National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Melanoma

Version 2.2013

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Clinical Trials: The 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

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NCCN Guidelines Version 2.2013 Updates Melanoma

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Summary of the changes in the 2.2013 version of the NCCN Melanoma Guidelines from the 1.2013 version include:

- **Follow-up for Stage IIB - IV NED; Third bullet: "Chest x-ray" was added as an imaging option to consider. (ME-7)**
- **The Discussion text was updated to correspond to the changes in the algorithm. (MS-1)**

Summary of the changes in the 1.2013 version of the NCCN Melanoma Guidelines from the 1.2012 version include:

ME-1

- **Pathology Report: "Ulceration status" and "Microsatellitosis" are now listed as "(present or absent)".**
- **Clinical Stage: The listing of the clinical stages were revised (Also see ME-2).**

ME-2

- **The initial stratification of Stage I and II patients was revised as follows:**
  - **Stage IA (≤ 0.75 mm thick, no ulceration, mitotic rate < 1 per mm^2)**
  - **Stage IB (≤ 0.75 mm with ulceration, and/or mitotic rate ≥ 1 per mm^2)**
  - **Stage IA (0.76-1.0 mm thick, no ulceration, mitotic rate < 1 per mm^2)**
  - **Stage IB, Stage II (0.76-1.0 mm thick with ulceration or mitotic rate ≥ 1 per mm^2 or > 1 mm thick, any characteristic), N0**
- **Workup for Stage IA (0.76-1.0 mm thick, no ulceration, mitotic rate < 1 per mm^2:**
  - **"Imaging (CT scan, PET/CT, MRI) only to evaluate specific signs or symptoms" was added**
- **The recommendation "Consider sentinel node biopsy" changed to "Discuss and consider sentinel node biopsy".**
- **Footnote e that states, "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 0.76-1.0 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," is new to the algorithm.**

ME-3

- **Workup:**
  - **"Chest x-ray (optional)" was removed.**
  - **"Further imaging (CT scan, PET/CT, MRI) only as clinically indicated" changed to "Imaging....only to evaluate specific signs or symptoms".**
- **Footnote "j", that states, "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," is new to the page.**

ME-4

- **Workup:**
  - **"Chest x-ray" was removed from the list of imaging recommendations for both Stage III (sentinel node positive) and Stage III (clinically positive node(s)). (Also for ME-5, ME-8, and ME-9)**
  - **Stage III (clinically positive node[s]):**
    - **"Consider baseline imaging..." changed to "Recommend baseline imaging...". (Also for ME-5, ME-8, and ME-9)**
    - **The recommendation "Pelvic CT if inguinofemoral nodes positive" was removed.**
- **Adjuvant Treatment for Stage III (clinically positive node[s]): The recommendation "RT to nodal basin if Stage IIIC with multiple nodes involved..." changed to "RT to nodal basin if multiple nodes involved..."**

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ME-5

- The primary treatment recommendations and layout for Stage III in-transit were revised (Also for ME-8) including:
  - "Complete surgical excision to clear margins, if feasible" changed from category 2B to category 2A.
  - The RT recommendation was clarified as "Consider palliative RT for unresectable disease (See ME-D)". Previously it was stated as "RT".
  - For clarity, "Hyperthermic perfusion/infusion with melphalan" changed to "Isolation limb infusion/perfusion (ILI/ILP)". This recommendation changed from category 2B to category 2A.

ME-6

- Workup for Stage IV Metastatic: The recommendation "FNA preferred, if feasible or biopsy" changed to "Biopsy preferred over FNA if archival tissue not available for genetic analysis".
- Footnote "q" was revised as follows, "Initial clinical recurrence should be confirmed pathologically whenever possible. Obtain tissue for genetic analysis from either archival material or biopsy of the metastasis if the patient is being considered for targeted therapy or if it is relevant to eligibility for participation in a clinical trial."

ME-7

- Follow-up for Stage IIB - IV NED; Third bullet: Chest x-ray was removed as an imaging option to consider. Also, "Consider CT and/or PET/CT scans every 6-12 mo to screen for recurrent/metastic disease" changed to "...every 3-12 mo..."
- Footnote "r": In the last bullet, the term "patient anxiety" changed to "patient/physician concern"
- Footnote "s" that states, "Consider more frequent imaging for higher-risk patients," is new to the algorithm..

ME-8

- Workup for Local, satellite, and/or in-transit recurrence: "FNA (preferred) or biopsy" changed to "FNA or biopsy".

ME-9

- Nodal recurrence, Previous dissection pathway: Best supportive care was added as a treatment option. Observation was removed as a treatment option.

ME-10

- Workup for Distant metastatic disease: "Encourage CT chest/abdomen/pelvis...." changed to "Recommend CT chest/abdomen/pelvis..."
- Treatment of Disseminated (Unresectable) disease:
  - After the "With brain metastases" pathway, the recommendation, "Consider resection and/or RT for patients with brain metastases" was added before the link to the NCCN Guidelines for CNS Cancers.
  - The treatment recommendations for "Without brain metastases" are now the same as those "With brain metastases". Previously, only systemic therapy and radiation were recommended.
- Footnote regarding symptoms in which to consider palliative treatment was removed.

ME-A Principles of Biopsy and Pathology

- Under Principles of Pathology: "Present or absent" were added to the second and third bullets.

ME-B Principles of Surgical Margins for Wide Excision of Primary Melanoma

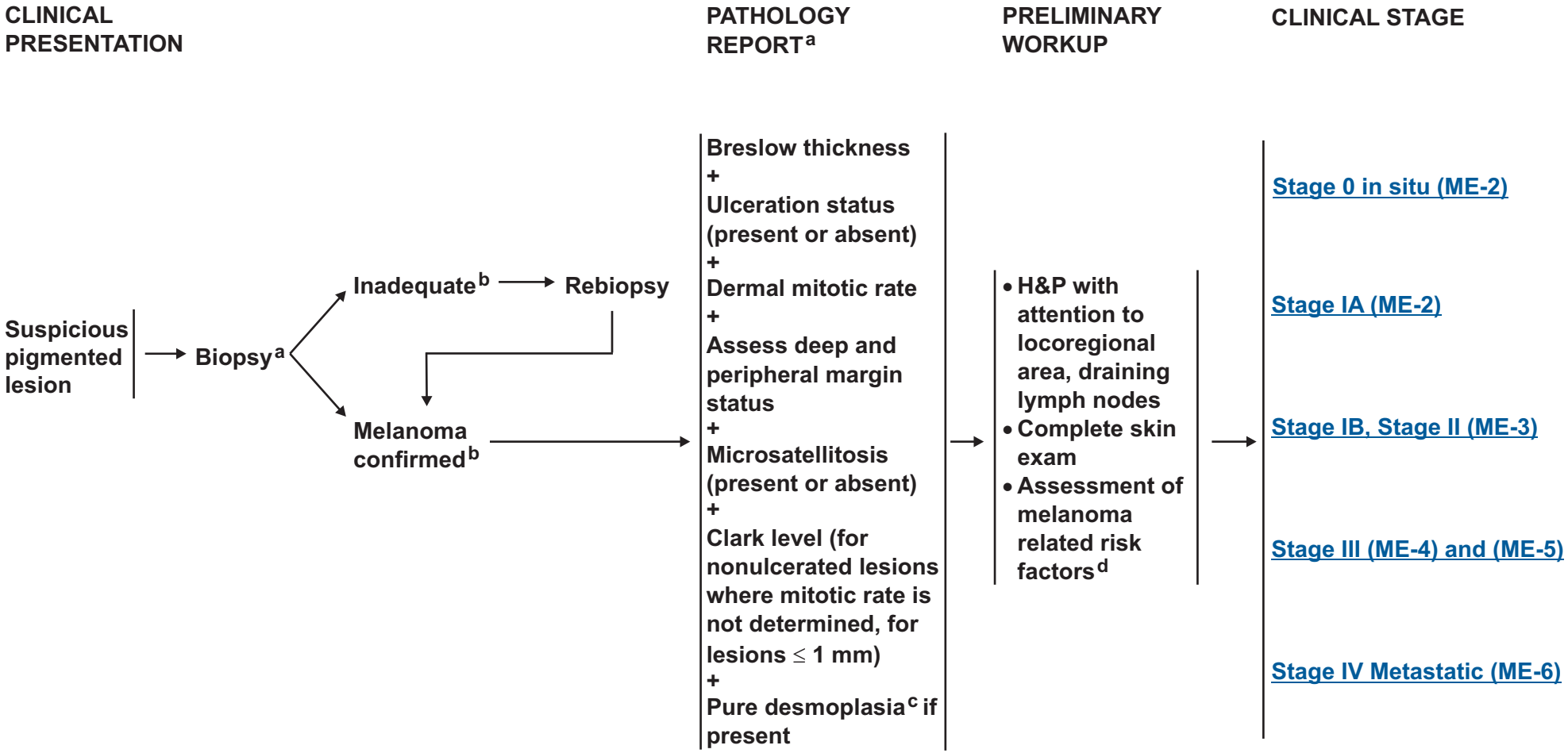
- For tumor thickness > 4 mm, the recommended clinical margin of 2.0 cm changed from category 2A to category 1.

