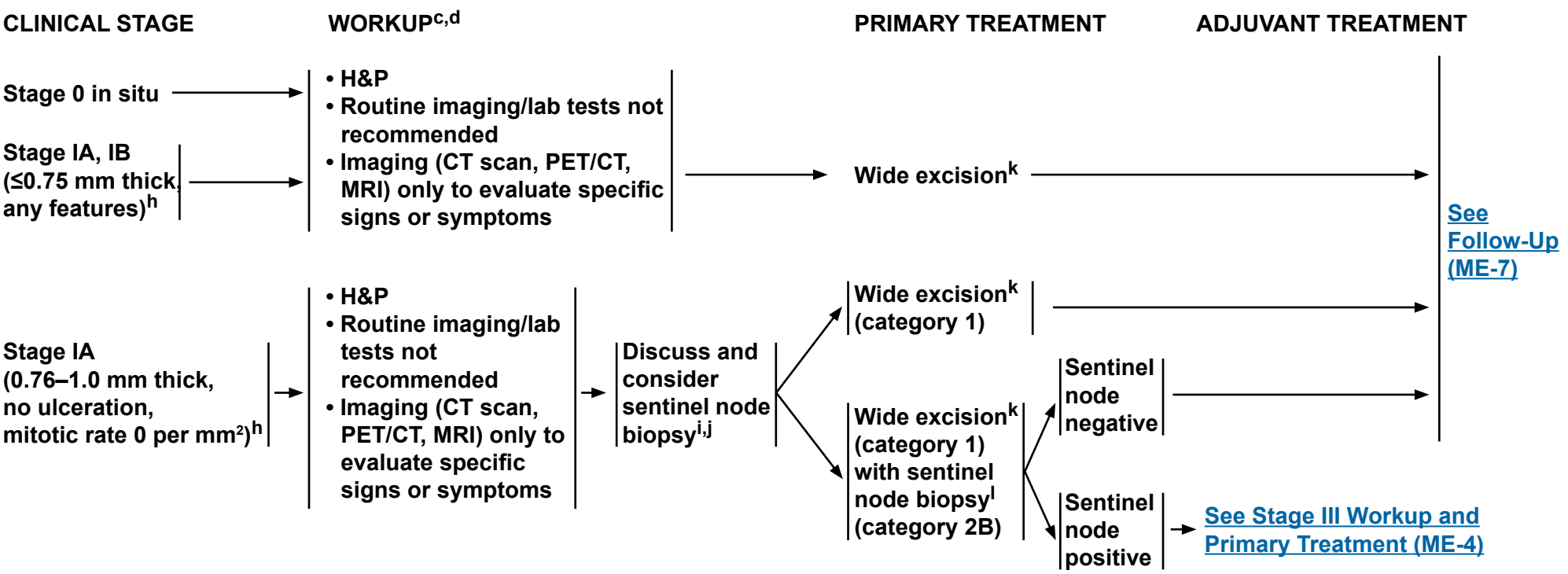
[d] In the absence of metastatic disease, *BRAF* testing of the primary cutaneous melanoma is not recommended.

[e] Microsatellitosis is defined in the CAP 2013 melanoma protocol (version 3.3.0.0) as “the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken" (Harrist TJ, Rigel DS, Day CL Jr, et al. “Microscopic satellites” are more highly associated with regional lymph node metastases than is primary melanoma thickness. Cancer 1984;53:2183-2187.).

[f] There is uncertainty regarding the diagnostic criteria for, the probability of a positive sentinel node in, and the prognostic significance of the sentinel node in pure desmoplastic melanoma. Multidisciplinary consultation including a dermatopathologist is recommended for determining staging and treatment options.

[g] Risk factors for melanoma include family history of melanoma, prior primary melanoma, and other factors such as atypical moles/dysplastic nevi.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[h]In general, SLNB is not recommended for primary melanomas ≤0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging. For melanomas 0.76 to 1.0 mm thick, SLNB may be considered in the appropriate clinical context. In patients with thin melanomas (≤1.0 mm), apart from primary tumor thickness, there is little consensus as to what should be considered "high-risk features" for a positive SLN. Conventional risk factors for a positive SLN, such as ulceration, high mitotic rate, and lymphovascular invasion (LVI), are very uncommon in melanomas ≤0.75 mm thick. When present, SLNB may be considered on an individual basis.

[c]While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside of a clinical study (trial).

[d]In the absence of metastatic disease, *BRAF* testing of the primary cutaneous melanoma is not recommended.

[i]Decision not to perform SLNB may be based on significant patient comorbidities, patient preference, or other factors.

[j]SLNB is an important staging tool, but has not been shown to improve disease-specific survival among all patients. Subset analysis of prospectively collected data suggest that SLNB is associated with improvement in distant metastasis-free survival among patients with melanomas 1.2–3.5 mm thick, compared to patients with melanomas of similar thickness who are initially observed and subsequently develop clinical nodal metastases.

[k]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).

[l]Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

Note: All recommendations are category 2A unless otherwise indicated.
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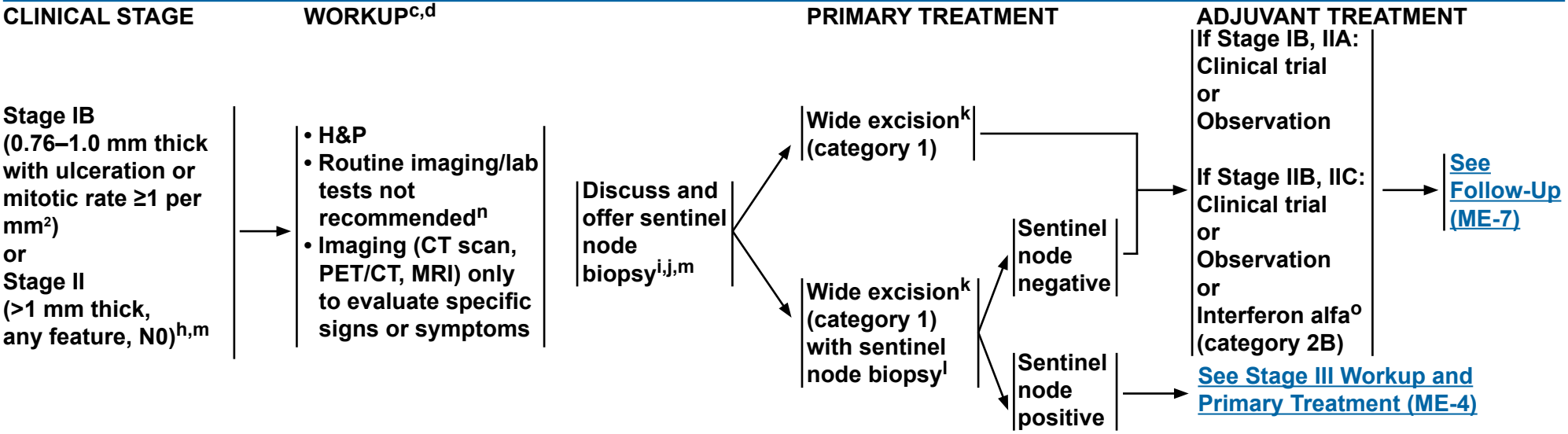

[h]In general, SLNB is not recommended for primary melanomas ≤0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging. For melanomas 0.76 to 1.0 mm thick, SLNB may be considered in the appropriate clinical context. In patients with thin melanomas (≤1.0 mm), apart from primary tumor thickness, there is little consensus as to what should be considered "high-risk features" for a positive SLN. Conventional risk factors for a positive SLN, such as ulceration, high mitotic rate, and LVI, are very uncommon in melanomas ≤0.75 mm thick. When present, SLNB may be considered on an individual basis.

[m]Microsatellitosis, when present in the initial biopsy or wide excision specimen, defines at least N2c and at least stage IIIB disease. SLN status does have prognostic significance in these patients, with a positive SLN upstaging a patient to N3, stage IIIC. However, the importance of SLNB in the management and outcome of these patients has not been clearly defined. Regardless of SLN status, these patients should be managed as stage III in discussions of workup, adjuvant therapy, and follow-up.

[c]While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside of a clinical study (trial).

[d]In the absence of metastatic disease, *BRAF* testing of the primary melanoma is not recommended.

[i]Decision not to perform SLNB may be based on significant patient comorbidities, patient preference, or other factors.

[j]SLNB is an important staging tool, but has not been shown to improve disease-specific survival among all patients. Subset analysis of prospectively collected data suggest that SLNB is associated with improvement in distant metastasis-free survival among patients with melanomas 1.2–3.5 mm thick, compared to patients with melanomas of similar thickness who are initially observed and subsequently develop clinical nodal metastases.

[k]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).

[l]Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

[n]Consider nodal basin ultrasound prior to SLNB for melanoma patients with an equivocal regional lymph node physical exam. Nodal basin ultrasound is not a substitute for SLNB. Negative nodal basin ultrasound is not a substitute for biopsy of clinically suspicious lymph nodes. Abnormalities or suspicious lesions on nodal basin ultrasound should be confirmed histologically.

[o]High-dose alfa interferon for one year has been shown to improve disease-free survival (DFS) (category 1); its impact on overall survival remains unclear (category 2B)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL/ PATHOLOGIC STAGE	WORKUP[p]	PRIMARY TREATMENT	ADJUVANT TREATMENT	
Stage III (sentinel node positive)	Consider baseline imaging for staging (category 2B) and to evaluate specific signs or symptoms (CT scan, PET/CT, MRI)	Discuss and offer complete lymph node dissection[q]	Clinical trial or Observation or Interferon alfa[r] or High-dose ipilimumab[s,t] (category 2B)	(See Follow-up ME-7)
Stage III (clinically positive node[s])	• FNA preferred, if feasible, or core, incisional, or excisional biopsy • Recommend baseline imaging for staging and to evaluate specific signs or symptoms (CT scan, PET/CT, MRI)	Wide excision of primary tumor[k] (category 1) + complete therapeutic lymph node dissection	Clinical trial or Observation or Interferon alfa[r] or High-dose ipilimumab[s] (category 2B) or Biochemotherapy[u] (category 2B) and/or Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, and/or macroscopic extranodal extension[v,w] (category 2B)	

[k] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).

[p] Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended for patients with cutaneous melanoma who are otherwise NED.

[q] CLND contributes to staging. Its impact on regional disease control and overall survival is the focus of ongoing clinical trials. Factors which predict non-sentinel lymph node positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor. See Principles of Complete Lymph Node Dissection (ME-C).

[r] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); but there is no impact on overall survival.

[s] Adjuvant ipilimumab is associated with improvement in recurrence-free survival. Its impact on overall survival has not been reported. The recommended dose of ipilimumab (10 mg/kg) was associated with adverse events which led to the discontinuation of treatment in 52% of patients. There was a 1% drug-related mortality rate.

[t] The clinical trial excluded patients with sentinel lymph node metastases ≤1 mm in size and who did not undergo CLND. The decision to use ipilimumab should be based on risk of recurrence balanced against the risk of treatment-related toxicity. It is unclear whether the decision should be based on CLND.

[u] For biochemotherapy, See Other Systemic Therapies (ME-E 2 of 5).

[v] Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in relapse-free or overall survival. Its benefits must be weighed against potential toxicities.

[w] See Principles of Radiation Therapy for Melanoma (ME-D).

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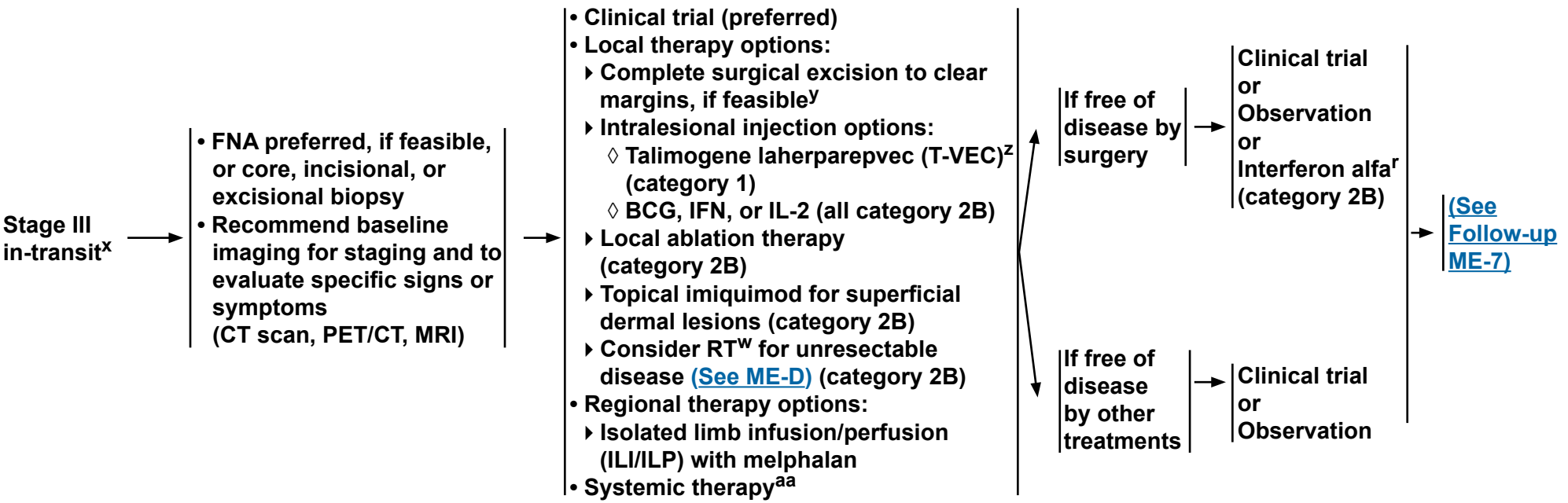

[p]Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but not recommended for patients with cutaneous melanoma who are otherwise NED.

[r]Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); but there is no impact on overall survival.

[w]See Principles of Radiation Therapy for Melanoma (ME-D).

[x]In-transit metastasis is defined as intralymphatic tumor in skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the nearest regional lymph node basin. (Definition from CAP 2012 Melanoma Protocol [version 3.2.0.0])

[y]Consider sentinel node biopsy for resectable in-transit disease (category 2B). Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

[z]T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was most pronounced in Stage IIIB, IIIC and Stage IV-M1a disease and in patients who were treatment naive.

[aa]See Systemic Therapy for Metastatic or Unresectable Disease (ME-E 1 of 5)

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CLINICAL/ PATHOLOGIC STAGE	WORKUP
Stage IV Metastatic	• Biopsy preferred over FNA if archival tissue not available for genetic analysis[bb] • LDH • Recommend chest/abdominal/pelvic CT, brain MRI, and/or PET/CT for baseline imaging and to evaluate specific signs and symptoms

→ See Treatment for Limited (Resectable) or Disseminated (Unresectable) Disease (ME-10)

[bb] Initial clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Obtain tissue for genetic analysis from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy or if the mutation status is relevant to eligibility for participation in a clinical trial.

