



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Melanoma

Version 2.2012

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NCCN Guidelines™ Version 2.2012 Panel Members Melanoma

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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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Summary of the changes in the 2.2012 version of the NCCN Melanoma Guidelines from the 1.2012 version include:

[ME-5](#)

- Footnote “r” changed from “Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial” to “Obtain tissue for genetic analysis if the patient is being considered for targeted therapy or if it is relevant to eligibility for participation in a clinical trial.”

[ME-9](#)

- Treatment of metastatic disease; Disseminated (Unresectable) pathway; Without brain metastases: Systemic therapy changed to “Systemic therapy and/or Radiation”.

[ME-D](#) Principles of Radiation Therapy

Primary Disease

- The following statement was removed: Special cases where complete surgical excision is not possible or not recommended due to potential morbidity.
- Bullet changed to “Adjuvant treatment for selected patients with desmoplastic melanoma with extensive neurotrophism.”

[ME-E](#) Systemic Therapy Options For Advanced Or Metastatic Melanoma

- Based on the supporting data and recent FDA approval, vemurafenib (category 1) was added as an option for the treatment of patients with advanced or metastatic melanoma. The following corresponding footnotes were also added:
 - ▶ Footnote “4”: “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.”
 - ▶ Footnote “5”: “Vemurafenib has the potential for significant dermatologic complications including cutaneous squamous cell carcinoma and extreme photosensitivity. Regular dermatologic evaluation with referral to a dermatologist as clinically indicated. Patients should also be carefully monitored for the development of other adverse reactions such as joint pain and swelling.”

Summary of the changes in the 1.2012 version of the NCCN Melanoma Guidelines from the 4.2011 version include:

[Global Changes](#)

- “PET” changed to “PET/CT” where appropriate throughout the guidelines.
- “CT ± PET” changed to “CT, PET/CT”.

[ME-1](#)

Pathology Report:

- Clark level was further clarified as “for nonulcerated lesions where mitotic rate is not determined”.
- Pure desmoplasia if present: Footnote “c” that states, “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).” was added to the algorithm.

[ME-2](#)

- Workup: The statement “Routine imaging not recommended” changed to “Routine imaging/lab tests not recommended”.
- Footnote “i” was changed as follows: “For lower risk patients such as those with IA lesions and IB lesions ≤ 0.5mm thick and mitotic rate < 2 per mm², SLNB should generally not be recommended, unless there are specific adverse features (category 2B)”.



[ME-6](#)

- “Local/satellitosis and/or in-transit recurrence” changed to “Local/satellite and/or...” (Also for [ME-7](#))
- Footnote “v” changed to “Local/satellite recurrence without in situ or radial growth phase...”

[ME-9](#)

- Treatment of Metastatic Disease: Limited (Resectable); Resect pathway: After Observation, “See Follow-up on ME-6” was added.

[ME-A](#) Principles of Biopsy and Pathology

Principles of Biopsy:

- New bullet added that states, “The orientation of the biopsy should be planned with definitive wide excision in mind.”
- Footnote 1 was clarified as “...consider narrow margin excisional biopsy.”

Principles of Pathology:

- Fourth bullet; Last arrow point: “Pure desmoplasia, if present (specify pure vs. mixed)” changed to “...(specify pure vs. desmoplastic with spindle cell and/or epithelioid cells)”.
- Fifth bullet: “Consider use of fluorescent in situ hybridization (FISH)...” changed to “Consider use of comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH)...” Corresponding footnote “4” that states, “CGH may be more accurate than FISH in identifying relevant genetic mutations” is new to the page.

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

- Footnote “1”: Second sentence changed to “For selected patients with positive margins after optimal surgery, consider imiquimod (for patients with MIS) or RT (category 2B)”.

[ME-D](#) Principles of Radiation Therapy

- This page was revised extensively.

[ME-E](#) Systemic Therapy Options For Advanced Or Metastatic Melanoma

- After ipilimumab, a new footnote “3” was added that states, “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”.