ME-D Principles of Radiation Therapy

- The Principles of Radiation Therapy page was revised extensively.

ME-E Systemic Therapy Options For Advanced Or Metastatic Melanoma

- The page was revised to distinguish between "Preferred Regimens" and "Other Active Regimens".
- Under "Other Active Regimens": "Imatinib for C-KIT mutated tumors" was added as an option. "Paclitaxel/cisplatin (category 2B)" was removed.
- Footnote "4": The second sentence was revised as follows, "Regular dermatologic evaluation with referral to a dermatologist is recommended". Previously this was "...as clinically indicated".
- Footnote regarding patients who progress after initial therapy and performance status was removed.



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

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

[c] Given the very low rates of sentinel lymph node positivity with pure desmoplastic melanoma, when a pure desmoplastic lesion is suspected, it is important that an experienced dermatopathologist examine the entire lesion before making the decision to perform a sentinel lymph node biopsy (SLNB). (Busam KJ. Desmoplastic Melanoma. Clin Lab Med 2011. 31:321-330.)

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

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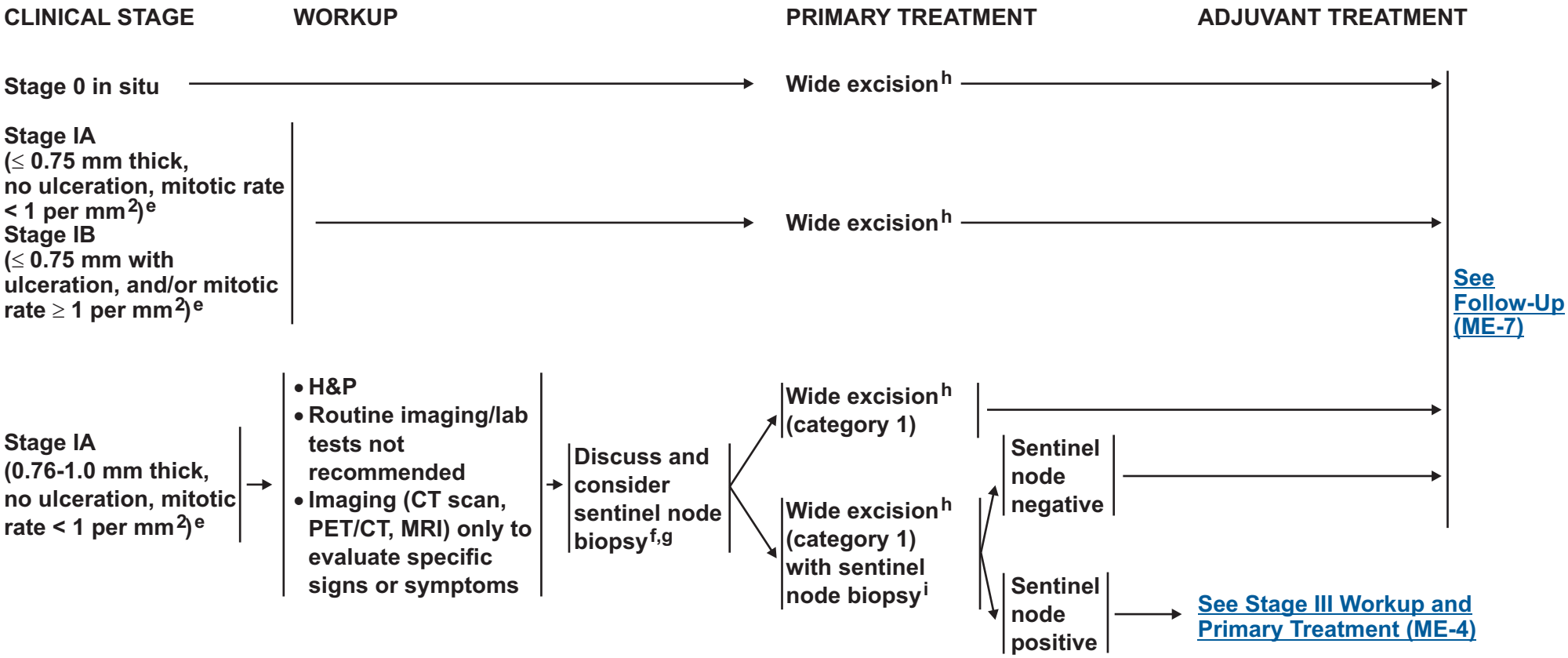

[e] **In general, SLNB is not recommended for primary melanomas ≤ 0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging. For melanomas 0.76-1.0 mm thick, SLNB may be considered in the appropriate clinical context. In patients with thin melanomas (≤ 1.0 mm), apart from 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.**

[f] Decision to perform SLNB may be based on significant patient comorbidities, patient preference or other factors.

[g] Sentinel node biopsy is an important staging tool, but the impact of SLNB on overall survival is unclear.

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

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

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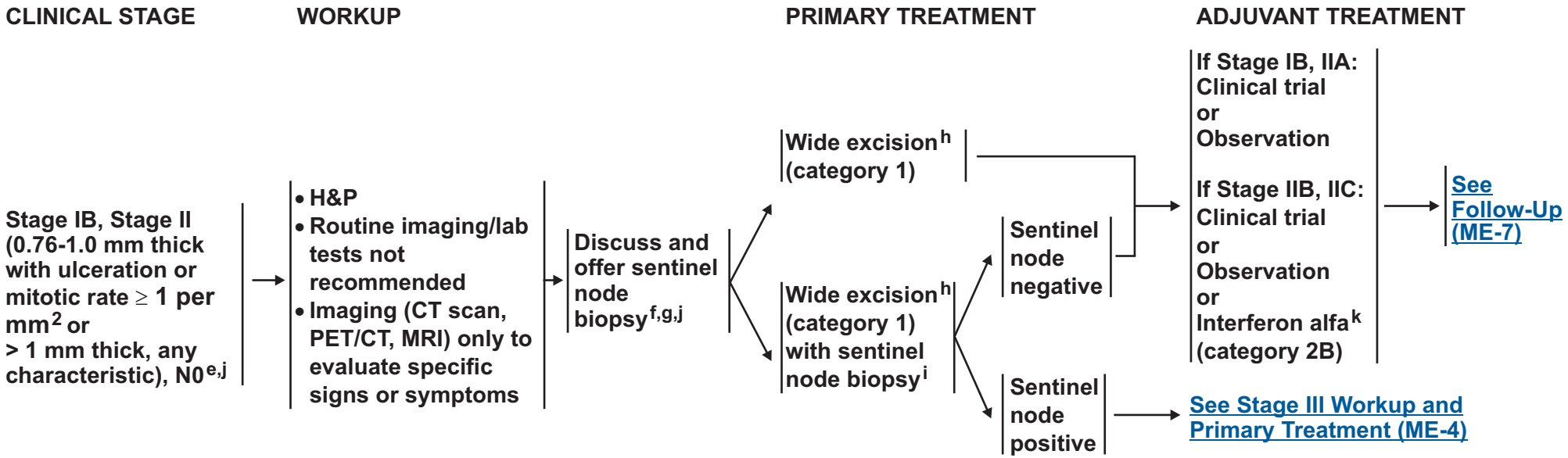

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[j] Microsatellitosis, when present in the initial biopsy or wide excision specimen, defines at least N2c and at least Stage IIIB disease. SLN status does have prognostic significance in these patients, with a positive SLN upstaging a patient to N3, 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.