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CLINICAL/PATHOLOGIC STAGE	FOLLOW-UP
Stage 0 in situ	See Common Follow-up Recommendations for All Patients[cc] (below)
Stage IA - IIA NED	• See Common Follow-up Recommendations for All Patients[cc] • H&P (with emphasis on nodes and skin) ▸ every 6–12 mo for 5 y, then ▸ annually as clinically indicated • Routine radiologic imaging to screen for asymptomatic recurrent/metastatic disease is not recommended
Stage IIB - IV NED	• See Common Follow-up Recommendations for All Patients[cc] • H&P (with emphasis on nodes and skin) ▸ every 3–6 mo for 2 y, then ▸ every 3–12 mo for 3 y, then ▸ annually as clinically indicated • Consider chest x-ray, CT, brain MRI and/or PET/CT scans every 3–12 mo[dd] (unless otherwise mandated by clinical trial participation) to screen for recurrent/metastatic disease (category 2B) • Routine radiologic imaging to screen for asymptomatic recurrent/metastatic disease is not recommended after 3–5 years

RECURRENCE[ee]

- Persistent disease or true local scar recurrence[ee] → (See ME-8)
- Local, satellite, and/or in-transit recurrence[bb,ff] → (See ME-8)
- Nodal recurrence[bb] → (See ME-9)
- Distant recurrence[bb] → (See ME-10)

[cc]Common Follow-up Recommendations for All Patients:
- At least annual skin exam for life
- Educate patient in regular self skin and lymph node exam
- Routine blood tests are not recommended
- Radiologic imaging is indicated to investigate specific signs or symptoms
- Regional lymph node ultrasound may be considered in patients with an equivocal lymph node physical exam, patients who were offered but did not undergo SLNB, patients in whom SLNB was not possible (or not successful), or patients with a positive SLNB who did not undergo complete lymph node dissection. At this point, nodal basin ultrasound has not been shown to be a substitute for SLNB or complete lymph node dissection (CLND).
- Follow-up schedule is influenced by risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors such as atypical moles/dysplastic nevi and patient/physician concern.

[bb]Initial clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Obtain tissue for genetic analysis from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy or if the mutation status is relevant to eligibility for participation in a clinical trial.

[dd]The frequency of follow-up and intensity of cross-sectional imaging should be based on the conditional probability of recurrence at any point in time after initial treatment. Follow-up recommendations listed here are for surveillance for recurrence in patients with no evidence of disease.

[ee]Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.

[ff]Local, satellite recurrence without in situ or radial growth phase, with deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar.

Note: All recommendations are category 2A unless otherwise indicated.
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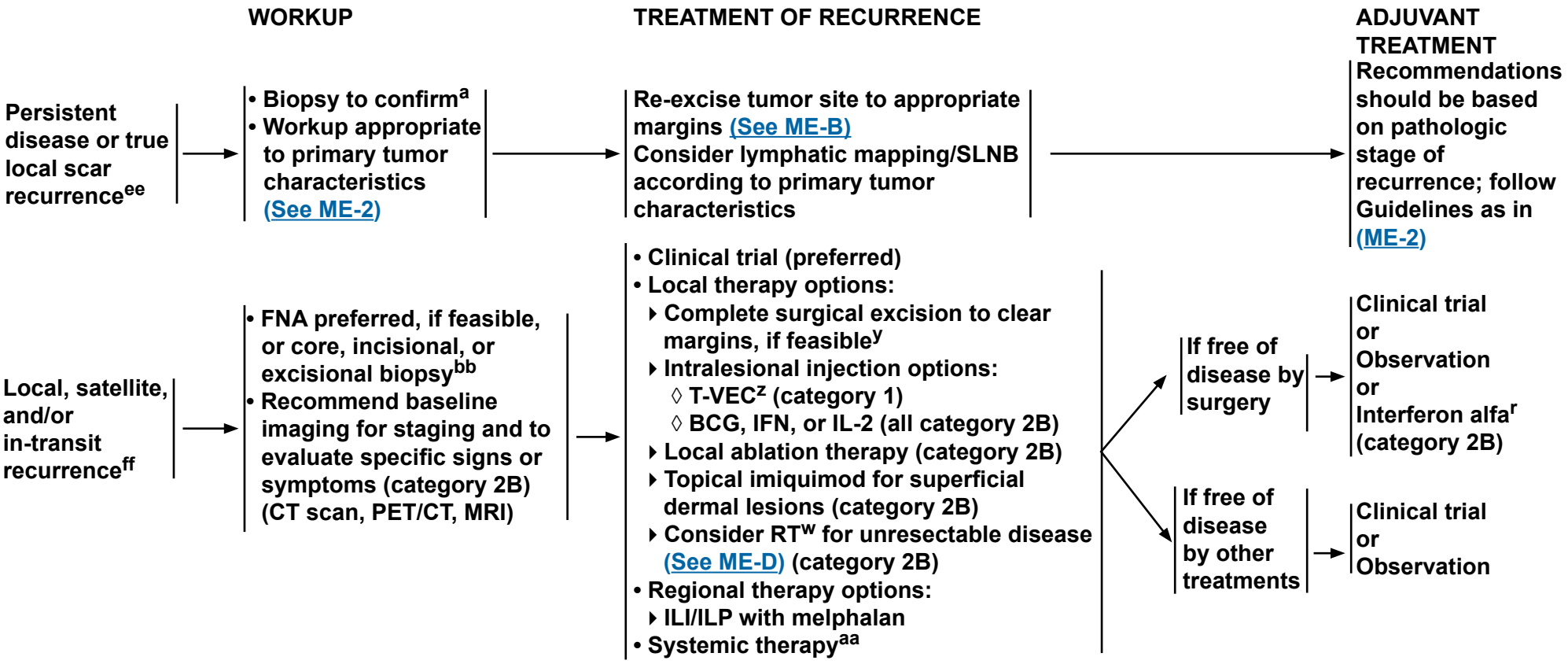

[a] See Principles of Biopsy and Pathology (ME-A).

[r] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); but there is no impact on overall survival.

[w] See Principles of Radiation Therapy for Melanoma (ME-D).

[y] Consider sentinel node biopsy for resectable in-transit disease (category 2B). Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

[z] T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was most pronounced in Stage IIIB, IIIC and Stage IV-M1a disease and in patients who were treatment naive.

[aa] See Systemic Therapy for Metastatic or Unresectable Disease (ME-E 1 of 5).

[bb] Initial clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Obtain tissue for genetic analysis from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy or if the mutation status is relevant to eligibility for participation in a clinical trial.

[ee] Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.

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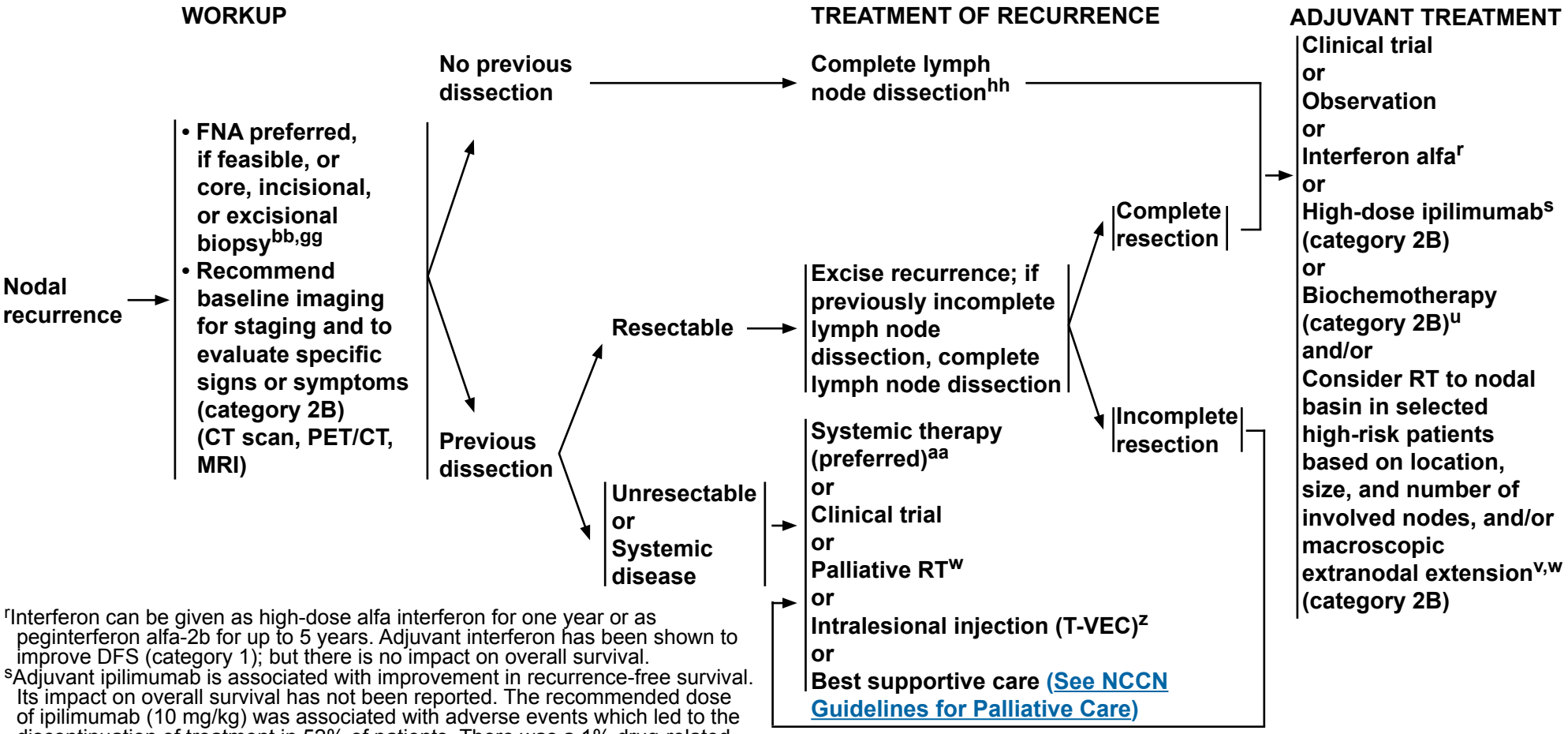

[r]Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); but there is no impact on overall survival.

[s]Adjuvant ipilimumab is associated with improvement in recurrence-free survival. Its impact on overall survival has not been reported. The recommended dose of ipilimumab (10 mg/kg) was associated with adverse events which led to the discontinuation of treatment in 52% of patients. There was a 1% drug-related mortality rate.

[u]For biochemotherapy, See Other Systemic Therapies (ME-E 2 of 5).

[v]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in relapse-free or overall survival, and its benefits must be weighed against potential toxicities.

[w]See Principles of Radiation Therapy for Melanoma (ME-D).

[z]T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was most pronounced in Stage IIIB, IIIC and Stage IV-M1a disease and in patients who were treatment naive.

[aa]See Systemic Therapy for Metastatic or Unresectable Disease (ME-E 1 of 5).

[bb]Initial clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Obtain tissue for genetic analysis from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy or if the mutation status is relevant to eligibility for participation in a clinical trial.

[gg]Biopsy preferred if recurrence is unresectable.

[hh]See Principles of Complete Lymph Node Dissection (ME-C).

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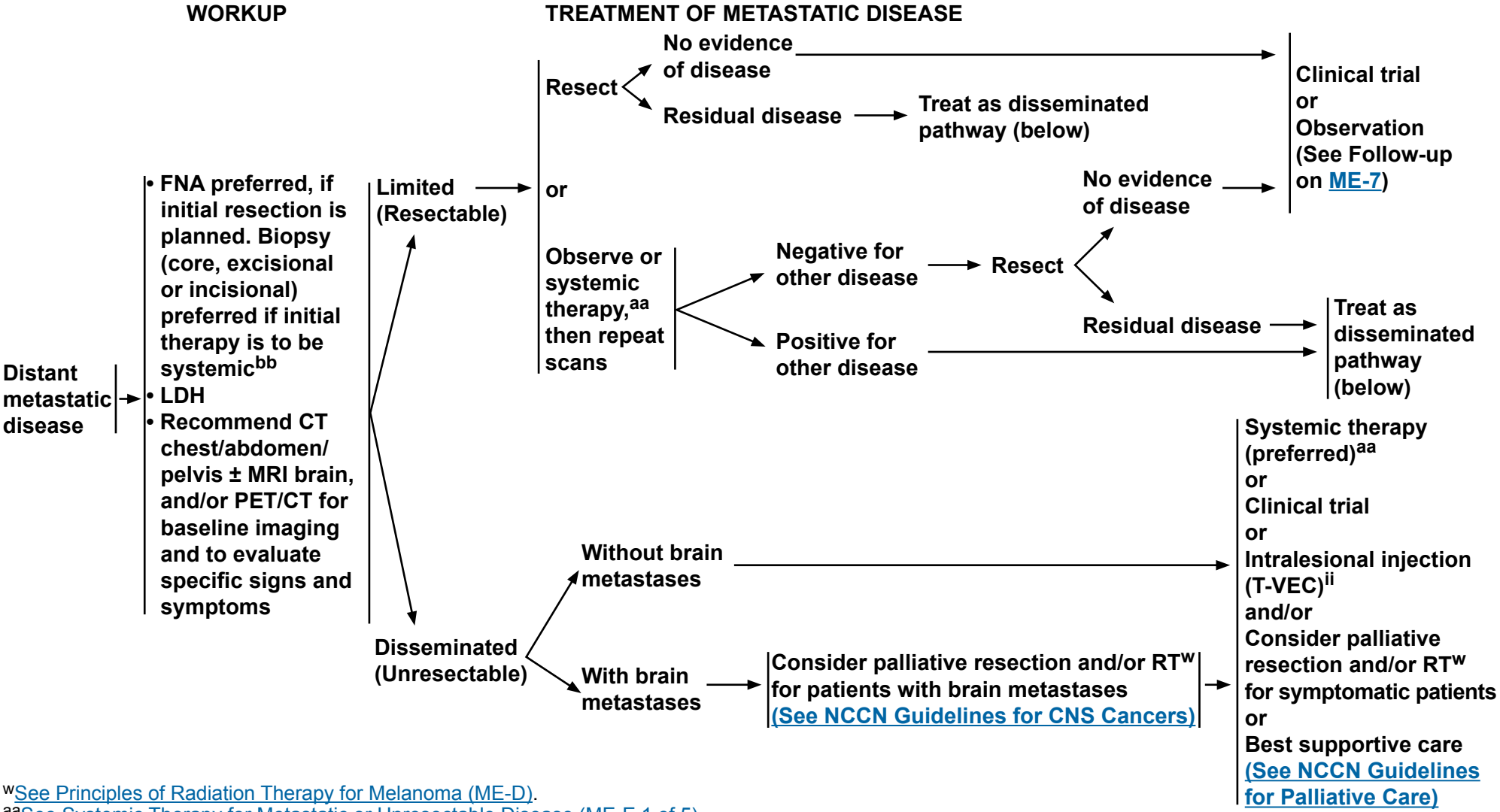

[w] See Principles of Radiation Therapy for Melanoma (ME-D).

[aa] See Systemic Therapy for Metastatic or Unresectable Disease (ME-E 1 of 5).