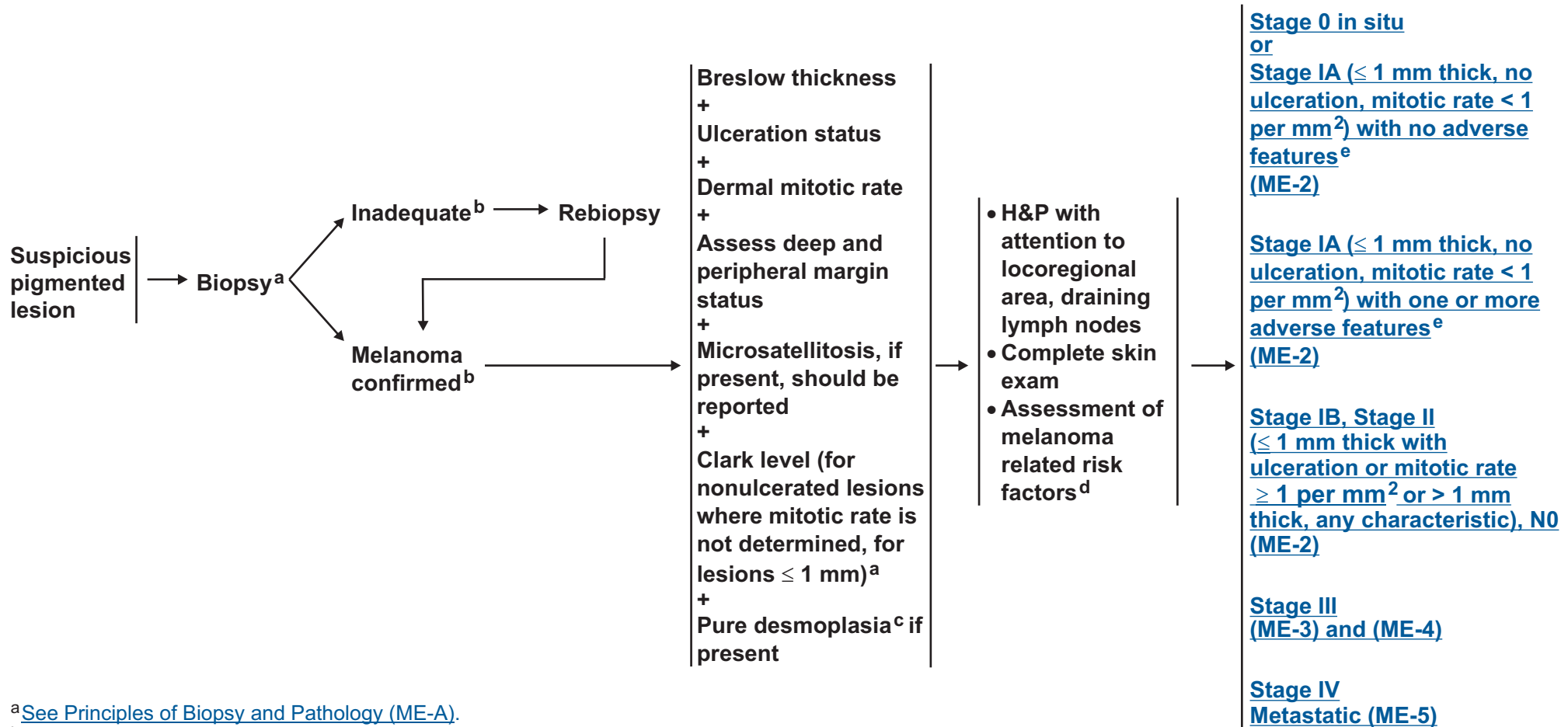


CLINICAL PRESENTATION

PATHOLOGY REPORT

PRELIMINARY WORKUP

CLINICAL STAGE



^aSee Principles of Biopsy and Pathology (ME-A).

^bIf diagnostic biopsy is inadequate for treatment decisions, rebiopsy may be appropriate.

^cGiven 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(2):321-330.)