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[k] 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 associated with improved DFS, but its impact on overall survival is unclear.

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CLINICAL/ PATHOLOGIC STAGE	WORKUP	PRIMARY TREATMENT	ADJUVANT TREATMENT	
Stage III (sentinel node positive)	Consider baseline imaging for staging and to evaluate specific signs or symptoms (CT, PET/CT, MRI)	Clinical trial[l] or Lymph node dissection[m]	Clinical trial or Observation or Interferon alfa[k] (category 2B)	(See Follow-up ME-7)
Stage III (clinically positive node[s])	• FNA preferred, if feasible, or lymph node biopsy • Recommend baseline imaging for staging and to evaluate specific signs or symptoms (CT, PET/CT, MRI)	Wide excision of primary tumor[h] (category 1) + complete lymph node dissection[m]	Clinical trial or Observation or Interferon alfa[k] (category 2B) and/or Consider RT[n] to nodal basin if multiple nodes involved or macroscopic extranodal extension	

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

[k] 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 associated with improved DFS, but its impact on overall survival is unclear.

[l] Clinical trials assessing alternatives to complete lymph node dissection, such as careful observation with nodal basin ultrasound.

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

[n] See Principles of Radiation Therapy (ME-D).

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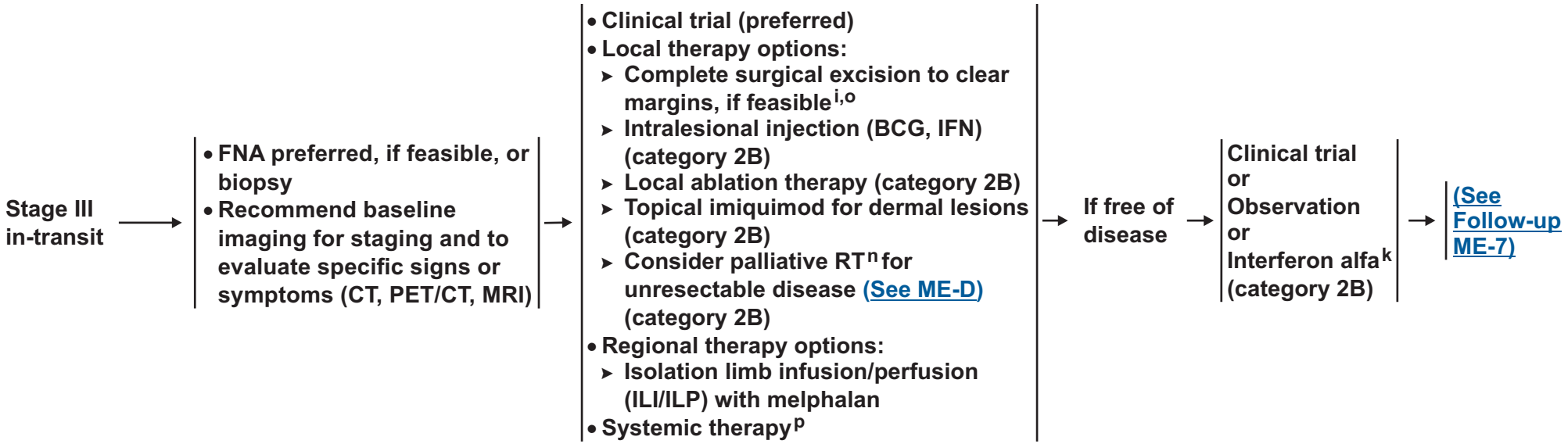

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[k] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.

[n] See Principles of Radiation Therapy (ME-D).

[o] Consider sentinel node biopsy for resectable in-transit disease (category 2B).

[p] See Systemic Therapy Options for Advanced or Metastatic Melanoma (ME-E).

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

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

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

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CLINICAL/PATHOLOGIC STAGE	FOLLOW-UP	RECURRENCE[t]
Stage 0 in situ	See Common Follow-up Recommendations For All Patients[r] (Below)	

Stage IA - IIA NED	• See Common Follow-up Recommendations For All Patients[r]
	• H&P (with emphasis on nodes and skin)
	  ▸ every 3-12 mo for 5 y, then
	  ▸ annually as clinically indicated
	• Routine radiologic imaging to screen for asymptomatic recurrent/metastatic disease is not recommended
		Persistent disease or true local scar recurrence[t] → (See ME-8)
		Local, satellite, and/or in-transit recurrence[q,u] → (See ME-8)

Stage IIB - IV NED	• See Common Follow-up Recommendations For All Patients[r]
	• 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 and/or PET/CT scans every 3-12 mo[s] to screen for recurrent/metastatic disease (category 2B)
	• Consider brain MRI annually (category 2B)
	• Routine radiologic imaging to screen for asymptomatic recurrent/metastatic disease is not recommended after 5 years
		Nodal recurrence[q] → (See ME-9)
		Distant recurrence[q] → (See ME-10)

[r] Common Follow-up Recommendations For All Patients:
- At least annual skin exam for life
- Educate patient in monthly self skin exam (and monthly lymph node self exam for Stage IA - IV NED)
- Routine blood tests are not recommended
- Radiologic imaging is indicated to investigate specific signs or symptoms
- Follow-up schedule 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.

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

[s] Consider more frequent imaging for higher risk patients.

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

[u] 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.

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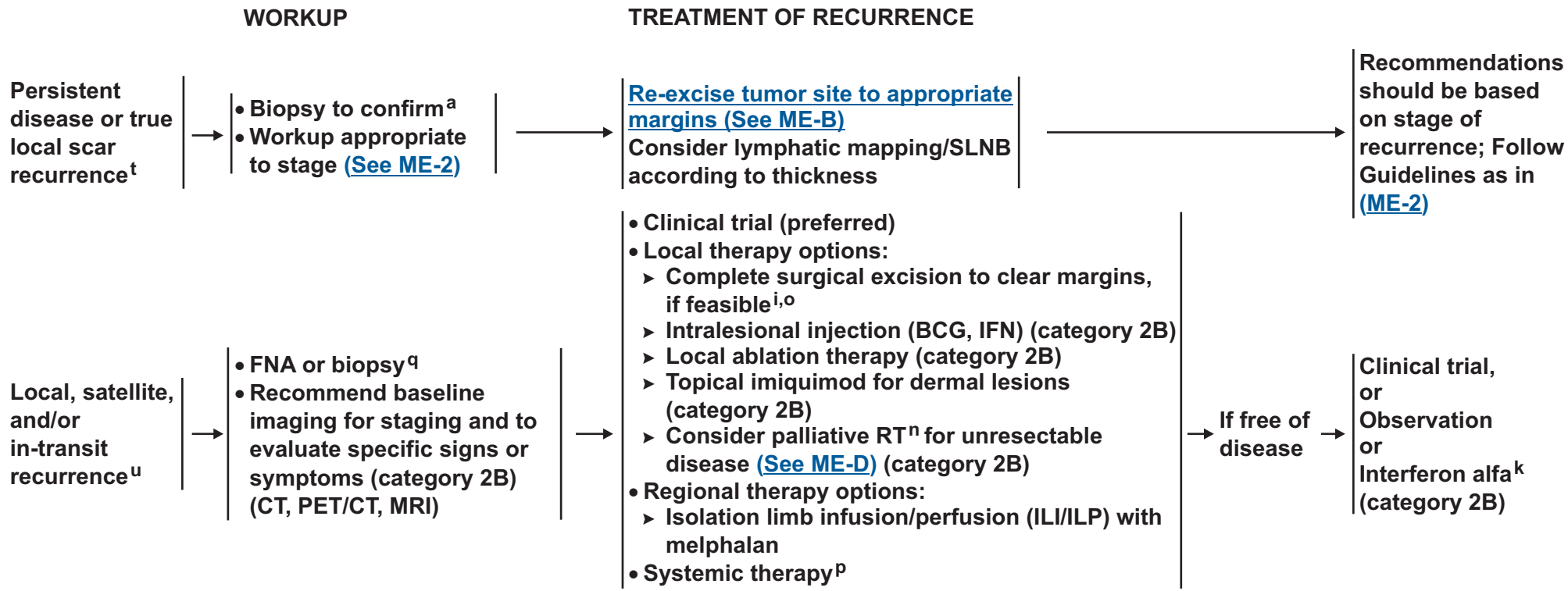

[a] See Principles of Biopsy and Pathology (ME-A).
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[k] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.
[n] See Principles of Radiation Therapy (ME-D).
[o] Consider sentinel node biopsy for resectable in-transit disease (category 2B).
[p] See Systemic Therapy Options for Advanced or Metastatic Melanoma (ME-E).
[q] Initial clinical recurrence should be confirmed pathologically whenever possible. Obtain tissue for genetic analysis from either archival material or biopsy of the metastasis if the patient is being considered for targeted therapy or if it is relevant to eligibility for participation in a clinical trial.
[t] Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.
[u] 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.