[bb] Initial clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Obtain tissue for genetic analysis from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy or if the mutation status is relevant to eligibility for participation in a clinical trial.

[ii] T-VEC has shown a response rate (lasting ≥6 months) of 16% in highly selected patients with Stage IV-M1a disease (skin, subcutaneous, and/or remote nodes).

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Melanoma

NCCN Guidelines Index
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Discussion

PRINCIPLES OF BIOPSY

- **Excisional biopsy (elliptical, punch, or saucerization) with 1–3 mm margins preferred. Avoid wider margins to permit accurate subsequent lymphatic mapping.**
- **The orientation of the biopsy should be planned with definitive wide excision in mind (eg, parallel to lymphatics).**
- **Full-thickness incisional or punch biopsy[1] of clinically thickest portion of lesion acceptable, in certain anatomic areas (eg, palm/sole, digit, face, ear) or for very large lesions.**
- **Shave biopsy[1,2] may compromise pathologic diagnosis and complete assessment of Breslow thickness, but is acceptable when the index of suspicion is low.**

PRINCIPLES OF PATHOLOGY[3,4]

- **Biopsy to be read by a pathologist experienced in pigmented lesions.**
- **Minimal elements to be reported should include Breslow thickness (mm), histologic ulceration (present or absent), dermal mitotic rate per mm[2,5] Clark level (encouraged for lesions ≤1 mm, optional for lesions >1 mm), and peripheral and deep margin status of biopsy (positive or negative).**
- **Microsatellitosis (present or absent)[6]**
- **Encourage consistent reporting of these additional factors (compatible with American Academy of Dermatology recommendations[7]):**
  - **Location**
  - **Regression**
  - **Tumor-infiltrating lymphocytes (TILs)**
  - **Vertical growth phase (VGP)**
  - **Angiolymphatic invasion**
  - **Neurotropism**
  - **Histologic subtype**
  - **Pure desmoplasia, if present, or specify pure vs. mixed desmoplastic with spindle cell and/or epithelioid cells**
- **Consider use of comparative genomic hybridization (CGH) or fluorescence in situ hybridization (FISH) for histologically equivocal lesions.[8]**

[1]If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.

[2]For lentigo maligna melanoma in situ, a broad shave biopsy may help to optimize diagnostic sampling.

[3]While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside of a clinical study (trial).

[4]In the absence of metastatic disease, *BRAF* testing of the primary cutaneous melanoma is not recommended.

[5]Dermal mitotic rate should be determined using the "hot spot" technique and expressed as number of mitoses per square millimeter. (Piris A, Mihm Jr. MC, Duncan LM. AJCC melanoma staging update: impact on dermatopathology practice and patient management. J Cutan Pathol 2011;38:394-400).

[6]Microsatellitosis is defined in the CAP 2013 melanoma protocol (version 3.3.0.0) as "the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken." (Harrist TJ, Rigel DS, Day CL Jr, et al. "Microscopic satellites" are more highly associated with regional lymph node metastases than is primary melanoma thickness. Cancer 1984;53:2183-2187.)

[7]Bichakjian C,Halpern AC, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2011;65:1032-1047.

[8]CGH may be more accurate than FISH in identifying relevant genetic mutations.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Clinical Margins[2]
In situ[1]	0.5–1.0 cm
≤1.0 mm	1.0 cm (category 1)
1.01–2 mm	1–2 cm (category 1)
2.01–4 mm	2.0 cm (category 1)
>4 mm	2.0 cm (category 1)

- **Margins may be modified to accommodate individual anatomic or functional considerations.**

[1]For large melanoma in situ (MIS), lentigo maligna type, surgical margins >0.5 cm may be necessary to achieve histologically negative margins; techniques for more exhaustive histologic assessment of margins should be considered. For selected patients with positive margins after optimal surgery, consider topical imiquimod (for patients with MIS) or RT (category 2B).
[2]Excision recommendations are based on measured clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist (category 1).

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PRINCIPLES OF COMPLETE LYMPH NODE DISSECTION

Adequacy of regional lymph node dissection:

- **An anatomically complete dissection[1] of involved nodal basin is required.**
- **In the groin, consider elective iliac and obturator lymph node dissection if clinically positive inguinofemoral nodes or ≥3 inguinofemoral nodes are positive (category 2B).**
- **Iliac and obturator lymph node dissection is indicated if pelvic CT is positive (category 2A) or if Cloquet's node is positive (category 2B).**
- **For primary melanomas of the head and neck with clinically or microscopically positive lymph nodes in the parotid gland, a superficial parotidectomy and appropriate neck dissection of the draining nodal basins is recommended.**

[1]Anatomic boundaries of lymph node dissection should be described in operative report.

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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Consider RT in the following situations:[1]

PRIMARY DISEASE

- **Adjuvant treatment in selected patients with factors including, but not limited to deep desmoplastic melanoma with narrow margins, extensive neurotropism, or locally recurrent disease.**

REGIONAL DISEASE[2]

- **Adjuvant treatment in selected patients following resection of clinically appreciable nodes (category 2B)[3] if**
  - **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**
- **Palliative**
  - **Unresectable nodal, satellite, or in-transit disease**

METASTATIC DISEASE

- **Brain metastases (See NCCN Guidelines for Central Nervous System Cancers)**
  - **Stereotactic radiosurgery either as adjuvant or primary treatment**
  - **Whole brain radiation therapy, either as adjuvant (category 2B) or primary treatment[4]**
- **Other symptomatic or potentially symptomatic soft tissue and/or bone metastases[2]**

[1]Interactions between radiation therapy and systemic therapies (eg, *BRAF* inhibitors, interferon alfa-2b, immunotherapies, and checkpoint inhibitors) need to be very carefully considered as there is potential for increased toxicity.
[2]A wide range of radiation dose/fractionation schedules is effective. Hypofractionated regimens may increase the risk for long-term complications.
[3]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in relapse-free or overall survival. Its benefits must be weighed against potential toxicities.
[4]Adjuvant whole brain radiation following resected melanoma brain metastasis is controversial and should be considered on an individual patient basis.

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Continue

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA
(References)

Primary Disease

- Chen JY, Hruby G, Scolyer RA, et al. Desmoplastic neurotropic melanoma: a clinicopathologic analysis of 128 cases. Cancer 2008;113:2770-2778.
- Guadagnolo BA, Prieto V, Weber R, et al. The role of adjuvant radiotherapy in the local management of desmoplastic melanoma. Cancer. 2014;120:1361-1368.
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Regional Disease

- Agrawal S, Kane JM, 3rd, Guadagnolo BA, et al. The benefits of adjuvant radiation therapy after therapeutic lymphadenectomy for clinically advanced, high-risk, lymph node-metastatic melanoma. Cancer 2009;115:5836-5844.
- Beadle BM, Guadagnolo BA, Ballo MT, et al. Radiation therapy field extent for adjuvant treatment of axillary metastases from malignant melanoma. Int J Radiat Oncol Biol Phys 2009;73:1376-1382.
- 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;13:589-597.
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- Lee RJ, Gibbs JF, Proulx GM, Kollmorgen DR, et al. Nodal basin recurrence following lymph node dissection for melanoma: implications for adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 2000;46:467-474.

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Continue

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA
(References)

Metastatic Disease

- Atkins MB, Sosman JA, Agarwala S, et al. Temozolomide, thalidomide, and whole brain radiation therapy for patients with brain metastasis from metastatic melanoma: a phase II Cytokine Working Group study. Cancer 2008;113: 2139-2145.
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- Fogarty G, Morton RL, Vardy J, et al. Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial. BMC Cancer 2011;11:142.

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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

Metastatic or unresectable disease →

FIRST-LINE THERAPY[1]

- Immunotherapy
  - Anti PD-1 monotherapy
    - ◊ Pembrolizumab[2]
    - ◊ Nivolumab (category 1)[2]
  - Nivolumab/ipilimumab[2,3]
- Targeted therapy if *BRAF* mutated; preferred if clinically needed for early response
  - Combination therapy (preferred)
    - ◊ Dabrafenib/trametinib[2] (category 1)
    - ◊ Vemurafenib/cobimetinib[2,4] (category 1)
  - Single agent therapy
    - ◊ Vemurafenib (category 1)[2]
    - ◊ Dabrafenib (category 1)[2]
- Clinical trial

→ **Disease progression or Maximum clinical benefit from *BRAF* targeted therapy**

PERFORMANCE STATUS (PS)

PS 0–2 →

SECOND-LINE OR SUBSEQUENT THERAPY[5]

- Anti PD-1 monotherapy
  - Pembrolizumab[2]
  - Nivolumab[2]
- Nivolumab/ipilimumab[2,3]
- Ipilimumab (category 1)[2,6]
- Targeted therapy if *BRAF* mutated
  - Combination therapy (preferred)
    - ◊ Dabrafenib/trametinib[2]
    - ◊ Vemurafenib/cobimetinib[2,4]
  - Single agent therapy
    - ◊ Vemurafenib[2]
    - ◊ Dabrafenib[2]
- High-dose IL-2[7]
- Biochemotherapy[8] (category 2B)
- Cytotoxic agents[8]
- Imatinib for tumors with activating mutations of *C-KIT*
- Clinical trial

PS 3–4 → **Consider best supportive care (See NCCN Guidelines for Palliative Care)**

[1]The choice of a treatment is based on evaluation of the individual patient.
[2]See Management of Toxicities of Immunotherapy and Targeted Therapy (ME-F)
[3]Nivolumab/ipilimumab combination therapy is associated with improved relapse-free survival compared with single agent nivolumab or ipilimumab, at the expense of significantly increased toxicity. Compared to single agent therapy, the impact of nivolumab/ipilimumab combination therapy on overall survival is not known. The phase III trial of nivolumab/ipilimumab versus either nivolumab or ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage III or IV melanoma.
[4]In previously untreated patients with unresectable Stage IIIC or Stage IV disease, the combination of vemurafenib/cobimetinib was associated with improved PFS and response rate when compared to vemurafenib alone. The impact on overall survival compared to single agent vemurafenib is unknown.
[5]Consider second-line agents if not used first line and not of the same class.
[6]Re-induction with ipilimumab may be considered for select patients who experienced no significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease >3 months.
[7]High-dose IL-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, IL-2 therapy may be considered (category 2B). Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.
[8]For a list of cytotoxic regimens and biochemotherapy regimens, see (ME-E 2 of 5)

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OTHER SYSTEMIC THERAPIES

Cytotoxic Regimens for Metastatic Disease[1]
- **Dacarbazine**
- **Temozolomide**
- **Paclitaxel**
- **Albumin-bound paclitaxel**
- **Carboplatin/paclitaxel**

Biochemotherapy for Metastatic Disease[1]
- **Dacarbazine or temozolomide, and cisplatin or carboplatin, with or without vinblastine or nitrosourea, and IL-2 and interferon alfa-2b (category 2B)**

Biochemotherapy for Adjuvant Treatment of High Risk Disease
- **Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b (category 2B)**

[1]In general, options for front-line therapy for metastatic melanoma include immunotherapy or targeted therapy.

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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE (REFERENCES)

Immunotherapy

Pembrolizumab

- Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015;16:908-918.
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Nivolumab

- Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375-384.
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Ipilimumab

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- Weber JS, Kahler KC, Hauschild A. Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab. J Clin Oncol 2012;30:2691-7.
- Hodi FS, O'Day SJ, McDermott DF, Weber RW, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Eng J Med 2010;363:711-723.
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517-2526.

Nivolumab/Ipilimumab

- 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.
- Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006-2017.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continue

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE (REFERENCES)

Targeted Therapy (Combination Therapy)

Dabrafenib/Trametinib

- Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015; 386:444-451.
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Vemurafenib/Cobimetinib

- Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867-1876.
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Targeted Therapy (Single-agent Therapy)

Vemurafenib

- Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;366:707-714.
- Chapman reference under Vemurafenib with: McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014;15:323-332.

Dabrafenib

- Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:1087-1095.
- Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358-365.

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Continue

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE (REFERENCES)

Targeted Therapy (Single-agent Therapy)

Imatinib for tumors with activating mutations of *C-KIT*

- Hodi FS1, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 2013;31:3182-3190.
- Carvajal RD, Antonescu CR, Wolchok, JD, et al. KIT as a therapeutic target in metastatic melanoma. JAMA 2011;395:2327-2334.

High-dose IL-2

- Rosenberg SA, Yang JC, Topalian SL, et al. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. JAMA 1994;271:907-913.
- Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17:2105-2116.
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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continue

OTHER SYSTEMIC THERAPIES (REFERENCES)

Cytotoxic Regimens for Metastatic Disease

Dacarbazine

- Serrone L, Zeuli M, Sega FM, et al. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J Exp Clin Cancer Res 2000;19:21-34.

Temozolomide

- Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000;18:158-166.

Paclitaxel

- Wiernik PH and Einzig AI. Taxol in malignant melanoma. J Natl Cancer Inst Monogr 1993;15:185-187.

Albumin-bound paclitaxel

- Hersh EM, O'Day SJ, Ribas A, et al. A phase 2 Clinical trial of nab-Paclitaxel in previously treated and chemotherapy-naïve patients with metastatic melanoma. Cancer 2010;116:155-163.
- Kottschade LA, Suman VJ, Amatruda T, et al. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage iv melanoma: a north central cancer treatment group study, N057E(1). Cancer 2011;117:1704-1710.

Paclitaxel/carboplatin

- Rao RD, Holtan SG, Ingle JN, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer 2006;106:375-382.
- Agarwala SS, Keilholz U, Hogg D, et al. Randomized phase III study of paclitaxel plus carboplatin with or without sorafenib as second-line treatment in patients with advanced melanoma. J Clin Oncol (Meeting Abstracts). 2007;25(18_suppl):8510.
- Hauschild A, Agarwala SS, Trefzer U, et al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. J Clin Oncol 2009;27:2823-2830.
- Flaherty KT, Lee SJ, Schuchter LM, et al. Final results of E2603: A double-blind, randomized phase III trial comparing carboplatin (C)/paclitaxel (P) with or without sorafenib (S) in metastatic melanoma. J Clin Oncol (ASCO Meeting Abstracts) 2010. 28:(suppl; abstr):8511.

Biochemotherapy for Metastatic Disease

Dacarbazine or temozolomide, and cisplatin or carboplatin, with or without vinblastine or nitrosourea, and IL-2 and interferon alfa-2b

- Legha SS, Ring S, Eton O, et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. J Clin Oncol 1998;16:1752-1759.
- Eton O, Legha SS, Bedikian AY, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. J Clin Oncol 2002;20:2045-2052.
- O'Day SJ, Boasberg PD, Piro L, et al. Maintenance biotherapy for metastatic melanoma with interleukin-2 and granulocyte macrophage-colony stimulating factor improves survival for patients responding to induction concurrent biochemotherapy. Clin Cancer Res 2002;8:2775-2781.
- Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. J Clin Oncol 2007;25:5426-5434.
- Atkins MB, Hsu J, Lee S, et al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2008;26:5748-5754.