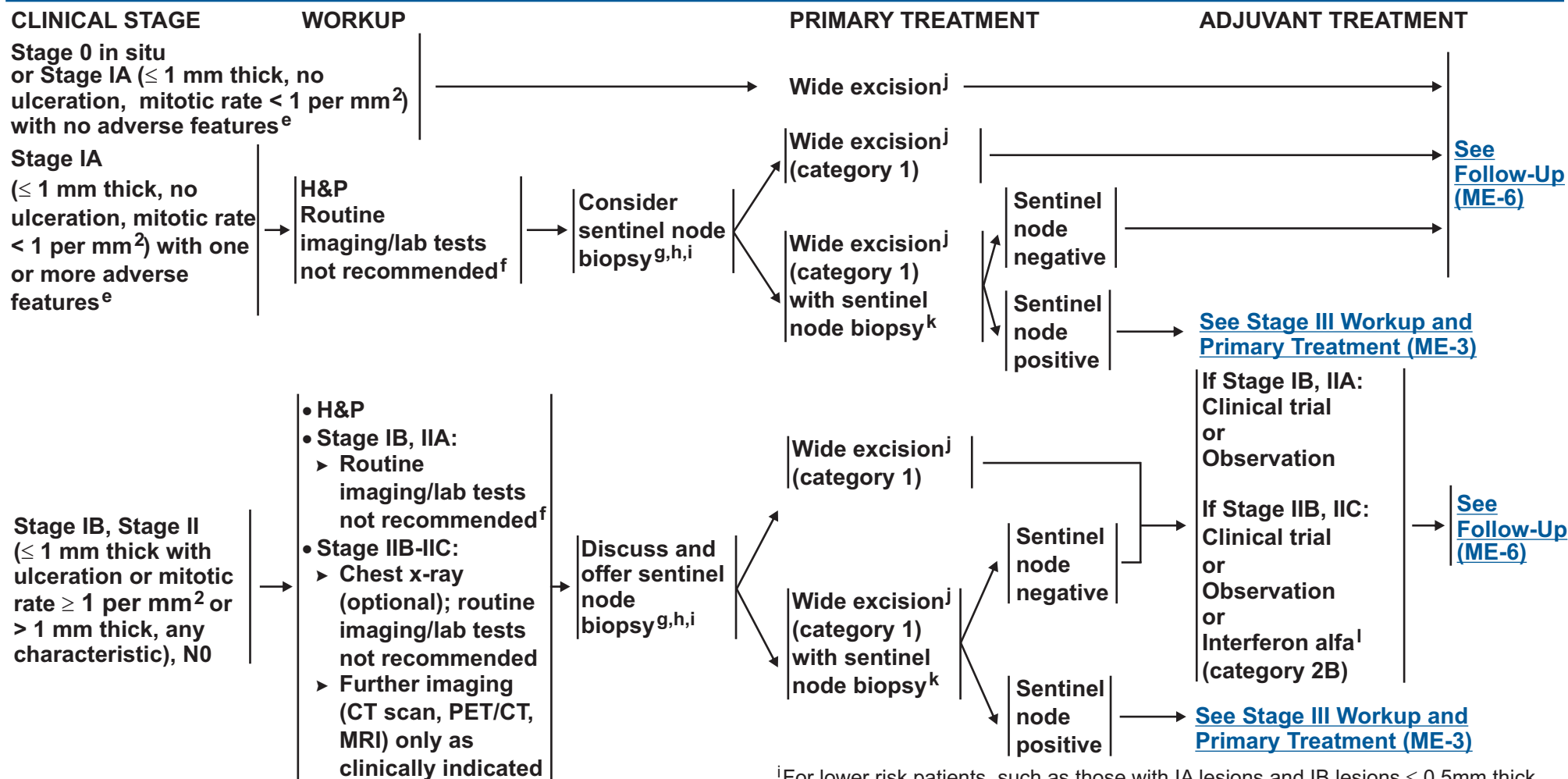
^dRisk factors for melanoma include family history of melanoma, prior primary melanoma, and other factors such as atypical moles/dysplastic nevi.

^eAdverse features include ≥ 0.75 mm thick, positive deep margins, lymphovascular invasion (LVI), or Clark level IV.