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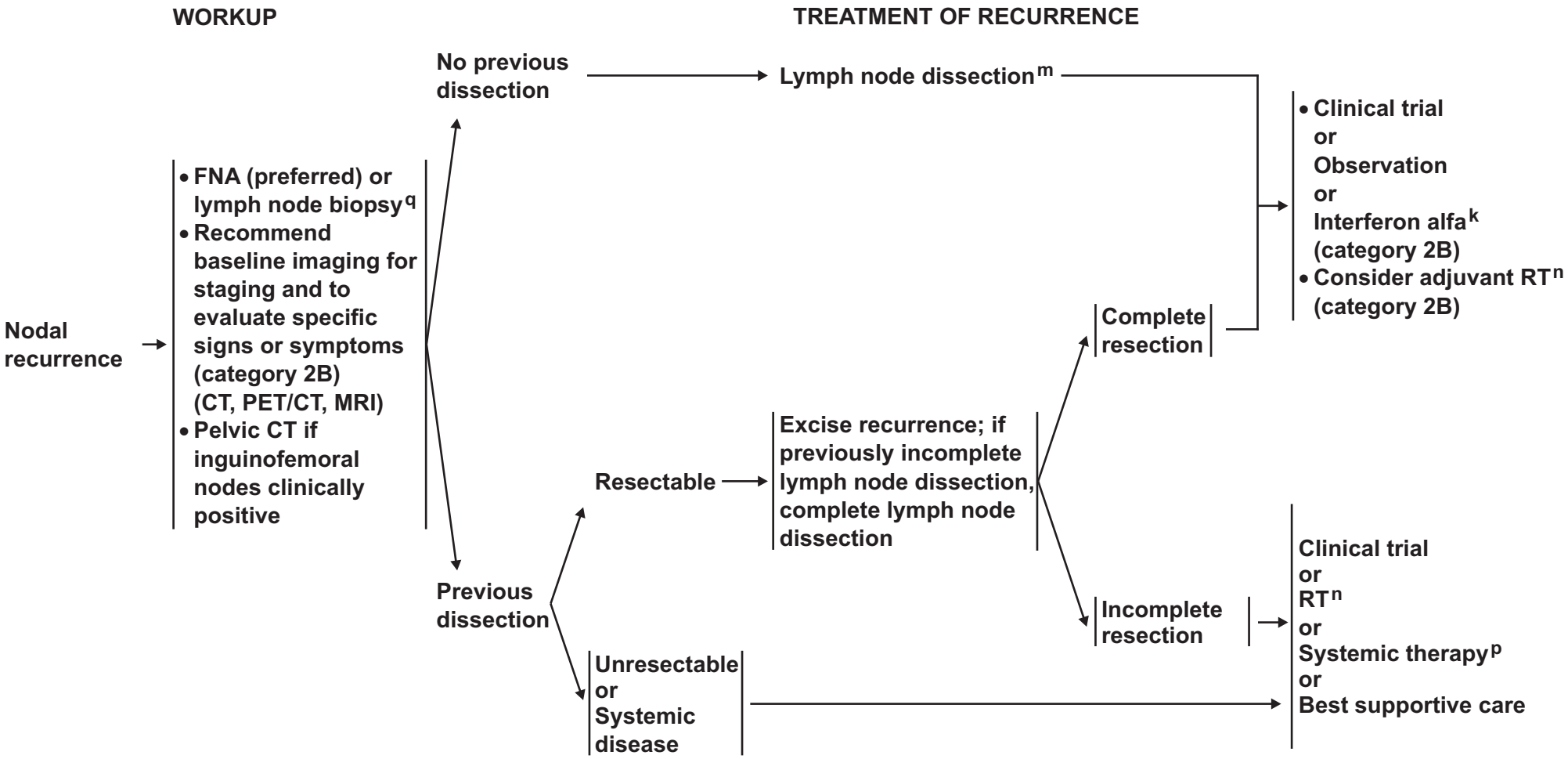

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[m] See Principles of Complete Lymph Node Dissection (ME-C).

[n] See Principles of Radiation Therapy (ME-D).

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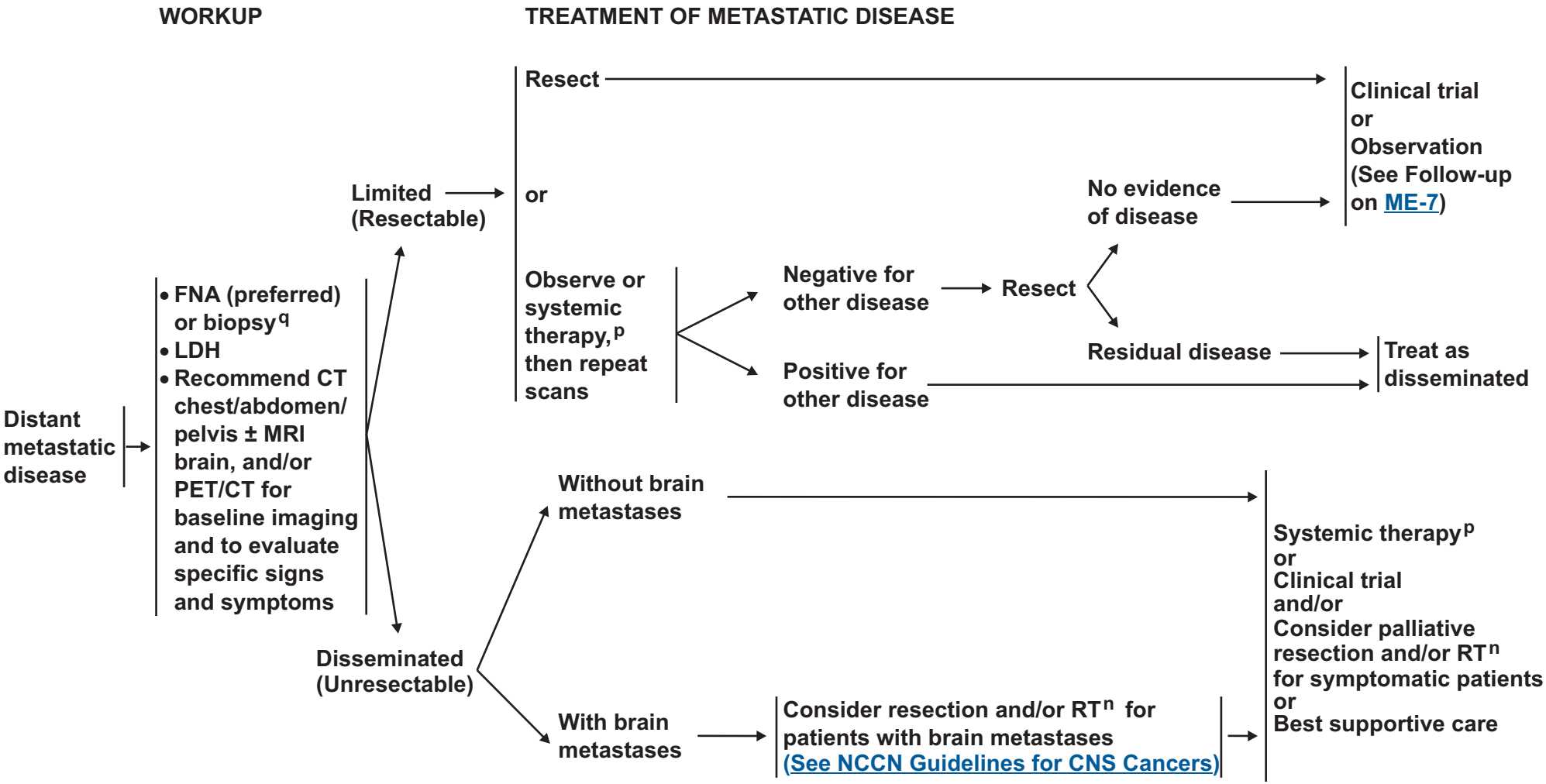

[n] See Principles of Radiation Therapy (ME-D).