Biochemotherapy for Adjuvant Treatment of High Risk Disease

Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b

- Flaherty LE, Othus M, Atkins MB, et al. Southwest Oncology Group S0008: a phase III trial of high-dose interferon Alfa-2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and interferon in patients with high-risk melanoma--an intergroup study of cancer and leukemia Group B, Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. J Clin Oncol 2014;32:3771-3778.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MANAGEMENT OF TOXICITIES ASSOCIATED WITH IMMUNOTHERAPY AND TARGETED THERAPY

Immunotherapy

- **Anti-PD1 Agents (pembrolizumab or nivolumab)**
  - Pembrolizumab and nivolumab may cause immune-mediated adverse reactions. Grade 3–4 toxicities are less common than with ipilimumab, but require similar expertise in management. The most common adverse events (>20% of patients) include fatigue, rash, pruritus, cough, diarrhea, decreased appetite, constipation, and arthralgia. Depending on the severity of the reaction, pembrolizumab and nivolumab should be discontinued
  - For moderate to severe immune-mediated pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hyperthyroidism, anti-PD1 therapy should be discontinued and systemic steroids should be administered.
  - Immune-mediated dermatitis sometimes responds to topical corticosteroids. For patients who do not respond, consider referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of immunotherapy.
  - Infliximab 5 mg/kg is preferred for treatment of severe immune-related colitis that does not respond promptly (within 1 week) to therapy with high-dose steroids. A single dose of infliximab is sufficient to resolve immune-related colitis in most patients.
  - For patients with preexistent hypophysitis due to ipilimumab, pembrolizumab may be administered if patients are on appropriate physiologic replacement endocrine therapy.
  - For more information on toxicities associated with pembrolizumab and nivolumab and the management of these toxicities, see the full prescribing information (www.fda.gov).
- **Ipilimumab**
  - Ipilimumab has the potential for significant immune-mediated complications. Although no longer required by the FDA, the Risk Evaluation and Mitigation Strategy program and/or experience in use of the drug as well as resources to follow the patient closely are essential for safe use of ipilimumab. Patient management information may be viewed at (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM249435.pdf). For more information and specific wording of the black box warning, see the full prescribing information (www.fda.gov)
  - For moderate to severe immune-mediated toxicity, ipilimumab should be discontinued and systemic steroids should be administered. See the prescribing information (www.fda.gov)
  - Immune-mediated dermatitis sometimes responds to topical corticosteroids. For patients who do not respond, consider referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of immunotherapy.
  - Infliximab 5 mg/kg is preferred for treatment of severe immune-related colitis that does not respond promptly (within 1 week) to therapy with high-dose steroids. A single dose of infliximab is sufficient to resolve immune-related colitis in most patients.
  - For severe hepatotoxicity refractory to high-dose steroids, mycophenolate is preferred over infliximab as second-line therapy.
  - Ipilimumab should be used with extreme caution, if at all, in patients with serious underlying autoimmune disorders.
- **Combination Therapy**
  - Clinically significant (grade 3 and 4) immune-related adverse events are seen more commonly with nivolumab/ipilimumab combination therapy compared to ipilimumab or nivolumab monotherapy. This emphasizes the need for careful patient education, selection and monitoring.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MANAGEMENT OF TOXICITIES ASSOCIATED WITH IMMUNOTHERAPY AND TARGETED THERAPY

Targeted Therapy (BRAF *or* combined BRAF/MEK inhibitors)

- **Dermatologic: Regular dermatologic evaluation and referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of targeted therapy is recommended. BRAF inhibitors are associated with cutaneous squamous cell carcinoma, extreme photosensitivity, and other dermatologic toxicities, which occur much less often with concurrent MEK inhibitors.**
- **Pyrexia: Pyrexia (defined as a temperature of 38.5 °C or greater) is a common (~55%) side effect of combining BRAF and MEK inhibitors and occurs less frequently with BRAF monotherapy (~20%). The pyrexia is episodic, and onset is often 2 to 4 weeks following the start of therapy with a median duration of 9 days. Pyrexia may be associated with chills, night sweats, rash, dehydration, electrolyte abnormalities, and hypotension. Stopping or holding dabrafenib and trametinib at the onset of pyrexia will often interrupt the episode, and treatment can be resumed with full-dose dabrafenib and trametinib upon cessation of pyrexia and pyrexia-related symptoms. Upon re-exposure to dabrafenib and trametinib, repeat pyrexia events can occur, but grade >3 events are uncommon (21%). In occasional instances of prolonged or severe pyrexia not responsive to discontinuation of dabrafenib and trametinib, low-dose steroids (prednisone 10 mg/day) can be used. Patients with pyrexia should be advised to use antipyretics as needed and increase fluid intake.**
- **For more information on toxicities associated with dabrafenib with or without trametinib, or vemurafenib with or without cobimetinib, and for the management of these toxicities, see the full prescribing information (www.fda.gov).**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Melanoma (7th ed., 2010)

Primary Tumor (T)

TX Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)

T0 No evidence of primary tumor

Tis Melanoma *in situ*

T1 Melanomas 1.0 mm or less in thickness

T2 Melanomas 1.01 -- 2.0 mm

T3 Melanomas 2.01 -- 4.0 mm

T4 Melanomas more than 4.0 mm

Note: a and b sub categories of T are assigned based on ulceration and number of mitoses per mm^2 as shown below:

T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤1.0	a: w/o ulceration and mitosis $<1/mm^2$ b: with ulceration or mitoses $\geq 1/mm^2$
T2	1.01-2.0	a: w/o ulceration b: with ulceration
T3	2.01-4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

NX Patients in whom the regional lymph nodes cannot be assessed (eg, previously removed for another reason)

N0 No regional metastases detected

N1-3 Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Note: N1-3 and a-c sub categories are assigned as shown below:

N Classification	*No. of Metastatic Nodes*	*Nodal Metastatic Mass*
N1	1 node	a: micrometastasis* b: macrometastasis**
N2	2-3 nodes	a: micrometastasis* b: macrometastasis** c: in transit met(s)/ satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) *with* meta-static node(s)	

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Continue

Distant Metastasis (M)

M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

M Classification	*Site*	*Serum LDH*
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Anatomic Stage/Prognostic Groups

Clinical Staging*

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	AnyT	≥N1	M0
Stage IV	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

Pathologic Staging**

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T(1–4)a	N1a	M0
	T(1–4)a	N2a	M0
Stage IIIB	T(1–4)b	N1a	M0
	T(1–4)b	N2a	M0
	T(1–4)a	N1b	M0
	T(1–4)a	N2b	M0
	T(1–4)a	N2c	M0
Stage IIIC	T(1–4)b	N1b	M0
	T(1–4)b	N2b	M0
	T(1–4)b	N2c	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

**Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/22/14

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

In 2014, an estimated 76,100 patients will be diagnosed and about 9710 patients will die of melanoma in the United States.[1] However, these figures for new cases may represent a substantial underestimate, as many superficial and in situ melanomas treated in the outpatient setting are not reported. The incidence of melanoma continues to increase dramatically, at an overall rate of 33% for men and 23% women from 2002 to 2006.[2] Melanoma is increasing in men more rapidly than any other malignancy, and in women more rapidly than any other malignancy except lung cancer. The lifetime risk of developing melanoma in the year 2005 for someone born in the United States may be as high as 1 in 55.[3] The median age at diagnosis is 59 years. On average, an individual loses 20.4 years of potential life as a result of melanoma mortality compared to 16.6 years for all malignancies.[4]

Risk factors for melanoma include a positive family history of melanoma, prior melanoma, multiple clinically atypical moles or dysplastic nevi,[5,6] and rarely inherited genetic mutations. Genetic counseling could be considered for individuals with a strong family history. In addition to genetic factors, sun exposure may also contribute to the development of melanoma.[7] The interaction between genetic susceptibility and environmental exposure is illustrated in individuals with an inability to tan and fair skin that sunburns easily who have a greater risk of developing melanoma.[8] However, melanoma can occur in any ethnic group and also in areas of the body without substantial sun exposure.

As with nearly all malignancies, the outcome of melanoma depends on the stage at presentation.[9] It is estimated that 82% to 85% of patients with melanoma present with localized disease, 10% to 13% with regional disease, and 2% to 5% with distant metastatic disease. In general, the prognosis is excellent for patients who present with localized disease and primary tumors 1.0 mm or less in thickness, with 5-year survival achieved in more than 90% of patients. For patients with localized melanomas more than 1.0 mm in thickness, survival rates range from 50% to 90%. The likelihood of regional nodal involvement increases with increasing tumor thickness. When regional nodes are involved, survival rates are roughly halved. However, within stage III, 5-year survival rates range from 20% to 70%, depending primarily on the nodal tumor burden. Long-term survival in patients with distant metastatic melanoma, taken as a whole, is less than 10%. However, even within stage IV, some patients have a more indolent clinical course that is biologically quite distinct from most patients with advanced disease.

With the advent of targeted therapy, there is increasing appreciation of the potential therapeutic implications of the variable incidence of specific genetic alterations among distinct clinical subtypes of melanoma. The four currently described subtypes are: non-chronic sun damage (non-CSD): melanomas on skin without chronic sun-induced damage; CSD: melanomas on skin with chronic sun-induced damage signified by the presence of marked solar elastosis; acral: melanomas on the soles, palms, or sub-ungual sites; and mucosal: melanomas on mucosal membranes. In an analysis of 102 primary melanomas, the non-CSD subtype was found to have the highest proportion of BRAF mutations (56%) compared to CSD, acral, and mucosal subtypes (6%, 21%, and 3%, respectively).[10] On the other hand, incidence of KIT aberrations was 28%, 36%, and 39% in CSD, acral, and mucosal subtypes, respectively, but 0% in non-CSD subtypes. NRAS mutations were found in 5% to 20% of the subtypes.

By definition, the National Comprehensive Cancer Network (NCCN) practice guidelines cannot incorporate all possible clinical variations and

are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members while developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The NCCN Melanoma Panel strongly supports early diagnosis and appropriate treatment of melanoma, including participation in clinical trials where available.

Clinical Presentation and Workup

Biopsy

Patients presenting with a suspicious pigmented lesion optimally should undergo an excisional biopsy, preferably with negative margins. The orientation of the excisional biopsy should always be planned with definitive treatment in mind (eg, a longitudinal orientation in the extremities). With the increasing use of lymphatic mapping and sentinel node biopsy, biopsies should also be planned so as not to interfere with this procedure. In this regard, wider margins for the initial diagnostic procedure should be avoided.

Excisional biopsy may be inappropriate for certain sites (including the face, palmar surface of the hand, sole of the foot, ear, distal digit, or subungual lesions) or for very large lesions. In these instances, a full-thickness incisional or punch biopsy of the clinically thickest portion of the lesion is an acceptable option. These procedures should provide accurate primary tumor microstaging, without interfering with definitive local therapy. If the initial biopsy is inadequate to make a diagnosis or to accurately microstage the tumor (based on evaluation by a dermatopathologist) for treatment planning, re-biopsy with narrow margin excision should be considered. Shave biopsy may compromise pathologic diagnosis and Breslow thickness assessment. However, it is acceptable in a low suspicion setting. Panelists recognized that melanomas are commonly diagnosed by shave biopsy during screening in a dermatologist office, and that any diagnosis is better than none even if microstaging may not be complete.

Pathology Report

In the revised AJCC staging system, patients with melanoma are categorized into three groups: localized disease with no evidence of metastases (stage I–II), regional disease (stage III), and distant metastatic disease (stage IV).[9,11] In patients with localized melanoma (stage I or II), Breslow tumor thickness, ulceration, and mitotic rate are the three most important characteristics of the primary tumor predicting outcome.[9]

Mitotic rate is an indicator of tumor proliferation and is measured as the number of mitoses per mm^2. The latest AJCC staging manual recommended the “hot spot” technique for calculating the mitotic rate.[11,12] Barnhill and colleagues[13] evaluated the importance of mitotic rate in the context of other known major prognostic factors in localized melanoma. In a multivariate analysis including mitotic rate and ulceration, tumor thickness and mitotic rate (<1, 1–6, >6) emerged as the most important independent prognostic factors. Several other studies have also confirmed the prognostic importance of mitotic rate in patients with primary cutaneous melanoma.[14-17] In the evidence-based derivation of the 2010 AJCC staging system, mitotic rate greater than or equal to 1 per mm^2 was independently associated with worse disease-specific survival (DSS), especially in patients with melanoma less than or equal to 1.0 mm thick. As such, mitotic rate has replaced Clark level as a criterion for upstaging patients with melanomas less than or equal to 1.0 mm in thickness from IA to IB.[18,19]

Consistent with the American Academy of Dermatology (AAD) Task Force, NCCN recommends the inclusion of additional factors such as vertical growth phase (VGP), tumor-infiltrating lymphocytes (TIL), and regression in the report.[20,21] The detection of microsatellites in the initial biopsy or wide excision specimen should be reported, as this defines at least N2c, stage IIIB disease. According to the 2013 College of American Pathologists protocol, a microsatellite is defined as the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken.[22,23]

Pathologists should also note cases of pure desmoplastic melanoma (as opposed to mixed desmoplasia with spindle cell and/or epithelioid cells) as this may impact decision on SLNB.

Some melanocytic proliferations can be diagnostically challenging. Examples include atypical melanocytic proliferation, melanocytic tumor of uncertain malignant potential, superficial melanocytic tumor of uncertain significance, atypical Spitz tumor, and atypical cellular blue nevus. These lesions are more frequently seen in younger patients, and when suspected, referral to a pathologist with expertise in atypical melanocytic lesions is recommended. In cases where melanoma is included in the differential diagnosis, the pathology report should include prognostic elements as for melanoma. Comparative genomic hybridization (CGH) or fluorescence in situ hybridization (FISH) may be helpful in detecting the presence of selected gene mutations for histologically equivocal lesions. CGH is a more comprehensive technique than FISH that may offer higher sensitivity and specificity in identifying relevant copy number changes, as suggested by a small study on atypical Spitz tumors.[24]

Among patients with nodal metastases (stage III), the number of metastatic nodes and clinical nodal status (nonpalpable vs. palpable) are the most important predictors of survival. For patients with a positive sentinel lymph node, prognostic factors include number of positive nodes, tumor burden in the sentinel node, primary tumor thickness, mitotic rate and ulceration, and patient age. For patients with clinically positive nodes, prognostic factors include number of positive nodes, primary tumor ulceration, and patient age.[25]

The site of metastases is the most significant predictor of outcome among patients with distant metastases (stage IV). The 3 risk categories recognized by the AJCC are skin soft tissue and remote nodes, visceral-pulmonary, and visceral-nonpulmonary.[9,11] Elevated lactate dehydrogenase (LDH) is also an independent predictor of poor outcome in patients with stage IV disease and has been incorporated into the AJCC staging system.[26-28]

NCCN Recommendations

For the pathology report, the NCCN Melanoma Panel recommends at a minimum the inclusion of Breslow thickness, ulceration status, mitotic rate, deep and peripheral margin status (positive or negative), presence or absence of microsatellites, pure desmoplasia if present, and Clark level for nonulcerated lesions 1.0 mm or less where mitotic rate is not determined. Ideally, mitotic rate should be reported for all lesions, as it is emerging as an independent predictor of outcome. When pure desmoplastic melanoma is suspected, referral to an experienced dermatopathologist for an examination of the entire lesion should be considered.