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^eAdverse features include ≥ 0.75 mm thick, positive deep margins, lymphovascular invasion (LVI), or Clark Level IV.

^fImaging only to evaluate specific signs or symptoms (CT scan, PET/CT, MRI).

^gDecision not to perform SLNB may be based on significant patient comorbidities, patient preference or other factors.

^hSentinel node biopsy is an important staging tool, but the impact of SLNB on overall survival is unclear.

ⁱFor lower risk patients, such as those with IA lesions and IB lesions ≤ 0.5 mm thick and mitotic rate < 2 per mm^2 , SLNB should generally not be recommended, unless there are specific adverse features. (category 2B).

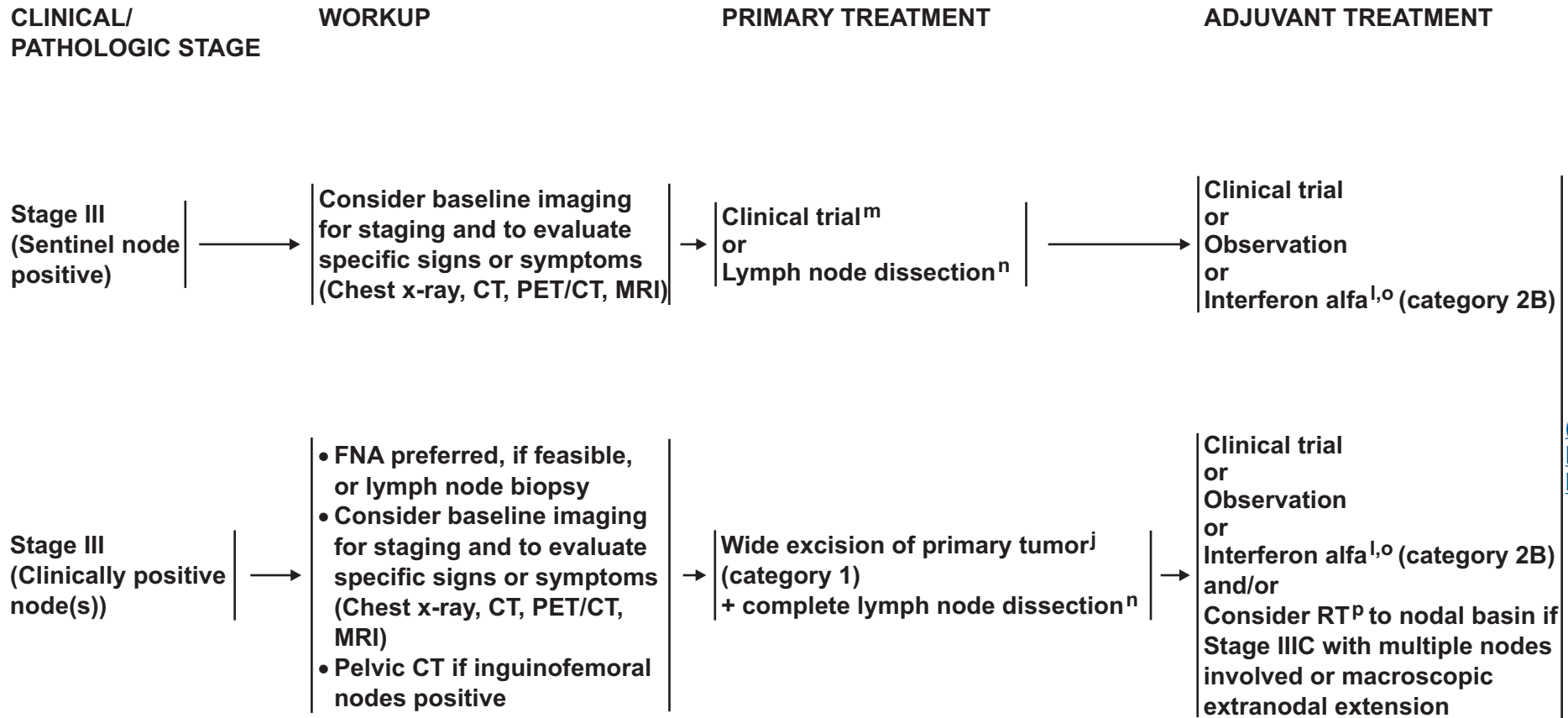
^jSee [Principles of Surgical Margins for Wide Excision of Primary Melanoma \(ME-B\)](#).

^kSentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

^lAdjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.

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(See
[Follow-up
ME-6](#))

^jSee Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).

^kSentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

^lAdjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.

^mClinical trials assessing alternatives to complete lymph node dissection, such as careful observation with nodal basin ultrasound.

ⁿSee Principles of Complete Lymph Node Dissection (ME-C).

^oInterferon alfa can be given as high-dose interferon for one year or as peginterferon alfa-2b for up to 5 years.

^pSee Principles of Radiation Therapy (ME-D).

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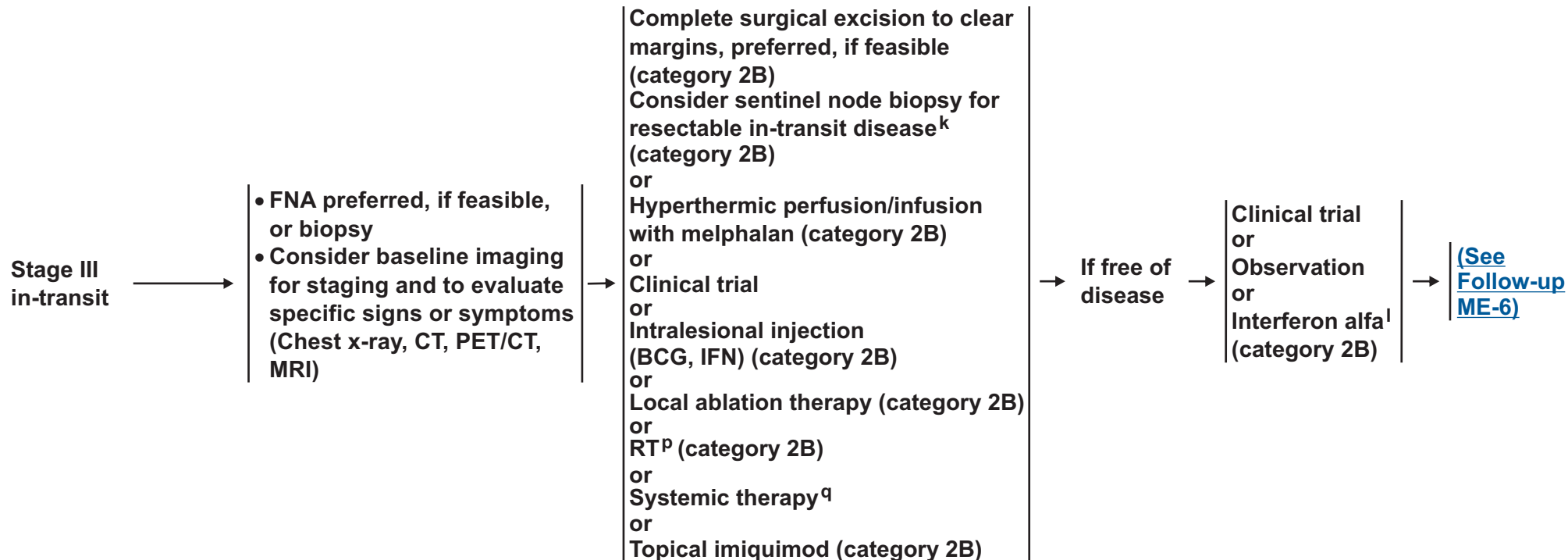


**CLINICAL/
PATHOLOGIC
STAGE**

WORKUP

PRIMARY TREATMENT

ADJUVANT TREATMENT



^kSentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

^l Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.

^p See [Principles of Radiation Therapy \(ME-D\)](#).

^q See [Systemic Therapy Options for Advanced or Metastatic Melanoma \(ME-E\)](#).