[p] See Systemic Therapy Options for Advanced or Metastatic Melanoma (ME-E).

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

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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.
- 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

- 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[2,3] 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).
- Encourage consistent reporting of these additional factors (compatible with American Academy of Dermatology recommendations[4]):
  - Location
  - Regression
  - Tumor infiltrating lymphocytes (TIL)
  - 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 fluorescent in situ hybridization (FISH) for histologically equivocal lesions.[5]

[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] Dermal mitotic rate should be determined using the “hot spot” technique and expressed as number of mitoses per square millimeter. (Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity; lessons learned from the generation of a probabilistic model. Annals of Surgical Oncology 2004;11:247-258 and Clark WH, Elder DE, Guerry D. Model Predicting survival in Stage I Melanoma Based on tumor Progression. Journal of the National Cancer Institute 1989;81:1893-1904.)
[4] Bichakjian C,Halpern AC, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2011;65:1032-1047.
[5] CGH may be more accurate than FISH in identifying relevant genetic mutations (Raskin L, Ludgate M, Iyer RK, et al. Copy number variations and clinical outcome in atypical spitz tumors. Am J Surg Pathol 2011;35:243-252).

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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 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 clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist (category 1).

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.

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 superficial nodes or ≥ 3 superficial nodes positive. (category 2B)**
- **Iliac and obturator lymph node dissection indicated if pelvic CT is positive (category 2A) or if Cloquet's node is positive (category 2B).**

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

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.

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Consider radiation therapy in the following situations:[1]

PRIMARY DISEASE

- **Adjuvant treatment for selected patients with desmoplastic melanoma with narrow margins, recurrent disease, or extensive neurotropism.**

REGIONAL DISEASE[2]

- **Adjuvant**
  - **Gross nodal extracapsular extension**
  - **≥ 4 involved nodes**
  - **Size of tumor within a node ≥ 3 cm**
  - **Cervical[3] > Axillary > Inguinal nodal basins**
  - **Following resection of recurrent nodal disease**
- **Palliative**
  - **Unresectable nodal, satellite, or in-transit disease**

METASTATIC DISEASE

- **Brain metastases (see NCCN Guidelines for Central Nervous System Cancers)**
  - **Stereotactic radiosurgery and/or whole brain radiation therapy either as adjuvant or the primary treatment**
- **Other symptomatic or potentially symptomatic soft tissue and/or bone metastases[2]**

[1] Interactions between radiation therapy and systemic therapies need to be very carefully considered.
[2] A wide range of radiation dose/fractionation schedules is effective. Hypofractionated regimens may increase the risk for long term complications.
[3] In the cervical location, consider adjuvant radiation after adequate lymph node dissection if ≥ 2 clinically involved nodes and/or if an involved lymph node contains ≥ 2 cm of tumor.

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.

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA (References)

Primary Disease

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Regional Disease

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SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA

Preferred Regimens

- **Ipilimumab (category 1)**[1,2]
- **Vemurafenib (category 1)**[3,4]
- **Clinical trial**
- **High-dose Interleukin-2**[5,6]

Other Active Regimens

- **Dacarbazine**
- **Temozolomide**
- **Imatinib for C-KIT mutated tumors**
- **Dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2B)**[6]
- **Paclitaxel (category 2B)**
- **Paclitaxel/carboplatin (category 2B)**

[1] Ipilimumab has the potential for significant immune-mediated complications. Participation in the risk evaluation and mitigation strategy (REMS) program and/or experience in use of the drug as well as resources to follow the patient closely are essential. Ipilimumab should be used with extreme caution, if at all, in patients with serious underlying autoimmune disorders.

[2] 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.

[3] Vemurafenib is recommended for patients with V600 mutation of the BRAF gene documented by an FDA-approved or Clinical Laboratory Improvement Amendments (CLIA)-approved facility.

[4] Vemurafenib has the potential for significant dermatologic complications including cutaneous squamous cell carcinoma and extreme photosensitivity. Regular dermatologic evaluation with referral to a dermatologist is recommended. Patients should also be carefully monitored for the development of other adverse reactions such as joint pain and swelling.

[5] High-dose interleukin-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).

[6] Administration of multiagent regimens and high-dose interleukin-2 is complex and associated with significant toxicities. Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.

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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.

References on next page

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC MELANOMA (REFERENCES)

Preferred Regimens

Ipilimumab

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Vemurafenib

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High-dose Interleukin-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.
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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.

Continued

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC MELANOMA (REFERENCES)

Other Active Regimens

Dacarbazine

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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.

Imatinib

- Carvajal RD, Antonescu CR, Wolchok, JD, et al. KIT as a therapeutic target in metastatic melanoma. JAMA 2011;395:2327-2334.

Dacarbazine or temozolomide-based combination chemotherapy or biochemotherapy including cisplatin, vinblastine, with or without interleukin-2 or interferon alfa

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Paclitaxel

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

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.

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC MELANOMA (REFERENCES)

Other Active Regimens

Paclitaxel and 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(2):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.
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- 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.

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 that 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 ≥ 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 Mass	*No. of Metastatic Nodes*	*Nodal Metastatic*
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.

Discussion

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.

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Overview

In the year 2012, an estimated 76,250 new cases of melanoma will be diagnosed and about 9,180 patients will die of the disease in the United States.[1,2] However, these figures for new cases may represent a substantial underestimation, because many superficial and in situ melanomas treated in the outpatient setting are not reported. The incidence of melanoma continues to increase dramatically. 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 one in 55.[3] The median age at diagnosis is 59 years. As such, melanoma ranks second to adult leukemia in terms of loss of years of potential life, per death.

Risk factors for melanoma include a positive family history of melanoma, prior melanoma, multiple clinically atypical moles or dysplastic nevi,[4,5] 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.[6] 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.[7] 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 initially depends on the stage at presentation.[8] It is estimated that 82-85% of melanoma patients present with localized disease, 10-13% with regional disease, and 2-5% 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 20-70%, 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.

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 members of the panel during the process of 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 of clinical trials where available.

Clinical Presentation and Workup

Biopsy

Patients presenting with a suspicious pigmented lesion optimally should undergo an excisional biopsy, preferably with 1-3 mm 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 they will not 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.

Pathology Report

In the revised American Joint Committee of Cancer (AJCC) staging system, melanoma patients 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).[8,9] 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.[8]

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.[9] Barnhill et al[10] compared the relative importance of mitotic rate vs. ulceration as 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.[11-14] 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, 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. In multivariate analyses, mitotic rate and younger age were identified as independent predictors of a positive sentinel lymph node (SLN), in addition to Breslow thickness.[15,16] 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 sufficient cause for performing sentinel lymph node biopsy (SLNB).

Consistent with the American Academy of Dermatology (AAD) Task Force, the NCCN recommends the inclusion of mitotic rate in the biopsy report, along with other additional optional factors such as vertical growth phase (VGP), tumor-infiltrating lymphocytes (TIL) and regression.[17,18] Microscopic satellitosis, if present, should be recorded, as this defines a patient subgroup at high risk for regional and systemic failure, prognostically similar to stage III. Clinicians should also note cases of pure desmoplastic melanoma (as opposed to mixed desmoplasia with spindle cell and/or epithelioid cells), as these patients have very low incidence of nodal involvement that does not support routine use of SLNB.[19-21] Mixed desmoplasia has a similar rate of lymph node spread as that of conventional melanoma. When pure desmoplastic melanoma is suspected, the entire lesion should be examined by an experienced dermatopathologist. SLNB should not be performed on confirmed pure desmoplastic melanoma.