The panel agreed that recording of additional parameters identified by the AAD task force would be helpful, but not mandatory. CGH or FISH

should be considered to detect the presence of selected gene mutations for histologically equivocal lesions.

For stage III patients, the NCCN Melanoma Panel recommends reporting the number of positive nodes, the total number of nodes examined, and the presence or absence of extranodal tumor extension. In addition, the panel recommends recording the size and location of tumor present in a positive sentinel node.

For stage IV patients, the NCCN Melanoma Panel recommends reporting all sites of metastatic disease, and the serum LDH (within normal limits or elevated) at diagnosis of stage IV.

Preliminary Workup

After the diagnosis of melanoma has been confirmed, a history and physical (H&P) examination as well as a complete dermatologic examination are recommended. Preliminary workup of the patient presenting with melanoma should include a detailed personal and family history, including any history of prior removal of melanoma or dysplastic nevi.[5] In the physical examination of patients with invasive melanoma, physicians should pay special attention to the locoregional area and lymph node drainage basin(s) of the established melanoma.

Clinical Staging

Patients can be clinically staged after histopathologic microstaging of the primary tumor, an H&P including examination of locoregional area and draining lymph nodes, and a complete skin examination. Patients are categorized according to the AJCC staging system. The NCCN Guidelines have further stratified clinical stage I patients into a group at very low risk of SLN involvement (ie, those with tumors ≤0.75 mm, regardless of other characteristics), for whom SLN biopsy is not generally recommended:

- Stage 0 (melanoma in situ)
- Stage IA or IB - 0.75 mm thick or less, regardless of other characteristics
- Stage IA - 0.76 to 1.0 mm thick, no ulceration, mitotic rate less than 1 per mm^2
- Stage IB-II - 0.76 to 1.0 mm thick with ulceration or mitotic rate greater than or equal to 1 per mm^2; or greater than 1.0 mm thick and any characteristic, clinically negative nodes
- Stage III - clinically positive nodes, microscopic satellitosis, and/or in-transit disease
- Stage IV - distant metastatic disease

Patients with microsatellites should be managed as stage III in workup, adjuvant therapy, and follow-up. In-transit metastasis is defined as intralymphatic tumor in skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the nearest regional lymph node basin.[22] The presence of microsatellites, clinically evident satellites, and/or regional intransit disease is all part of the biologic continuum of regional lymphatic involvement, and these are all associated with a poor prognosis.

Pathologic Staging

Patients with clinically localized stage I-II melanoma may be further pathologically staged by lymphatic mapping with sentinel lymph node biopsy (SLNB). Among patients with localized melanoma undergoing SLNB, the status of the sentinel node is the most important prognostic factor.[26] In multivariate analyses, Breslow thickness, mitotic rate and younger age were identified as independent predictors of a positive

sentinel lymph node (SLN).[18,19] In contrast to mitotic index, no threshold of age has been determined to be an independent predictor of a positive SLN. Young age alone is not a sufficient indication for performing SLNB.

While some studies suggest that patients with desmoplastic melanoma have a very low incidence of nodal involvement (0%–4%),[29-32] others have reported a higher rate of SLN positivity in pure desmoplastic melanoma (up to 14%).[33,34] In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial. Mixed desmoplastic melanomas have a rate of sentinel lymph node involvement similar to that of conventional melanoma.

Depending on the primary tumor thickness, ulceration, and other factors described above, 5% to 40% of patients undergoing SLNB will be upstaged from clinical stage I-II to pathologic stage III, based on subclinical micrometastatic disease in the SLN. Patients with a positive sentinel node have a distinctly better prognosis than those patients with clinically positive nodes containing macrometastatic disease.[26,35] The AJCC staging system has recognized this difference in prognosis among patients with pathologic stage III melanoma.[9]

Workup

There are several reasons to embark on a workup to determine the extent of disease in the melanoma patient. One is to establish a set of baseline images against which to compare future studies in a patient at risk for relapse. Another is to detect clinically occult disease that would affect immediate treatment decisions. A third reason is to define homogeneously staged patients for inclusion into clinical trials. Although patients greatly value the negative result of a cross-sectional imaging study, physicians need to be cautious about over interpreting the significance of the findings, recognizing that all tests have relatively insensitive lower limits of resolution. Finally, any test carries the very real possibility of detecting findings unrelated to the melanoma, findings that can lead to morbid invasive biopsy procedures, or at the very least substantial patient anxiety while awaiting results of interval follow-up studies.

The yield of routine blood work and imaging studies in screening patients with clinical stage I-II melanoma for asymptomatic distant metastatic disease is very low. Screening blood tests are very insensitive, and the findings of cross-sectional imaging are often nonspecific, with frequent false-positive findings unrelated to melanoma.[36-38]

The yield of imaging studies has been more extensively evaluated in the context of patients with stage III melanoma. In patients with a positive SLN, the yield of cross-sectional imaging in detecting clinically occult distant metastatic disease ranges from 0.5% to 3.7%.[39-42] True positive findings are most often found in patients with ulcerated thick primary tumors and a large tumor burden in their sentinel nodes. In asymptomatic patients with clinically positive nodes, the yield of routine cross sectional imaging is a bit higher than in patients with positive sentinel nodes, reported at 4% to 16%.[43-45] All of these series also report a significant incidence of indeterminate or false-positive radiologic findings that are unrelated to the melanoma.

These retrospective studies report minimum estimates, as it is very difficult to define a study population of truly “imaging-naïve” stage III patients. It is probable that, among the entire denominator of stage III patients, some would have been defined as stage IV based on imaging before the study cohort was assembled. Furthermore, as a substantial proportion of clinical stage III patients will ultimately develop distant metastases, the inability of cross-sectional imaging studies to detect

metastatic disease at diagnosis of stage III is a relatively poor predictor of future events.

Positron emission tomography (PET) scanning has attracted interest as a means of enhancing detection of subclinical metastatic disease. Most investigators have described very low yield and poor sensitivity in detecting metastatic disease in patients with clinically localized melanoma.[46-48] In patients with stage III disease, PET/CT scan may be more useful. In particular, PET/CT scans can help to further characterize lesions found to be indeterminate on CT scan, and can image areas of the body not studied by the routine body CT scans (ie, arms and legs).[49] A systematic review of 17 diagnostic studies documented PET sensitivity ranging from 68% to 87% and specificity ranging from 92% to 98% for stage III and IV melanoma compared to sensitivity ranging from 0% to 67% and specificity ranging from 77% to 100% for stage I and II melanoma.[50] Another large meta-analysis suggested that PET/CT was superior over CT in detecting distant metastases.[51]

NCCN Recommendations

Practices among the NCCN Member Institutions vary greatly with respect to the appropriate workup of a melanoma patient. In the absence of compelling data beyond the retrospective series cited above, for the most part, recommendation for the appropriate extent of workup is based on non-uniform consensus within the panel.

Routine blood tests are not recommended for patients with melanoma in situ or stage I and II disease. Routine cross-sectional imaging (CT, PET/CT, or MRI) is also not recommended for these patients. These tests should only be used to investigate specific signs or symptoms. The panel stressed the importance of a careful physical examination of the primary site, the regional lymphatic pathways and lymph node basin, and the remainder of the skin by the examining clinician. Although nodal basin ultrasound is not a substitute for SLNB, the procedure should be considered for patients with an equivocal regional lymph node physical exam prior to SLNB. Abnormalities or suspicious lesions on nodal basin ultrasound should be confirmed histologically.

Most panel members acknowledged the low yield of screening CT or PET/CT scans in patients with stage III melanoma. Based on the results of the studies reported in the literature and the absence of conclusive data, the panel left the extent of cross-sectional imaging to the discretion of the treating physician. In the case of positive SLNB findings, baseline imaging may be considered for staging and to assess specific signs or symptoms. For patients presenting with clinical stage III disease who have clinically positive node(s), all panel members believe it is appropriate to confirm the suspicion of regional metastatic disease, preferably with fine-needle aspiration (FNA), core biopsy, or open biopsy of the clinically enlarged lymph node. Clearly, in patients without an antecedent history of melanoma, this would have been the initial diagnostic test. At a minimum, a pelvic CT scan is recommended in the setting of inguinofemoral lymphadenopathy to rule out associated pelvic or retroperitoneal lymphadenopathy. Most of the panel also endorsed baseline cross sectional imaging for staging purposes and to evaluate specific signs or symptoms.

For the small group of patients presenting with stage III microsatellitosis or in-transit disease, the workup outlined above for clinical stage III nodal disease, including histologic confirmation of the in-transit metastasis, is appropriate.

For patients presenting with stage IV distant metastatic disease, all panel members agree it is appropriate to confirm the suspicion of metastatic disease with either FNA or open biopsy of the lesion. When

archival tissue is not available, biopsy is preferred to obtain sufficient tissue for genetic analysis (eg, BRAF or KIT mutational status) if considering targeted therapy or if it potentially impacts enrollment in clinical trials of targeted therapy (see *Treatment of Metastatic Melanoma*). However, the panel also recognized that brain metastases are typically treated without routine biopsy.

Panelists encourage baseline chest abdominal/pelvic CT with or without PET/CT in patients with stage IV melanoma. Because patients with metastatic melanoma have a high incidence of brain metastases, brain MRI or CT scan with contrast should be performed at presentation with stage IV disease, if patients have even minimal symptoms or physical findings suggestive of central nervous system (CNS) involvement, or if results of imaging would affect decisions about treatment.

Although LDH is not a sensitive marker for detecting metastatic disease, the panel recognizes its prognostic value. It is recommended that serum LDH be obtained at diagnosis of stage IV disease. Other blood work may be done at the discretion of the treating physician.

Treatment of Primary Melanoma

Wide Excision

Surgical excision is the primary treatment for melanoma. Several prospective randomized trials have been conducted in an effort to define optimal surgical margins for primary melanoma (Table 1).

In an international prospective study carried out by WHO, 612 patients with primary melanomas not thicker than 2.0 mm were randomized to wide excision with 1 cm or 3 cm margins.[52,53] At a median follow-up of 90 months, local recurrence, disease-free and overall survival rates were similar in both groups. Similarly, Swedish and French randomized trials confirmed that survival was not compromised by narrower margins in melanomas thinner than 2 mm.[54,55]

A multicenter European trial randomized 936 patients with melanoma thicker than 2.0 mm to wide excision with 2 or 4 cm margins.[56] The 5-year overall survival rate was similar in the two groups. This is in keeping with previous trials that found no survival benefits with margins wider than 2 cm for thicker lesions.[57-59] A systematic review and meta-analysis also reported that surgical excision margins of at least 1 cm and no more than 2 cm are adequate.[60]

Table 1. Studies that evaluated surgical margins of wide excision of melanoma

Study	Year	N	Followup (years)	Thickness (mm)	Margin (cm)	LR	OS
WHO[53]	1991	612	9	≤2	1 vs. 3	NS	NS
Sweden[54]	2000	989	11	0.9–2.0	2 vs. 5	NS	NS
Intergroup[57]	2001	468	10	1–4	2 vs. 4	NS	NS
France[55]	2003	326	16	≤2	2 vs. 5	NS	NS
UK[59]	2004	900	5	≥2	1 vs. 3	NS	NS
Sweden[56]	2011	936	6.7	>2	2 vs. 4	NS	NS

LR = local recurrence; OS = overall survival; NS = non-significant

Management of lentigo maligna and in situ melanoma may present unique problems because of the characteristic, yet unpredictable, subclinical extension of atypical junctional melanocytic hyperplasia, which may extend several centimeters beyond the visible margins.[61] In a prospective study of 1,120 patients with melanoma in situ treated by

Mohs surgery, 9-mm surgical margins resulted in removal of 99% of melanomas while 6-mm margins removed 86%.[62] Staged excision with or without immunohistochemical staining aimed at complete surgical excision with meticulous margin control have demonstrated high local control rates in lentigo maligna.[63]

Alternatives to Excision

Although surgical excision remains the standard of care for in situ melanoma, it is sometimes not feasible due to comorbidity or cosmetically sensitive tumor location. Topical imiquimod has emerged as a treatment option, especially for lentigo maligna.[64-68] However, long-term, comparative studies are still needed. Radiotherapy has also been used selectively for lentigo maligna. In a retrospective review by Farshad et al,[69] there was a 5% crude local failure rate with definitive radiation, with a mean time to recurrence of 45.6 months. Patients were prescribed up to 120 Gy in 10 fractions using low-energy Grenz rays, which deliver the full dose at the skin but attenuate to 50% of the dose at a depth of 1 mm. Four of the five recurrences were at the edge of the radiation field, and the authors suggested targeting a margin of at least 10 mm around the visible lesion. With more conventional doses between 35 Gy in 5 fractions to 50 Gy in 20 fractions using orthovoltage radiation, Harwood et al[70] reported only 1 marginal failure out of 19 patients, with a median time to tumor regression of 7 months. Since tumor border delineation for lentigo maligna is smaller on clinical exam than with Wood lamp or digital epiluminescence microscopy, collaboration with a dermatologist who can perform these procedures is necessary to help prevent these marginal failures.[71]

NCCN Recommendations

The clinical/surgical margins discussed below refer to those taken at the time of surgery and do not necessarily correlate with gross pathologic/histologic margins measured by pathologists.

For in situ melanoma, a measured margin of 0.5 to 1 cm around the visible lesion should be obtained. For large in situ lentigo maligna melanoma, surgical margins greater than 0.5 cm may be necessary to achieve histologically negative margins. In the absence of prospective clinical trials, this margin range is recommended based on panel consensus. More exhaustive histologic assessment of margins such as staged excision for lentigo maligna melanoma should be considered. Imiquimod and/or RT can be considered as non-standard options in highly selected cases.

For melanomas 1.0 mm or less, wide excision with a 1 cm margin is recommended (category 1). Wide excision with a 1 to 2 cm margin is recommended for melanomas measuring 1.01 to 2 mm in thickness (category 1). For melanomas measuring more than 2 mm in thickness, wide excision with 2 cm margins is recommended (category 1). Surgical margins may be modified to accommodate individual anatomic or cosmetic considerations. The panel recognized that 1 to 2 cm margins might be acceptable in anatomically difficult areas where a full 2 cm margin would be difficult to achieve.

Sentinel Lymph Node Biopsy

SLNB is a minimally invasive staging procedure developed to identify patients with subclinical nodal metastases at higher risk of recurrence, who could be candidates for complete lymph node dissection or adjuvant systemic therapy.[72] MSLT-I, an international, multicenter, phase III trial, was initiated in 1994 to evaluate the impact of initial management with SLNB on the DSS of patients presenting with localized melanoma. The final long-term results of this trial were recently reported.[73] This report largely confirmed the known role of SLNB as a very important staging test, but found no measurable impact of SLNB on DSS compared to wide excision alone, when considering all

patients. Patients undergoing SLNB had relapse-free survival improved by 7% to 10% compared to those being observed. This is in large part due to the higher rate of nodal relapse in the nodal observation group. In a prespecified retrospective subset analysis comparing patients with intermediate-thickness (1.2–3.5 mm) melanoma who had a positive SLN to patients with intermediate thickness melanomas who subsequently developed a clinically positive node while on nodal basin observation, this report confirmed a survival advantage to those with microscopic disease (56% vs. 41.5%, *P* = .04, by intention to treat). A similar survival advantage was not seen in patients with thick (>3.5 mm) melanomas and positive nodes.

The value of SLNB for patients with thin melanomas (1.2 mm or less) was not addressed specifically in the MSLT-I trial. Since patients with thin melanoma have a generally favorable prognosis, the role of SLNB in this cohort is unclear.[74] Among patients with thin melanoma, primary tumor thickness is the single factor that most consistently predicts SLN positivity, in large part because other high-risk features such as ulceration and high mitotic rate are seen so infrequently. A review by Andtbacka and Gershenwald[75] reported an overall SLN metastasis rate of 2.7% in patients with melanoma thinner than 0.75 mm. In patients with melanoma 0.75 to 1.0 mm thick, 6.2% of patients selected to undergo SLNB were found to have a positive SLN. A multi-institutional review of 1250 patients with thin melanomas (≤1 mm) found that less than 5% of melanomas thinner than 0.75 mm had positive SLNs regardless of Clark level and ulceration status.[76] For patients with thin melanomas and at least one risk factor (ulceration, Clark level IV, nodular growth, mitosis, regression, or age ≤40 years), the SLN positivity rate was higher (18%).[77] A number of studies have associated SLN status with disease-free or melanoma-specific survival in melanomas less than or equal to 1 mm thick,[78-80] but others reported no association.[81,82]

Other than thickness, individual studies have identified additional factors to be predictive of a positive SLN among patients with thin melanoma. These include Clark level,[76,78,79,81] mitotic rate,[19,79,83] ulceration,[26,76,84] lymphovascular invasion,[82] VGP,[85,86] and TIL.[87-89] However, data are not consistently reproducible in patients with thin melanomas.[75] The significance of tumor regression as a predictor is controversial, though most studies have reported no association.[90-92]

Meticulous pathologic examination of all sentinel nodes is mandatory. When micrometastases are not identified by routine hematoxylin and eosin (H&E) staining, serial sectioning and immunohistochemical staining should be performed. As the presence of even scattered clusters of melanoma cells in a sentinel node is clinically relevant, the AJCC was unable to determine a sentinel node tumor burden too low to report as metastatic disease. On the other hand, the presence of bland or benign-appearing melanocytes should be interpreted with caution. These “nodal nevi” can masquerade as metastatic disease. When any doubt is present, review by an experienced dermatopathologist is recommended.

NCCN Recommendations

The NCCN Melanoma Panel does not recommend SLNB for patients with in situ melanoma (stage 0). The panel discussed at length the lower limit of probability of sentinel node positivity that should prompt a discussion of SLNB for stage I melanoma. According to data discussed above, Breslow thickness is the main factor associated with SLN positivity for these lesions. There is little consensus on what other features are important, as conventional risk factors such as ulceration, high mitotic rate, and lymphovascular invasion are rare in melanomas

0.75 mm thick or less. In general, the panel does not recommend SLNB for stage IA or IB lesions that are very thin (0.75 mm or less). In the rare event that a conventional high-risk feature is present, the decision about SLNB should be left to the patient and the treating physician.

SLNB should be considered for patients with stage IA (ie, no ulceration, mitotic rate <1 per mm^2) melanomas that are 0.76 to 1.0 mm thick. As the yield of a positive SLNB in patients with stage IA melanoma is low and the clinical significance of a positive SLN in these patients remains unclear, panel consensus is not uniform. This is reflected in the category 2B designation. Any discussion of the procedure in this patient population should reflect the caveats, and should include a discussion about who should not undergo SLNB.

For patients with stage IB melanoma or stage II melanoma (0.76–1.0 mm thick with ulceration or mitotic rate greater than or equal to 1 per mm^2; or more than 1.0 mm thick), SLNB should generally be discussed and offered.

SLNB may also be considered for patients with resectable solitary in-transit stage III disease (category 2B recommendation). However, while SLNB may be a useful staging tool, its impact on the overall survival of these patients remains unclear. Likewise for patients with microsatellitosis, while SLN positivity would upstage the disease to N3, stage IIIC, its significance in treatment decisions has not been clearly defined. In patients who otherwise would be candidates for SLNB, the decision to not perform SLNB may be based on significant patient comorbidities or individual patient preference. Clinicians may consider forgoing SLNB on confirmed pure desmoplastic melanoma.

The validity of SLNB in accurately staging patients after prior wide excision is unknown. As such, wide excision before planned SLNB is discouraged, although patients may be considered for the procedure on an individual basis if they present after initial wide excision.

The panel discussed the appropriate management of clinically negative lymph nodes in patients at risk for regional metastases, in the event that SLNB is unavailable. Based on the results of three prospective randomized trials, the panel does not recommend routine elective lymph node dissection for this group. Wide excision alone or referral to a center where lymphatic mapping is available are both acceptable options in this situation. While nodal basin ultrasound surveillance would seem to be another reasonable option in this setting, its value has not been defined in prospective studies.

Lymph Node Dissection

Among patients with a positive sentinel node, published studies have revealed additional positive non-sentinel nodes in approximately 18% of the completion lymph node dissection specimens.[93,94] Factors most predictive of additional non-sentinel node involvement include the largest size of the SLN metastasis, the distribution of metastasis in the SLN (subcapsular vs, parenchymal), the number of SLNs involved, and primary tumor characteristics of thickness and ulceration. However, the impact of completion lymph node dissection on regional control and survival in the setting of a positive SLN has not been clearly demonstrated. MSLT-II is a prospective randomized trial in which patients with sentinel node metastases were randomized to undergo either immediate completion lymph node dissection or nodal basin ultrasound surveillance. This trial, which has completed accrual, should resolve the issue of whether complete lymph node dissection has an impact on outcome. (clinicaltrials.gov/show/NCT00297895).

Complete lymph node dissection consists of an anatomically thorough dissection of the involved nodal basin. The extent of lymph node

dissection is often modified according to the anatomic area of lymphadenopathy. In the absence of clinical or radiologic evidence, patients with melanoma metastatic to inguinal nodes are at risk for pelvic node involvement and candidates for elective pelvic lymph node dissection when there are more than three superficial nodes involved, when the superficial nodes are clinically positive, or when Cloquet's node is positive.[95-97]

NCCN Recommendations

If the sentinel node is negative, regional lymph node dissection is not indicated. Patients with stage III disease based on a positive SLN should be offered a complete lymph node dissection of the involved nodal basin. Nodal basin observation for these patients has not been studied sufficiently to be recommended as a standard option.

Patients presenting with clinically positive nodes without radiologic evidence of distant metastases should undergo wide excision of the primary site (if present) and complete lymph node dissection of the involved nodal basin. In the setting of inguinal lymphadenopathy, a pelvic dissection is recommended if the PET/CT or pelvic CT scan reveals iliac and/or obturator lymphadenopathy or if a positive Cloquet's lymph node is found intraoperatively (category 2B). Pelvic dissection also should be considered for clinically positive nodes or if more than three superficial nodes are involved (category 2B). For lesions in the head and neck with clinically or microscopically positive lymph nodes in the parotid gland, a parotidectomy alone is insufficient and the panel also recommended appropriate neck dissection of the draining nodal basins.[98]

One measure of the completeness of a regional lymph node dissection is the number of lymph nodes examined. However, the NCCN committee felt that available retrospective evidence to date was insufficient to mandate that a specific number of nodes be required to deem a lymph node dissection adequate for any designated lymph node basin. As a measure of quality control to ensure adequacy of lymphadenectomy, the committee recommended that the operative note fully describe the anatomic boundaries of the lymph node dissection.

Adjuvant Treatment for Melanoma

Low-Dose and Intermediate-Dose Interferon

Studies of low-dose and intermediate-dose interferon as adjuvant therapy for resected, high-risk melanoma have shown no improvement in overall survival with interferon. Some but not all trials have shown an improvement in relapse-free survival.[99-103] NCCN does not recommend use of low-dose or intermediate-dose interferon.

High-Dose Interferon and Pegylated Interferon

High-dose interferon (including one month of IV induction interferon followed by eleven months of subcutaneous maintenance interferon) has been evaluated in several randomized clinical trials. The ECOG 1684 trial compared high-dose interferon alfa-2b with observation in patients with stage IIB and III melanomas.[104] At a median follow-up of 6.9 years, a statistically significant improvement in relapse-free and overall survival was demonstrated for patients in the interferon group. However, at 12.6 years of follow-up, overall survival was not significantly different between the two groups, even though there was a significant benefit for relapse-free survival.[104] The results of a larger follow-up trial, ECOG 1690, also showed a relapse-free survival advantage but no overall survival advantage.[105] E1694 compared high-dose interferon alfa-2b with an experimental vaccine, GM2-KLH21. At approximately 2 years of median follow-up, the relapse-free and overall survivals were better in the interferon alfa-2b group compared to the vaccine group. More recently, concerns have been raised about the

worse-than-expected survival observed in the vaccine control group used in ECOG 1694.

A shorter course of high-dose interferon has also been evaluated. E1697 enrolled 1150 patients with resected cutaneous melanoma (T3 or T_{any}N1a-2a) randomized to receive one month of IV interferon versus observation.[106] The trial was closed after interim analysis showed no benefit for interferon in either relapse-free or overall survival. To investigate contribution of maintenance interferon, a phase II trial randomized 194 patients to either one month of high-dose IV interferon or the same induction followed by 11 months of subcutaneous interferon (the ECOG 1684 regimen). Although this study found no difference in median or 2-year relapse-free survival, overall survival favored the longer regimen (median 41.5 months vs. not reached, P = .05).[107]

The EORTC protocol (18991) randomized 1256 patients with completely resected stage III melanoma to either observation or pegylated interferon alfa treatment for an intended duration of five years.[108] Four-year relapse-free survival was significantly better in the interferon group compared to the observation group (45.6% vs. 38.9%); however, there was no significant effect of pegylated interferon on overall survival. Based on this data, pegylated interferon alfa received approval by the U.S. Food and Drug Administration (FDA) in 2011 as an option for adjuvant therapy for patients with melanoma with nodal involvement. The NCCN Panel has included pegylated interferon as an adjuvant option for completely resected nodal disease.

A post-hoc analysis of two large randomized phase III trials (EORTC1892 and EORTC18991) indicated that a reduction in risk for recurrence and death in patients treated with adjuvant interferon was observed primarily in patients with ulcerated primary melanomas.[109] The clinical and biologic significance of this observation remains unclear.

Although recent meta-analyses have confirmed a significant relapse-free survival benefit with adjuvant interferon therapy, evidence on overall survival benefits are mixed.[110-112] One analysis reported improved overall survival in 4 of 14 studies comparing interferon with observation,[111] while another found no significant difference.[112] There is panel consensus that high-level evidence supports interferon therapy for improving disease-free survival, but there is disagreement on its impact on overall survival. Adjuvant high-dose interferon is a toxic therapy that is not being used in all institutions, but panelists agree that it still may have a role in certain settings. If the decision is made to use adjuvant interferon, the best available evidence suggests that options include using either high-dose interferon with a planned duration of at least a year, or pegylated interferon with a planned duration of up to five years.

Adjuvant Radiation Therapy

Adjuvant radiation therapy (RT) is rarely necessary for excised local melanoma. One exception may be desmoplastic neurotropic melanoma (DNM), which tends to be locally aggressive. In a retrospective series of 128 patients with DNM (84% stage II), patients who did and did not receive adjuvant radiation had a similar incidence of local failure (7% with RT vs. 6% without) despite worse prognostic features in the radiated group (thicker tumors, deeper Clark level invasion, and narrower excision margins).[113] The authors concluded that radiation should be considered for patients with inadequate margins, which in this series occurred predominately in the head and neck region.

Radiation has a role in controlling nodal relapse in patients at risk. The largest retrospective review investigating the role of RT was performed by Agrawal et al.[114] Six hundred fifteen patients were evaluated who met the specific criteria portending a “high risk” of regional nodal relapse,

based on lymph node number, size, location, and extracapsular extension. At a median follow-up of 5 years, regional recurrence occurred in only 10.2% of the patients selected to receive adjuvant RT, compared to 40.6% of the non-radiated patients. Adjuvant radiation was associated with improved locoregional control on multivariate analysis ($P < .0001$). Of note, treatment-related morbidity was significantly increased with RT (5-year rate of 20% versus 13%, $P = .004$), particularly lymphedema. Interpretation of these results should take into consideration selection bias and many other potential forms of bias inherent in retrospective studies.

A prospective randomized trial of adjuvant nodal basin RT versus observation in patients at risk for nodal relapses has been recently reported. In this phase III trial, 250 non-metastatic patients with palpable lymphadenopathy at diagnosis or as an isolated palpable site of relapse underwent lymphadenectomy followed by either adjuvant radiation (48 Gy in 20 fractions) to the nodal basin or observation.[115] Eligible patients were required to have an LDH <1.5 times the upper limit of normal, as well as ≥1 parotid, ≥2 cervical or axillary or ≥3 groin positive nodes, a maximum nodal diameter ≥3 cm in neck, ≥4 cm in the axilla or groin, or nodal extracapsular extension. Lymph node field recurrence was significantly less frequent in the adjuvant radiation group (HR = 0.56; 95% CI, 0.32–0.98; $P = .041$) for all nodal basins. There was a statistically insignificant trend towards worse overall survival in the RT group (HR, 1.37; 95% CI, 0.94–2.01; $P = .12$). In the final analysis (mean follow-up of 73 months) reported in abstract form, locoregional symptoms were higher in the RT group ($P = .035$).[116] Adjuvant radiation was also associated with frequent grade 2 to 4 long-term toxicities in the head and neck (33%), axilla (41%–44%), and groin (38%–67%). Quality of life was statistically similar in both groups.

The NCCN Panel discussed at length the value of adjuvant RT in patients at high risk of recurrence. Panelists agreed that high-level evidence indicates that adjuvant RT is useful in preventing nodal relapse. However, some institutions argued that the increased incidence of late RT-related toxicity could potentially outweigh the benefit of reducing nodal basin recurrence. This, coupled with the trend towards worse overall survival in the RT arm resulted in substantial heterogeneity of opinion among panel members as to the role of adjuvant nodal basin RT.

Postoperative radiation with various fractionation schemes have been used in other clinical studies.[117-119] Hypofractionated radiotherapy appears as equally effective as standard fractionation. Although particular concern for toxicity should be exercised when using higher doses per fraction, all studied regimens appear to be similarly tolerated.

Some systemic therapy regimens may increase toxicity when given concurrently with radiation. For example, patients with surgically resected stage III melanoma receiving concurrent adjuvant radiation and interferon alfa experienced significant toxicity.[120] On the other hand, studies have demonstrated the safety of combining temozolomide with radiation when treating brain metastases.[121,122]

NCCN Recommendations

Most patients with in situ or early-stage melanoma will be cured by primary excision alone. However, patients who have desmoplastic lesions, especially those with extensive neurotrophism, are at high risk for local recurrence, especially if margins are suboptimal. Adjuvant radiation following surgery may be considered to improve local control. If optimal surgery cannot achieve a negative margin, topical imiquimod (for melanoma in situ) or radiotherapy may be considered in selected patients (category 2B). For patients with node-negative, early-stage

melanoma who are at risk for recurrence (stage IB or stage II, 1.0 mm thick or less with ulceration or mitotic rate greater than or equal to 1 per mm^2, or more than 1.0 mm thick) adjuvant treatment options include a clinical trial or observation. For patients with node-negative stage IIB or IIC disease, adjuvant treatment options include clinical trial, observation, or high-dose interferon alfa (category 2B).