Some melanocytic proliferations can be diagnostically challenging. Examples are atypical melanocytic proliferation (AMP), melanocytic tumor of uncertain malignant potential (MELTUMP), superficial melanocytic tumor of uncertain significance (SAMPUS), 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 in the differential diagnosis, the pathology report should include prognostic elements as for melanoma. Comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH) can 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 recent small study on atypical Spitz tumors.[22]

Among patients with localized melanoma undergoing SLNB, the status of the sentinel node is the most important prognostic factor.[23] 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, 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.[24]

The site of metastases is the most significant predictor of outcome among patients with distant metastases (stage IV). Elevated LDH is also an independent predictor of poor outcome in patients with stage IV disease and has been incorporated into the AJCC staging system.[23,25,26]

NCCN Recommendations

The NCCN melanoma panel recommends the inclusion of Breslow thickness, ulceration status, mitotic rate, deep and peripheral margin status (positive or negative), microsatellitosis (present or absent), and Clark level for nonulcerated lesions 1.0 mm or less where mitotic rate is not determined in the pathology report. Ideally, mitotic rate should be reported for all lesions, as it is emerging as an independent predictor of outcome. The panel agreed that recording of additional parameters identified by the AAD task force would be helpful, but not mandatory. Consider CGH or FISH 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 at diagnosis of stage IV.

Preliminary Workup

After the diagnosis of melanoma has been confirmed, a history and physical examination (H&P) as well as a complete dermatologic examination are recommended. Preliminary work up 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.[4] 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 further stratified stage I patients based on risk on SLN involvement:

- Stage 0 (melanoma in situ)
- Stage IA (0.75 mm thick or less, no ulceration, mitotic rate less than 1 per mm^2) and Stage 1B (0.75 mm thick or less with ulceration and/or mitotic rate 1 per mm^2 or more)
- Stage IA (0.76-1.0 mm thick, no ulceration, mitotic rate less than 1 per mm^2)
- Stage IB-II (0.76-1.0 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 and/or in-transit disease)
- Stage IV (distant metastatic disease)

The detection of microsatellitosis in the initial biopsy or wide excision tissue specimen defines at least N2c, stage IIIB disease. Patients with microsatellitosis should be managed as stage III in work-up, adjuvant therapy, and follow-up.

Pathologic Staging

Patients with clinically localized stage I-II melanoma may be further pathologically staged by lymphatic mapping with sentinel lymph node biopsy. Depending on the primary tumor thickness, ulceration, and other factors described above, 5-40% of patients undergoing SLNB will be upstaged from clinical stage I-II to pathologic stage III, based on subclinical micrometastatic disease in the SLN. These patients have a distinctly better prognosis than those patients with clinically positive nodes containing macrometastatic disease.[23,27] The AJCC staging system clearly recognizes this difference in prognosis among patients with pathologic stage III melanoma.[8]

Workup

There are several reasons to embark on an extent of disease workup 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 that is ordered has with it 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 incurred 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.[28-30]

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 0.5-3.7%.[31-34] True positive findings are most often found in patients with ulcerated thick primary tumors with 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 4-16%.[35-37] 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 are reporting 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 significant 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.[38-40] In patients with more advanced 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).[41]

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 stage I and II disease. Routine cross-sectional imaging (CT, PET/CT, MRI) is not recommended for patients with stage I to II melanoma. These tests should only be used to investigate specific signs or symptoms.

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) 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 imaging for staging purposes and to evaluate specific signs or symptoms.

For the small group of patients presenting with stage III 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 with open biopsy of the lesion. If archival tissue is not available, biopsy is preferred to obtain tissue for genetic analysis (eg., BRAF or c-KIT mutational status) if considering targeted therapy or if it potentially impacts enrollment in clinical trials of targeted therapy (see section “Treatment of Metastatic Melanoma”).

Panelists encourage baseline chest abdominal/pelvic CT and MRI of the brain 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 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 role. 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 the World Health Organization (WHO), 612 patients with primary melanomas not thicker than 2.0 mm were randomized to wide excision with one cm or three cm margins.[42,43] 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.[44,45]

A multicenter European trial randomized 936 patients with melanoma thicker than 2.0 mm to wide excision with 2 or 4 cm margins.[46] 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.[47-49] A systemic review and meta-analysis also reported that surgical excision margins no more than 2 cm are adequate and surgical margins should not be less than 1 cm around primary melanoma.[50]

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

Study	Year	N	Followup (years)	Thickness (mm)	Margin (cm)	LR	OS
WHO[43]	1991	612	9	≤2	1 vs. 3	NS	NS
Sweden[44]	2000	989	11	0.9-2.0	2 vs. 5	NS	NS
Intergroup[47]	2001	468	10	1-4	2 vs. 4	NS	NS
France[45]	2003	326	16	≤2	2 vs. 5	NS	NS
UK[49]	2004	900	5	≥2	1 vs. 3	NS	NS
Sweden[46]	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.[51] In a prospective study of 1,120 cases of melanoma in situ treated by Mohs surgery, 9-mm surgical margins resulted in removal of 99% of melanomas while 6-mm margins removed 86%.[52] 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.[53]

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.[54-58] 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,[59] 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 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 at least a margin of 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[60] 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 (DELM), collaboration with a dermatologist who can perform these procedures is necessary to help prevent these marginal failures.[61]

NCCN Recommendations

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

For in situ melanoma, a measured margin of 0.5 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 is recommended based on panel consensus. Consider more exhaustive histologic assessment of margins such as staged excision for lentigo maligna melanoma. Imiquimod and/or RT can be considered as non-standard options in highly selected cases.

For patients with stage IA melanoma (1.0 mm or less), wide excision with a 1.0 cm margin is recommended (category 1). Wide excision with a 1-2 cm margin is recommended for patients with melanomas measuring 1.01-2.0 mm in thickness (category 1). For melanomas measuring more than 2.0 mm in thickness, wide excision with 2.0 cm margins is recommended (category 1). Surgical margins may be modified to accommodate individual anatomic or cosmetic considerations. The panel recognized that 1-2 cm margins might be acceptable in anatomically difficult areas where a full 2.0 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.[62] MSLT- I, an international multicenter phase III trial, was initiated to evaluate the accuracy, morbidity and use of lymphatic mapping and SLNB for staging patients with early stage

melanoma. In a preliminary publication, Morton et al reported an initial sentinel node identification rate of 95%. SLNB was also associated with a low false negative rate and low complication rate.[63]

Data from the third interim analysis of results from the MSLT-I trial have been published.[64] In patients with intermediate thickness primary melanoma (1.2-3.5 mm), those undergoing wide excision with SLNB (and completion lymph node dissection if their sentinel nodes were positive) had no significant improvement in melanoma-specific survival compared to those undergoing initial wide excision and nodal observation and delayed therapeutic lymphadenectomy if necessary. There was an improvement in the estimated 5-year disease-free survival in the SLNB group (78% after SLNB vs. 73% after observation (P= 0.009); this was in large part due to the higher nodal relapse rate in the observation group. Among patients undergoing SLNB, the sentinel node status was the most important prognostic factor for disease specific survival. Furthermore, among all patients with nodal metastases, those who had immediate lymph node dissection following lymphatic mapping and positive SLNB had higher survival rate than patients who underwent delayed lymphadenectomy for clinical disease (72% vs. 52%). This difference was largely attributed to a lower nodal tumor burden in the SLN positive patients than the clinically node positive patients. These results confirm that SLNB is of prognostic value, and that the procedure can identify patients with low volume nodal metastases whose survival is superior to that of patients whose nodal metastases are detected on clinical examination.

The value of SLNB for patients with thin melanomas (1.0 mm or less) and thick melanomas (4.0 mm or greater) 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. [65] A review by Andtbacka and Gershenwald[66] reported an overall SLN metastasis rate of 2.7% in patients with melanoma thinner than 0.75 mm from 7 studies. In patients with melanoma 0.75-1.0 mm thick, 6.2% of patients undergoing SLNB were found to have a positive SLN. Factors predicting an increased probability of a positive SLN in patients with thin melanomas include increasing Breslow thickness and less consistently, Clark level, higher mitotic rate, and younger age. However, with relatively short follow-up, only one center has demonstrated any convincing evidence that the SLN status was predictive of outcome in this low risk group of patients.[67] Larger series and longer term follow-up will be required to assess the prognostic value of the SLN in patients with thin melanoma.[68-70]

The probability of a positive sentinel node in patients with thick melanoma, 4 mm or greater, is 30-40%. Almost every retrospective series has demonstrated that SLN status is a strong independent predictor of outcome in patients with thick melanoma.[71-73] Thus, in these high-risk patients, it would seem reasonable to offer SLNB, to help define prognostically homogeneous groups for participation in clinical trials of adjuvant therapy.