For patients with stage III melanoma, adjuvant treatment options include clinical trial, observation, or interferon alfa (category 2B). Adjuvant RT (category 2B) may be considered for select patients with clinically positive nodes and features predicting a high risk of nodal basin relapse.

Consideration of adjuvant RT is a category 2B recommendation for patients with palpable high-risk nodal disease, reflecting a lack of uniform panel consensus on its value. The panel recognized that adjuvant RT may not be appropriate for many patients and emphasized that it is included not as a mandatory recommendation, but as an option to consider for select cases. Careful patient selection based on location, size, number of positive nodes, and gross (instead of histologic) extranodal extension is critical. The benefits of adjuvant RT must be weighed against the increased likelihood of long-term skin and regional toxicities that can affect quality of life.

Patient characteristics that suggest potential use of radiation are outlined in the study by Burmeister et al[115] and summarized above. Consideration should be given to potential interactions between radiation and systemic therapy.

Adjuvant high-dose and pegylated interferon are both appropriate options for patients with completely resected stage III disease, either positive sentinel nodes or clinically positive nodes Planned short-course IV interferon (as in E1697) is not recommended in any adjuvant setting. Treatment with adjuvant high-dose or pegylated interferon is currently a category 2B recommendation in all of the above cases because of its low benefit-to-risk ratio. Decisions about adjuvant interferon treatment should be made on an individual basis, after a thorough discussion with the patient about the potential benefits and side effects of therapy.

The use of adjuvant interferon in completely resected stage III intransit and in stage IV disease has not been tested in prospective trials, and the panel does not recommend that as an option in those settings. As such, the main option for adjuvant therapy in those settings is participation in a clinical trial. See *Treatment of Metastatic Melanoma*. For adjuvant therapy of recurrent disease, see *Treatment of Recurrence*.

Treatment of Metastatic Melanoma

Treatment for In-transit Disease

Many different treatment options, mostly locoregional, are available to patients presenting with stage III in-transit metastases. Treatment is based on the size, location, and number of tumor deposits, but evidence is limited and there is no consensus on the optimal approach. Enrollment in a clinical trial, if available, is the preferred choice.

Excision to clear margins is the mainstay for resectable regional recurrence. Although in-transit disease has a high probability of clinically occult regional nodal involvement, and a positive sentinel node in the presence of in-transit metastasis portends a more ominous prognosis, the impact of SLNB on outcome remains unknown.[123]

A number of non-surgical local approaches are being used. These include intralesional local injections with bacillus Calmette-Guérin

(BCG)[124], interleukin-2, or interferon alfa, laser ablation, and topical imiquimod.[125] Imiquimod may have some activity for small superficial dermal lesions but not for subcutaneous disease.[126] RT may be used for patients with unresectable symptomatic regional recurrence.

Isolated limb perfusion or infusion are techniques to regionally administer high doses of chemotherapy to an affected extremity while avoiding systemic drug exposure.[127,128] Melphalan is the drug most widely used for this technique. Isolated limb infusion has been reported by Thompson et al to be a simpler technique with response rates comparable to limb perfusion.[129] A study of isolated limb infusion in 128 patients achieved a complete response (CR) rate of 31%.[130] On the other hand, a modified hyperthermic isolated limb perfusion procedure achieved a higher CR rate of 63%, with 5-year survival observed in 38% of patients.[131]

Systemic therapy for locoregional recurrence is an option as well (see below).

Systemic Therapy

The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents, which have demonstrated better efficacy than traditional chemotherapy.

Immunotherapy

Ipilimumab, a monoclonal antibody directed to the immune checkpoint receptor termed “cytotoxic T lymphocyte antigen-4 (CTLA-4),” received FDA approval for treatment of metastatic melanoma in March 2011. Approval was based on a randomized phase III trial of 676 patients with unresectable metastatic disease that progressed during systemic therapy.[132] Patients received ipilimumab plus a glycoprotein 100 peptide vaccine (gp100), ipilimumab alone, or gp100 alone in a 3:1:1 ratio. Overall survival was significantly longer in patients receiving the combination (10.0 months; HR = 0.68 compared to gp100 alone; $P < .001$) or ipilimumab alone (10.1 months; HR = 0.66 compared to gp100 alone; $P = .003$) compared to those receiving gp100 only (6.4 months). Of note, 15 of 23 patients achieved partial response (PR) or stable disease after re-induction.

Ipilimumab stimulates T cells and is associated with substantial risk of immune-related reactions. Patients with underlying autoimmune disorders may be especially susceptible to serious reactions. In this pivotal trial, immune-related events were recorded in 60% of patients treated with the agent. Ten to 15% of treated patients experienced grade 3 or 4 events. Diarrhea was the most common immune-related reaction; severe cases were treated by high-dose corticosteroids. In all, 7 deaths were attributed to immune-related toxicity in the trial.

A second phase III study was conducted in 502 patients with previously untreated metastatic melanoma.[133] Patients were randomly assigned to dacarbazine plus ipilimumab or dacarbazine plus placebo. The primary endpoint was reached with the ipilimumab arm showing longer overall survival than the control arm (11.2 vs. 9.1 months). The 3-year survival rate was 20.8% and 12.2% for patients receiving ipilimumab and placebo, respectively (HR = 0.72; $P < .001$). A 56% incidence of grade 3 or 4 adverse events was recorded in the ipilimumab arm, but no drug-related deaths occurred. This trial employed a dose of ipilimumab more than three times higher than the FDA-approved dose. Outside of clinical trials, NCCN Member Institutions use ipilimumab at the FDA-approved dose and schedule and do not use the combination of dacarbazine and ipilimumab. Another open-label, phase II study in 72 patients with melanoma with brain metastases reported a 24% disease control rate of the brain in the neurologically asymptomatic cohort.[134]

Therapies Targeted Against BRAF Mutations

Approximately half of patients with metastatic melanoma harbor an activating mutation of the intracellular signaling kinase, BRAF.[135] Vemurafenib is a specific inhibitor of signaling by mutated BRAF.[136] A randomized phase III trial compared vemurafenib to dacarbazine in 675 patients with previously untreated metastatic melanoma containing a V600 mutation of BRAF.[137] Vemurafenib was associated with improved overall and progression-free survival (RR of death = 0.37; RR of death or progression = 0.26; $P < .001$). At six months, 84% and 64% of patients were alive in the vemurafenib and dacarbazine groups, respectively. Overall, 38% of patients receiving vemurafenib required dose modification due to adverse events. Skin complications were frequently associated with the agent: 18% of vemurafenib-treated patients developed cutaneous squamous cell carcinoma or keratoacanthoma that required simple excision, while 12% experienced grade 2 or 3 photosensitivity skin reactions. Arthralgia was the most common (21%) non-cutaneous side effect. Based on results of this randomized study, vemurafenib was approved by the FDA in August 2011 for treatment of metastatic or unresectable melanoma with the BRAF mutation. Another phase II trial in 132 previously treated patients reported an overall response rate of 53% and median survival of 15.9 months.[138] Secondary skin lesions were detected in 26% of patients.

Following vemurafenib, two additional agents targeting BRAF-mutated disease have been approved by the FDA. Dabrafenib is a BRAF inhibitor studied in an open-label, phase III trial.[139] The trial randomized 250 patients with untreated stage IV or unresectable stage III melanoma harboring the BRAF V600E mutation to receive dabrafenib or dacarbazine. The primary endpoint was progression-free survival, which was reached as dabrafenib resulted in 5.1 months versus 2.7 months for dacarbazine (HR, 0.30; 95% CI, 0.18–0.51; $P < .0001$). Grade 2 or higher adverse events occurred in 53% of patients receiving dabrafenib, although grade 3 or 4 events were uncommon. The most frequent side effects were skin-related toxicity, fever, fatigue, arthralgia, and headache. Compared to vemurafenib, dabrafenib was associated with less cutaneous squamous cell carcinoma or keratoacanthoma (6%) and phototoxic reactions were rare; however, pyrexia was more common (11%). A phase II study was conducted on 172 patients with BRAF-mutated melanoma and asymptomatic brain metastases.[140] An overall intracranial response was achieved in 39% and 31% of previously untreated and treated patients, respectively.

Trametinib is an oral small-molecule inhibitor of MEK1 and MEK2, which are downstream of BRAF in the MAP kinase signal transduction pathway. A phase III, open-label study randomly assigned 322 patients with metastatic melanoma to trametinib or chemotherapy.[141] All participants had V600E or V600K BRAF mutations. Compared to the chemotherapy group, the trametinib arm showed improved progression-free survival (4.8 vs. 1.5 months; HR, 0.45; 95% CI, 0.33–0.63; $P < .001$) and 6-month overall survival (81% vs. 67%; HR, 0.54; 95% CI, 0.32–0.92, $P = .01$). The most common side effects associated with trametinib include rash, diarrhea, and peripheral edema. Unlike BRAF inhibitors, trametinib was not associated with secondary skin lesions.

In an open-label, phase II study, trametinib failed to induce objective responses in 40 patients previously treated with a BRAF inhibitor.[142] Compared to BRAF inhibitors, trametinib is associated with a lower response rate in previously untreated patients (22% vs. 48%–50%).[137,141,143]

The Cobas 4800 BRAF V600 mutation test, a companion diagnostic test to determine the tumor mutational status, received approval along with vemurafenib. Mutational status should be tested by an FDA-approved test or by a facility approved by Clinical Laboratory Improvement

Amendments (CLIA). The THxID BRAF test, a companion genetic test for the V600E or V600K BRAF mutation, received approval along with dabrafenib and trametinib.

Combined Targeted Therapies

Despite high initial response rates, half of the patients treated with targeted monotherapies relapse within around 6 months.[138,141,143] A phase I/II, open-label trial was conducted on 247 patients with metastatic melanoma and V600 mutations to test the efficacy and safety of combination therapy.[144] Patients were randomly assigned to dabrafenib plus trametinib or dabrafenib alone. Compared to monotherapy, combination therapy improved the response rate (76% vs. 54%; *P* = .03) and progression-free survival (9.4 vs. 5.8 months; HR, 0.39; 95% CI, 0.25–0.62; *P* < .001). Incidence of secondary squamous cell skin carcinoma was lower in the combination arm (7% vs. 19%), but pyrexia was more common (71% vs. 26%). Two important phase III trials comparing combination therapy with dabrafenib or vemurafenib monotherapy are ongoing.

Other Targeted Therapies

KIT (commonly known as *c-kit*) mutations have been associated most commonly with mucosal and acral subtypes of melanoma.[10] Imatinib is a tyrosine kinase inhibitor active against BCR-ABL in chronic myelogenous leukemia and mutated KIT in gastrointestinal stromal tumors. A phase II study of 43 patients with *KIT*-mutated metastatic melanomas demonstrated a 23% overall response rate with imatinib therapy.[145] Unfortunately, most of these responses were of limited duration. Like BRAF inhibitors, patient selection by molecular screening is essential to identify patients who might potentially benefit; previous studies on unselected patients yielded no meaningful responses.[146,147]

New Challenges

Although approval of immunotherapeutic and targeted agents has significantly altered the initial management of patients with stage IV melanoma, each agent has unique limitations. For ipilimumab, there is the potential for serious autoimmune toxicity, clinical responses may take months to become apparent, and the overall response rate is less than 20%. However, when responses are seen, they can be quite durable. BRAF inhibitors, on the other hand, are associated with a high response rate of 50% in patients with a V600 mutated BRAF gene, and responses may be seen in days to weeks after starting the drug. Unfortunately, the median duration of response is only 5 to 6 months.

The success of these agents has prompted a new wave of clinical trials to address their use in the adjuvant setting and to define mechanisms of primary and acquired resistance. The pace of change underscores the importance of participating in a clinical trial whenever possible.

Chemotherapy and Biological Therapy

Common cytotoxic agents being used in patients with metastatic melanoma include dacarbazine,[148,149] temozolomide,[149] high-dose interleukin-2 (IL-2),[150-153] and paclitaxel with or without carboplatin.[154-158] These have demonstrated modest response rates less than 20% in first-line and second-line settings.

Traditional paclitaxel formulation is solvent-based. Albumin-bound paclitaxel, also known as *nab*-paclitaxel, is a solvent-free formulation bound by stable albumin particles that has lower toxicity and higher bioavailability. This formulation yielded response rates of 22% to 26% in phase II trials among chemotherapy-naïve patients with metastatic melanoma.[159,160]

Little consensus exists regarding optimal standard chemotherapy for patients with metastatic melanoma, which most likely reflects the low level of activity of older FDA-approved agents.[161,162]

Biochemotherapy

Biochemotherapy is the combination of chemotherapy and biological agents. In single institutional phase II trials, biochemotherapy (cisplatin, vinblastine, dacarbazine, interferon alfa, and IL-2) produced overall response rates of 27% to 64% and CR rates of 15% to 21% in patients with metastatic melanoma.[163-165] A small phase III randomized trial comparing sequential biochemotherapy (dacarbazine, cisplatin, vinblastine with IL-2, and interferon alfa administered on a distinct schedule) with dacarbazine plus cisplatin and vinblastine (CVD) showed response rates of 48% for biochemotherapy regimen compared to 25% for CVD alone; median survival for patients treated with biochemotherapy was 11.9 months versus 9.2 months for CVD.[166] In a phase III randomized intergroup trial (E3695), biochemotherapy (cisplatin, vinblastine, dacarbazine, IL-2, and interferon alpha-2b) produced a slightly higher response rate and progression free-survival than CVD alone, but it was not associated with either improved quality of response or overall survival.[167] Biochemotherapy was substantially more toxic than CVD. Additional attempts to decrease toxicity of biochemotherapy by administering subcutaneous outpatient IL-2 did not show a substantial benefit of biochemotherapy versus chemotherapy alone.[168-170] A meta-analysis also showed that although biochemotherapy improved overall response rates, there was no survival benefit for patients with metastatic melanoma.[171]

Palliative Radiation Therapy

Contrary to common perception that melanoma is radio-resistant, radiation often achieves good palliation of symptomatic metastatic disease. Studies have shown a 39% to 55% and 68% to 84% incidence of significant symptom relief for CNS and non-CNS metastasis, respectively.[172-174] The reported clinical CR rate ranges from 17% to 69%, with 49% to 97% achieving either a PR or CR.[119,175,176] Stereotactic radiosurgery (SRS) is gaining importance in the management of brain metastases from melanoma with a local tumor control rate of 73%.[177]

NCCN Recommendations

Stage III: In-transit Metastases

Treatment in the context of a clinical trial is the preferred option. For those with a single or a small number of in-transit metastases, complete surgical excision with histologically negative margins is preferred, if feasible. In the patient undergoing curative resection of a solitary in-transit metastasis, SLNB can be considered (category 2B).

If the patient has a limited number of in-transit metastases, particularly dermal lesions, which are not amenable to complete surgical excision, intralesional local injections (with BCG, interleukin-2, or interferon alfa) or topical imiquimod can be used. Laser ablation or RT may be given to selected patients. These non-surgical treatments are category 2B recommendations. For patients with multiple regional in-transit metastases, regional chemotherapy by hyperthermic perfusion or infusion is an option. Systemic therapy, particularly after failure of local and/or regional therapy, is another alternative.

Distant Metastatic Disease (Stage IV)

Multidisciplinary tumor board consultation is encouraged for patients with stage IV metastatic melanoma. Treatment depends on whether disease is limited (resectable) or disseminated (unresectable) as outlined below.

Resection, if feasible, is recommended for limited metastatic disease. In selected patients with a solitary site of visceral metastatic melanoma, a

short period of observation or systemic treatment followed by repeat scans may be appropriate to rule out the possibility that the visceral metastasis is the first of many metastatic sites, and to better select patients for surgical intervention. Following observation or treatment, patients with resectable solitary sites of disease should be reassessed for surgery. If completely resected, patients with no evidence of disease (NED) can be observed or offered adjuvant treatment on clinical trial. There is panel consensus that adjuvant interferon alpha monotherapy outside of a clinical trial is inappropriate for resected stage IV disease. Alternatively, limited metastatic disease can be treated with systemic therapy either in the context of a clinical trial (preferred) or as a standard of care. Residual disease following incomplete resection for limited metastases is treated as described below for disseminated disease.

Disseminated disease can be managed by systemic therapy, clinical trial, or best supportive care (see the NCCN Guidelines for Palliative Care). In addition, symptomatic patients may receive palliative resection and/or radiation. A number of options are available for systemic therapy. Preferred regimens include ipilimumab (category 1), vemurafenib (category 1), dabrafenib (category 1), dabrafenib and trametinib combination therapy, treatment in a clinical trial, and high-dose IL-2. Other regimens include trametinib monotherapy (category 1), imatinib for tumors with c-*KIT* mutations, dacarbazine, temozolomide, albumin-bound paclitaxel, dacarbazine- or temozolomide-based combination chemotherapy or biochemotherapy (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2B), and paclitaxel as monotherapy or in combination with carboplatin (category 2B).

Vemurafenib, dabrafenib, and trametinib are recommended only for patients with documented V600 BRAF mutations. The panel preferred BRAF inhibition or combined BRAF/MEK inhibition over trametinib monotherapy, and did not recommend trametinib monotherapy for patients who have progressed from previous treatment with BRAF inhibitors. Trametinib monotherapy can be used in patients who show intolerance to toxicities related to vemurafenib or dabrafenib. Pending phase III data, panelists pointed out the likelihood that combination therapy may be superior over targeted monotherapy in terms of toxicity and efficacy.

For patients on vemurafenib, the panel recommends regular dermatologic evaluation with referral to a dermatologist to monitor for skin complications. Although dabrafenib is not associated with significant photosensitivity, regular skin evaluation and referral to a dermatologist is still recommended as secondary skin lesions can develop. Fever is common in patients receiving dabrafenib and should be managed by treatment discontinuation and use of anti-pyretics such as acetaminophen and/or NSAIDs. After resolution of fever, resumption of dabrafenib or dabrafenib/trametinib at reduced dose may be tried. Patients treated by vemurafenib or dabrafenib should also be educated to report joint pain and swelling.

Close monitoring of potentially lethal immune-related events in patients receiving ipilimumab is essential[178]. Panelists strongly recommend participation in the risk evaluation and mitigation strategy (REMS) program during the course of ipilimumab treatment. Patients treated with ipilimumab who experience stable disease of three months' duration after week 12 of induction or partial or CR, who subsequently experience progression of melanoma, may be offered re-induction with up to four doses of ipilimumab at 3 mg/kg every three weeks.

Caution is warranted in the administration of high-dose IL-2 or biochemotherapy due to the high degree of toxicity reported. Some patients may attempt biochemotherapy for palliation or to achieve a

response that may render them eligible for other therapies. In any case, if such therapy is considered, the NCCN Panel recommends patients to receive treatment at institutions with relevant expertise. Contraindications for IL-2 include inadequate organ reserve, poor performance status, and untreated or active brain involvement. Additionally, panelists raised concerns over potential synergistic toxicities between ipilimumab and high-dose IL-2 therapy, especially in the gastrointestinal tract.

The recommendation for first-line systemic therapy of melanoma is based on several factors, including the BRAF mutation status, the tempo of disease, and the presence or absence of cancer-related symptoms. Patients with low-volume, asymptomatic metastatic melanoma may be good candidates for immunotherapy (ipilimumab or IL-2), as there may be time for a durable antitumor immune response to emerge. Patients with BRAF-mutant melanoma who have symptomatic disease or who have progressed despite immunotherapy should be considered for targeted therapies. Clinical trials are underway to address unanswered questions regarding the optimal sequencing and/or combination of these agents.

For patients with brain metastases, treatment of the CNS disease usually takes priority in an effort to delay or prevent intratumoral hemorrhage, seizures, or neurologic dysfunction. Treatment of melanoma brain metastases is based on symptoms, number of lesions present, and location of the lesions, as described in the NCCN Guidelines for Central Nervous System Cancers. SRS and/or whole brain radiotherapy (WBRT) may be administered either as the primary treatment or as an adjuvant following surgical resection. After treatment of the brain, options for management of extracranial sites are the same as for patients without brain metastases. Ipilimumab therapy is associated with the potential for long-term disease control outside the CNS. The late adverse effects of WBRT on cognitive function may favor the use of SRS.[179] The use of SRS may allow documentation of stable CNS disease sooner than with WBRT, thus allowing earlier access to systemic agents and clinical trials that require stable CNS disease. Further, the omission of WBRT in patients with ≤ 5 metastases does not appear to harm overall survival.[180]

In patients with both brain and extracranial metastases, systemic therapy may be administered during or after treatment of the CNS disease with the exception of high-dose IL-2, which has low efficacy in patients with previously untreated brain metastases and which may worsen edema surrounding the untreated metastases. There is disagreement on the value of IL-2 therapy in patients with small brain metastases but no significant peritumoral edema; IL-2 may be considered in selected cases (category 2B).

Follow-up

In the absence of clear data, opinions vary widely regarding the appropriate follow-up of patients with melanoma. The follow-up schedule is influenced by risk of recurrence, previous primary melanoma, and family history of melanoma; other factors, such as the presence and extent of dysplastic nevi and patient or physician concern will impact follow-up schedule as well.[181] The optimal duration of follow-up remains controversial. Although most patients who are going to recur will do so in the first five years after treatment, late recurrence (more than 10 years later) is well documented, especially for patients initially presenting with early-stage melanoma.[182,183] It is probably not cost effective to follow all patients intensively for metastatic disease beyond five years (depending on relative risk for recurrence).[184]

Patients cured of an initial primary melanoma are at increased risk for developing a second primary melanoma. Estimates of that increased

risk range from 8% to 10%.[181,185] Factors that increase that risk even further include multiple primary melanomas, a positive family history, and the presence of multiple dysplastic nevi. Patients with these risk factors should be enrolled in more intensive surveillance programs, and may benefit from adjuncts such as high-resolution total body photography. While most of the benefit of dermatologic screening occurs in the first few years after initial diagnosis, and accrues to patients with stage I-II melanoma, patients with more advanced disease may benefit as well. An analysis of 7778 patients found that 5% of patients had at least one additional primary melanoma found after diagnosis of stage III melanoma.[186] The panel felt that a recommendation for lifetime dermatologic surveillance for patients with melanoma at a frequency commensurate with risk is appropriate.

Romano and colleagues[187] conducted a large retrospective review on relapsing stage III patients. The risk of initial locoregional or nodal relapse falls below 5% in three years for stage IIIA patients, two years for stage IIIB patients, and 7 months for stage IIIC patients. This suggests that frequent physical examinations beyond these time points will unlikely detect many recurrences. On the other hand, increasing risk of systemic or brain relapse was associated with higher substage, with stage IIIC having a 48% risk of non-brain recurrence and 13% risk of brain involvement. The authors suggested that periodic surveillance CNS imaging for three years might avert some of the substantial morbidity incurred by stage IIIC patients who present with symptomatic CNS recurrence.

It is difficult to document the effect of intensive surveillance on the outcome of patients with melanoma. A structured follow-up program could permit the earlier detection of recurrent disease at a time when it might be more amenable to potentially curative surgical resection. This follow-up would be particularly appropriate for patients at risk for a second primary melanoma, regional nodal recurrence who have not undergone SLNB, or in those patients with a positive sentinel node who elected not to undergo completion lymphadenectomy. Several other reasons for a structured follow-up program include provision of ongoing psychosocial support, identification of familial kindreds, screening for second non-melanoma primary malignancies, patient education, and documentation of the results of treatment.[188-190]

Studies on medical imaging have reported low yield, significant false positivity, and risks of cumulative radiation exposure.[191-195] Therefore, frequent imaging should not be part of the routine follow-up for all patients. A large meta-analysis compared ultrasound imaging, CT, PET, and PET/CT for the staging and surveillance of patients with melanoma.[51] Data from 74 studies containing 10,528 patients were included. For both staging and surveillance purposes, ultrasound was found to be associated with the highest sensitivity and specificity for lymph node metastases, while PET/CT was superior for detecting distant metastases. Nodal basin ultrasound is emerging as a modality for surveillance in patients with a positive sentinel node who have elected not to undergo completion lymph node dissection. The safety of this approach has not yet been shown in prospective clinical trials.

Skin cancer preventive education should be promoted for patients with melanoma and their families.[196,197] There is increasing evidence that regular sunscreen use may diminish the incidence of subsequent melanoma.[198] Patients can be made aware of the various resources that discuss skin cancer prevention. A list of useful resources is provided by the National Council on Skin Cancer Prevention at http://www.skincancerprevention.org/resources.

NCCN Recommendations

Common Recommendations for All Patients

Skin examination and surveillance at least once a year for life is recommended for all patients with melanoma, including those with stage 0, in situ melanoma. Clinicians should educate all patients about regular post-treatment self-exam of their skin and of their lymph nodes if they had stage IA to IV melanoma and have NED. Specific signs or symptoms are indications for additional radiologic imaging. Routine blood testing to detect recurrence is not recommended.

Regional lymph node ultrasound may be considered in patients with an equivocal lymph node physical exam, patients who were offered but did not undergo SLNB, or patients with a positive SLNB who did not undergo complete lymph node dissection. Nodal basin ultrasound is not a substitute for SLNB.

Follow-up schedule should be tailored by risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors such as atypical moles, moles/dysplastic nevi, and patient/physician concern.

Specific Recommendations

For patients with stage IA to IIA melanoma, NED, comprehensive H&P with specific emphasis on the regional nodes and skin should be performed every 6 to 12 months for five years and annually thereafter as clinically indicated. The consensus of the panel is that routine blood testing or imaging is not useful for these patients.

For patients with stage IIB-IV melanomas, NED, comprehensive H&P should be performed every 3 to 6 months for two years; then every 3 to 12 months for three years; and annually thereafter, as clinically indicated. Surveillance interval should be tailored to substage. Although not recommended at baseline, chest x-ray, CT, and/or PET/CT every 4 to 12 months (unless otherwise mandated by clinical trial criteria) and annual brain MRI can be considered to screen high-risk patients for recurrent or metastatic disease at the discretion of the physician (category 2B). Surveillance for patients at higher risk should be more frequent than for those at lower risk, especially for the first two years. Because most recurrences manifest within the first 5 years, routine imaging is not recommended beyond this period.

Treatment of Recurrence

NCCN Recommendations

Local Scar Recurrence

The panel recognized the distinction between true local scar recurrence after inadequate initial excision (which most likely represents locally persistent disease) and local recurrence after adequate initial excision, (which likely represents dermal lymphatic disease appearing in proximity to the wide excision scar).[199] In the former situation, the prognosis after re-excision is related to the microstaging of the recurrence, whereas the latter scenario is prognostically similar to recurrent regional disease.

For true local scar recurrence after inadequate primary therapy, a biopsy is required for confirmation. The workup should be similar to that of the primary tumor based on microstaging characteristics. Re-excision to appropriate margins is recommended, with or without lymphatic mapping and SLNB. Adjuvant treatment should be based on pathologic stage of the recurrence.

Local, Satellite, and/or In-Transit Recurrence

Initial clinical recurrence should be confirmed pathologically by FNA cytology or biopsy whenever possible. If the patient is seeking enrollment in a clinical trial of targeted therapy, biopsy should be

performed to obtain tissue for genetic testing. Baseline imaging (CT and/or PET/CT or MRI) is recommended for staging and to evaluate specific signs or symptoms.

Participation in a clinical trial is preferred in all cases. In the absence of extra regional disease, surgical excision with negative margin is recommended whenever feasible for local recurrence after initial adequate wide excision. Lymphatic mapping with SLNB may be considered in patients with resectable in-transit disease on an individual basis (category 2B).

Options for treatment of unresectable in-transit recurrence include hyperthermic limb perfusion or infusion with systemic therapy. The following are category 2B alternatives: intralesional injections (with BCG, interferon-alfa, or interleukin-2), topical imiquimod (for superficial dermal lesions), laser ablation therapy, or RT.

After CR to any of these modalities, options include a clinical trial or observation, or high-dose interferon alfa (category 2B).

Regional Nodal Recurrence

For patients presenting with regional nodal recurrence, the clinical diagnosis should be confirmed by FNA (preferred) or lymph node biopsy. The workup is similar to the one previously outlined for patients with clinically positive lymph nodes.

For patients who have not undergone prior lymph node dissection or had an incomplete lymph node dissection, a complete lymph node dissection is advised. If the patient underwent a previous complete lymph node dissection, excision of the recurrence to negative margins is recommended if possible. After complete resection of nodal recurrence, options for adjuvant treatment include a clinical trial, observation, or, in patients who were not previously treated, high-dose or pegylated interferon alfa (category 2B). Adjuvant radiation to the nodal basin may also be considered in select patients based on size, location, and number of involved nodes, and extranodal extension (category 2B). For patients with incompletely resected nodal recurrence, unresectable disease, or systemic disease, options include clinical trial, radiation, systemic therapy, or best supportive care (see NCCN Guidelines for Palliative Care).

Distant Recurrence

For patients presenting with distant recurrence, the workup and treatment options are similar to those outlined previously for patients presenting initially with stage IV metastatic disease.

Summary

The NCCN Guidelines for Melanoma represent an effort to distill and simplify an enormous body of knowledge and experience into fairly simple management algorithms. In general, treatment recommendations for primary tumors are based on better data than the recommendations for treating recurrent disease. These guidelines are intended as a point of departure, recognizing that all clinical decisions about individual patient management must be tempered by the clinician's judgment and other factors, such as local resources and expertise as well as the individual patient's needs, wishes, and expectations. Furthermore, the NCCN Guidelines for Melanoma undergo annual revision and are continually updated as new data become available.

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