Among other potential predictors of SLN positivity, the significance of tumor regression is controversial. Recent studies have reported no association between the presence of regression and the incidence of SLN positivity.[74,75]

Meticulous pathologic examination of all sentinel nodes is mandatory. 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.

Discussion of SLNB should be considered for patients with stage IA (ie, no ulceration, mitotic rate < 1 per mm^2) melanomas that are 0.76-1.0 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, any discussion of the procedure in this patient population should reflect those facts.

For patients with stage thicker 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 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 is 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.

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.

Lymph Node Dissection

Among patients with a positive sentinel node, published studies have revealed additional positive non-sentinel nodes in approximately 15% of the completion lymph node dissection specimens.[76,77] However the impact of completion lymph node dissection on regional control and survival in this setting has not been clearly demonstrated. MSLT-II is an ongoing trial in which patients with sentinel node metastases are randomized to undergo either completion lymph node dissection or observation. This trial 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 complete dissection of the involved nodal basin. The extent of complete 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.[78-80]

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, either as standard of care or in the context of a clinical trial evaluating alternative strategies (such as close monitoring with nodal basin ultrasound). Participation in MSLT-II, assessing the option of nodal observation in patients with positive sentinel nodes, is encouraged where available. Nodal basin observation for these patients has not been studied sufficiently to recommend 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).

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 describes the anatomic boundaries of the lymph node dissection.

Adjuvant Treatment for Melanoma

Low-Dose and Intermediate-Dose Interferon

In the first major randomized trial of adjuvant interferon for completely resected stage III melanoma conducted by the WHO,[81] there was no improvement in the overall survival (35% for the interferon group vs. 37% for those assigned to observation alone). In the French Cooperative Group trial evaluating adjuvant interferon in patients with melanoma > 1.5 mm thick and clinically negative nodes, at a median follow-up of 5 years, adjuvant interferon therapy was associated with a significant relapse-free survival benefit and a non-significant trend towards increases overall survival.[82] In another prospective randomized study, adjuvant interferon prolonged disease-free survival for resected stage II patients at a median follow-up of 41 months.[83]

Two other randomized clinical trials (EORTC 18952 and AIM HIGH Study) compared adjuvant interferon with observation in patients with resected stage IIB and stage III melanoma. In AIM HIGH Study, low-dose interferon alfa-2a did not improve either overall survival or recurrence-free survival.[84] No significant improvement in progression-free survival was reported for intermediate-dose interferon alfa-2b in EORTC 18952.[85]

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 three randomized clinical trials. ECOG 1684 trial compared high dose interferon alfa-2b with observation in patients with stage IIB (4.0 mm or thicker with no evidence of lymph node involvement) and stage III melanomas with either regional lymph node disease or in transit metastases. 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.[86] The results of a larger follow-up trial, ECOG 1690, also showed a relapse-free survival advantage, but no overall survival advantage, for high-dose interferon alfa-2b.[87] E1694 compared high-dose interferon alfa-2b with an experimental vaccine, GM2-KLH21. At approximately 2 years of median followup, 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 concerning the vaccine control group used in ECOG 1694. The randomized Phase III trial (EORTC 18961) of adjuvant GM2-KLH21 in 1,314 patients with stage II melanoma was closed early by the data monitoring committee because of inferior survival in the vaccine arm.[88] A shorter course of high dose interferon has also been evaluated. E1697 enrolled 1,150 patients with resected cutaneous melanoma (T3 or T_{any}N1a-2a) who were randomized to receive one month of IV interferon versus observation.[89] The trial was closed after interim analysis showed no benefit for interferon in either relapse-free or overall survival.

A recent retrospective review of 200 patients with melanoma (stage IIB, IIC, or III) reported that those who had autoantibodies or clinical manifestations of autoimmunity after treatment with high-dose interferon alfa-2b had improved relapse-free and overall survival compared to patients who did not show manifestation of autoimmunity.[90]

Review of data combined from the randomized controlled trials found that adjuvant interferon alfa was not associated with improved overall survival in patients with melanoma who were at increased risk for recurrence.[91] A pooled analysis of E1684, E1690 and E1694 confirmed an improvement in relapse-free survival in patients with high risk resected melanoma (two-sided log-rank *P* value = .006) but did not find a significant improvement in overall survival.[92]

ECOG studies discussed above included patients with stage IIB (4.0 mm or thicker with no evidence of lymph node involvement) and stage III melanomas with either regional lymph node disease or in transit metastases. In a recent systematic review, the authors concluded that even though high dose interferon alfa is associated with improved disease free survival in high-risk primary melanomas, the role of adjuvant interferon for patients with intermediate to high-risk melanoma remains undefined.[93] Adjuvant high-dose interferon is a toxic therapy that is decreasingly being used in most institutions, but panelists agree that it still may have a role in certain settings.

The EORTC protocol (18991) randomized 1,256 patients with completely resected stage III melanoma to either observation or pegylated interferon alfa treatment for an intended duration of five years. 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.[94] Based on this data, pegylated interferon alfa received

approval by the Food and Drug Administration (FDA) in 2011 as an option for adjuvant therapy for melanoma patients with nodal involvement. The NCCN panel included pegylated interferon as an adjuvant option for completely resected nodal disease.

A recent 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.[95] The clinical and biologic significance of this observation remains unclear.

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).[96] 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.[97] 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 radiated patients versus 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.

A prospective randomized trial of adjuvant nodal basin RT versus observation in patients at risk for nodal relapses has been reported. In this phase III trial, 250 non-metastatic patients with palpable lymphadenopathy at diagnosis or as an isolated site of relapse underwent lymphadenectomy followed by either adjuvant radiation to the nodal basin or observation.[98] 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, or ≥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; $P = .04$) for all nodal basins, but there was no improvement in overall survival.

Post-operative radiation with various fractionation schemes have been used in other clinical studies.[99-101] 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 well 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.[102] On the other hand, studies have demonstrated the safety of combining temozolomide with radiation when treating brain metastases.[103,104]

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 positive margins remain after optimal surgery, 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. For patients with stage III melanoma, adjuvant treatment options include clinical trial (preferred), observation, or interferon alfa. Pegylated interferon alfa is an alternative to high-dose interferon in completely-resected stage III disease with either positive sentinel nodes or clinically positive nodes, but not for stage III in-transit disease. Planned short-course IV interferon (as in E1697) is not recommended in any adjuvant setting. Adjuvant RT to the nodal bed should be considered for high-risk nodal disease: four or more positive nodes, nodes 3 cm or larger, or macroscopic extranodal soft tissue extension, with a lower threshold for using RT in the cervical lymph node location following adequate lymphadenectomy (two or more clinically involved nodes and/or 2 cm or larger tumor mass in the node). In general, the cervical basin benefits more from radiation than the axillary basin, which in turn will benefit more than the inguinal basin.

Careful consideration should be given to potential interactions between radiation and systemic therapy.

Treatment with adjuvant high-dose or pegylated interferon alfa is currently a category 2B recommendation in all of the above cases due to low benefit-to-risk ratio. Decisions about the appropriateness of adjuvant interferon alfa-2b treatment for patients should be made on an individual basis, after discussion with the patient, including an explanation of the potential benefits and side effects of interferon therapy.

For all patients who have been rendered free of disease following initial treatment for recurrent regional disease, adjuvant interferon alpha is a category 2B option. There is no evidence in support of the use of adjuvant interferon alpha for completely resected stage IV disease and the panel does not recommend that as an option in that setting. As such, the main option for adjuvant therapy in this setting is participation in a clinical trial. See sections “Treatment of Metastatic Melanoma” and “Treatment of Recurrence”.

Treatment of Metastatic Melanoma

Treatment for In-transit Disease

Many different treatment options, mostly local/regional, 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 best approach. Hence 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.[105]

A number of non-surgical local approaches are being used. These include intralesional local injections with bacillus Calmette-Guérin (BCG)[106] or interferon alfa, laser ablation, and topical imiquimod.[107] Imiquimod may have some activity for small superficial dermal lesions but not for subcutaneous disease.[108] Radiation therapy may be used for patients with unresectable symptomatic regional recurrence.

Isolation limb perfusion or infusion is a technique to regionally administer high doses of chemotherapy to an affected extremity while avoiding systemic drug exposure.[109,110] Melphalan is the drug most widely used for this technique. Isolation limb infusion has been reported by Thompson et al to be a simpler technique with response rates comparable to limb perfusion.[111] A recent study of isolated limb infusion in 128 patients achieved a complete response rate of 31%.[112] On the other hand, a modified hyperthermic isolated limb perfusion procedure achieved a higher complete response rate of 63%, with 5-year survival observed in 38% of patients.[113]

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.

Novel Therapies

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.[114] 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 < 0.001) or ipilimumab alone (10.1 months; HR = 0.66 compared to gp100 alone; P = 0.003) compared to those receiving gp100 only (6.4 months). Of note, 15 of 23 patients achieved partial response 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.[115] 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. Another open-label, phase II study in 72 melanoma patients with brain metastases reported a 24% disease control rate of the brain in the neurologically asymptomatic cohort.[116]

Approximately 45% of patients with metastatic melanoma harbor an activating mutation of the intracellular signaling kinase, BRAF.

Vemurafenib is a specific inhibitor of signaling by mutated BRAF.[117] A randomized phase III trial compared vemurafenib to dacarbazine in 675 patients with previously untreated metastatic melanoma containing a V600 mutation of BRAF.[118] 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.[119] Secondary skin lesions were detected in 26% of patients.

The Cobas 4800 BRAF V600 mutation test, a companion diagnostic test to determine the tumor mutational status, received approval along with the agent. The NCCN panel added vemurafenib to the list of available systemic treatments for patients with a documented V600 E or K mutation of the BRAF gene. Mutational status should be tested by an FDA-approved test or by a facility approved by Clinical Laboratory Improvement Amendments (CLIA).

Although approval of ipilimumab and vemurafenib 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. Vemurafenib, on the other hand, is associated with a 40-50% response rate 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 5-6 months.

The success of these two agents has prompted a new wave of questions regarding their use in the adjuvant setting, augmenting response by combining them with cytotoxic chemotherapy, and defining mechanisms of drug resistance.

The pace of change underscores the importance of participating in a clinical trial whenever possible.

Chemotherapy and Biological Therapy

Common agents being used in community practice include dacarbazine,[120,121] temozolomide,[121] imatinib for melanoma with c-KIT mutation,[122] high-dose interleukin-2 (IL-2),[123-126] and paclitaxel with or without carboplatin.[127-131] These have demonstrated modest response rates under 20% in first-line and second-line settings. Little consensus exists regarding standard chemotherapy for patients with metastatic melanoma, which most likely reflects the low level of activity of older FDA-approved agents.[132,133]

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 27-64% and complete response rates of 15-21% in patients with metastatic melanoma.[134-136] 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 vs. 9.2 months for CVD.[137] 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.[138] 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.[139-141] A recent meta-analysis also showed that although biochemotherapy improved overall response rates, there was no survival benefit for patients with metastatic melanoma.[142]

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% and 68%-84% incidence of significant symptom relief for CNS and non-CNS metastasis, respectively.[143,144] The reported clinical complete response (CR) rate ranges from 17-69%, with 49-97% achieving either a partial response (PR) or CR.[101,145,146] In a single-institutional review of 121 patients receiving palliative radiation, a 49% overall response and 17% CR rate were observed in the stage IV group.[146] The brain metastases response rate was 54%. For nodal or in-transit metastases, a 77% overall response was reported, including 44% with a CR.

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 or interferon alfa, or topical imiquimod can be used. Laser ablation or radiation therapy 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)

Treatment for stage IV metastatic melanoma 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 resected, patients can be 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. 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 for patients with documented BRAF mutation (category 1), treatment in a clinical trial, and high-dose IL-2. Other regimens include dacarbazine, temozolomide, imatinib for tumors with c-KIT mutations, dacarbazine- or temozolomide-based combination chemotherapy or biochemotherapy (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2B), paclitaxel as monotherapy or in combination with carboplatin (category 2B).

Close monitoring of potentially lethal immune-related events in patients receiving ipilimumab is essential,[147] and 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 complete response, 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. For patients on vemurafenib, the panel recommends regular dermatologic evaluation with referral to a dermatologist to monitor for skin complications.

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. Contra-indications for IL-2 include inadequate organ reserve, poor performance score, 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 is hopefully time for an antitumor immune response to emerge. Patients with BRAF-mutant melanoma who have symptomatic disease or who have progressed despite immunotherapy should be considered for vemurafenib. 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 neurological dysfunction. Treatment of melanoma brain metastases is based on symptoms, number of lesions present, and location of the lesions, as described in NCCN Central Nervous System Cancers Guidelines. Stereotactic radiosurgery (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 lesions, options for management of

extracranial sites are the same as for patients without brain metastases. Ipilimumab therapy brings the possibility of long-term disease control outside the CNS; in this context, the late adverse effects of WBRT on cognitive function may favor the use of SRS.[148] 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.[149]

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.[150] 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 ten years later) is well documented especially for patients initially presenting with early-stage melanoma.[151,152] It is probably not cost effective to follow all patients intensively for metastatic disease beyond five to ten years (depending on relative risk for recurrence).[153] However, because the lifetime risk of developing a second primary melanoma is 4-8% the panel felt that a recommendation for lifetime dermatologic surveillance for melanoma patients was justified.

Romano and colleagues[154] recently 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 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 detection of a subsequent second primary melanoma, 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.[155-157] Studies on medical imaging have reported low yield, significant false-positivity, and risks of cumulative radiation exposure.[158-

[161] Therefore, frequent imaging should not be part of the routine follow-up for all patients.

Skin cancer preventive education including sun protection measures should be promoted for patients with melanoma and their families.[162] There is increasing evidence that regular sunscreen use may diminish the incidence of subsequent melanoma.[163] Patients can be made aware of the various resources that discuss skin cancer prevention. Some useful resources are listed below:

- American Academy of Family Physicians. "Safe-Sun" Guidelines. American Academy of Family Physicians, 2000. (www.aafp.org/afp/20000715/375ph.html).
- Skin protection from ultraviolet light exposure: American College of Preventive Medicine Practice Policy Statement. Washington, DC: American College of Preventive Medicine. (http://www.acpm.org/resource/resmgr/policy-files/polstmt_ultraviolet.pdf).
- Centers for Disease Control and Prevention. Preventing skin cancer: findings of the Task Force on Community Preventive Services on reducing exposure to ultraviolet light. (www.cdc.gov/mmwr/preview/mmwrhtml/rr5215a1.htm).

NCCN Recommendations

Skin examination and surveillance at least once a year for life is recommended for all melanoma patients, including those with stage 0, in situ melanoma. Clinicians should educate all patients about post-treatment monthly self-exam of their skin and of their lymph nodes if they had stage 1A to IV melanoma and are otherwise NED. Specific signs or symptoms are indications for additional radiologic imaging.

For patients with stage IA to IIA melanoma, no evidence of disease (NED), comprehensive H&P with specific emphasis on the regional nodes and skin should be performed every 3-12 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 3-6 months for two years; then every 3-12 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 3-12 months and annual brain MRI can be considered to screen for recurrent or metastatic disease at the discretion of the physician (category 2B). More frequent imaging may be considered for higher-risk patients. Routine blood testing to detect recurrence is not recommended for these patients.

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). In the former situation, the prognosis after re-excision is much better, 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 lesion thickness. Re-excision to appropriate margins is recommended, with or without lymphatic mapping and SLNB, appropriate to the microstaging 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 or with systemic therapy. The following are category 2B alternatives: intralesional injections with BCG or interferon-alfa, topical imiquimod (for small dermal lesions), laser ablation therapy or radiation therapy.

After complete response 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 may also be considered (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.

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 Melanoma Guidelines 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. Few, if any, firm recommendations can be made about more controversial issues for the melanoma patient, such as the extent of workup or intensity of follow-up. 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 Melanoma Guidelines undergo annual revision and are continually updated as new data become available.

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