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**CLINICAL/
PATHOLOGIC
STAGE**

WORKUP

**Stage IV
Metastatic**

- FNA preferred, if feasible or biopsy^r
- LDH
- Encourage chest/abdominal/pelvic CT, MRI brain, and/or PET/CT for baseline imaging and to evaluate specific signs and symptoms

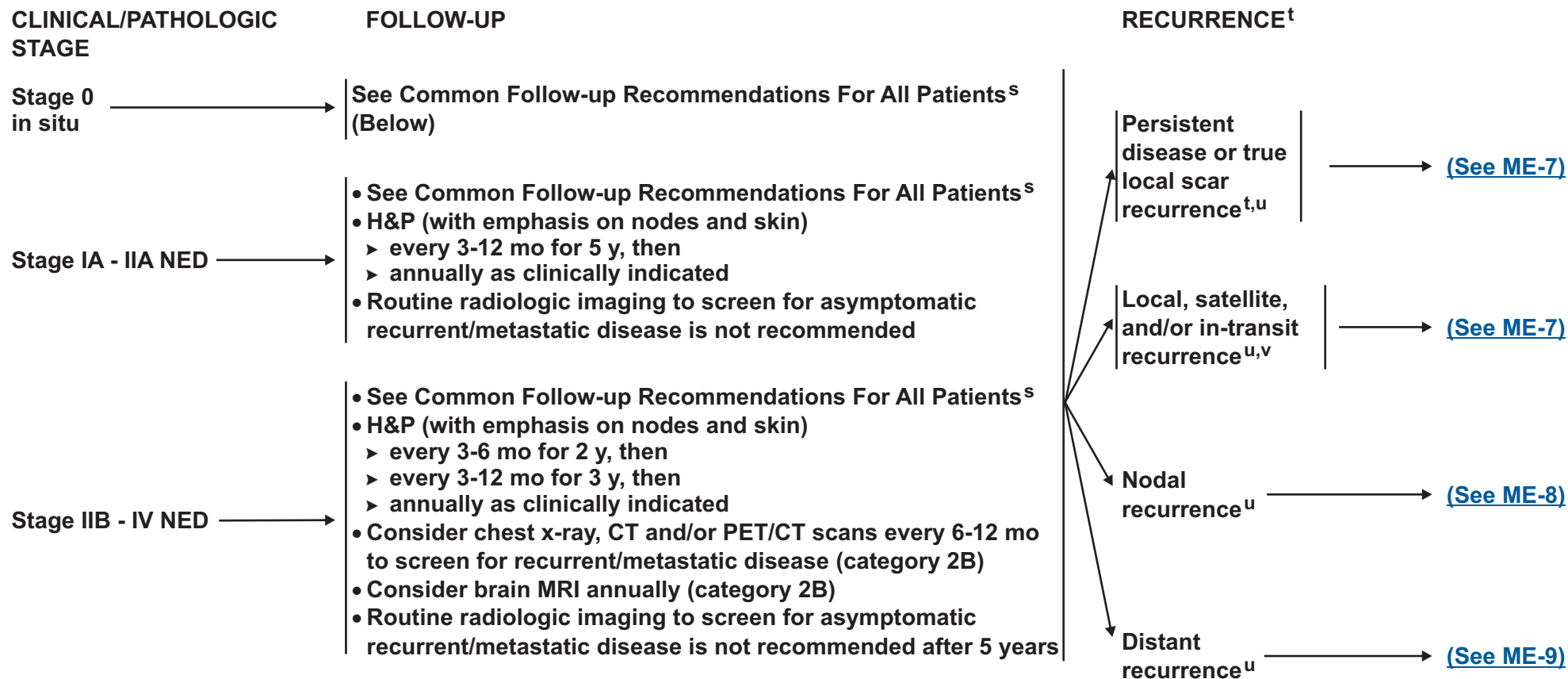
[See Treatment for Limited \(Resectable\) or Disseminated Disease \(Unresectable\) ME-9\)](#)

^rObtain tissue for genetic analysis 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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[§]Common Follow-up Recommendations For All Patients:

- At least annual skin exam for life
 - Educate patient in monthly self skin exam (and monthly self lymph node 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 anxiety.

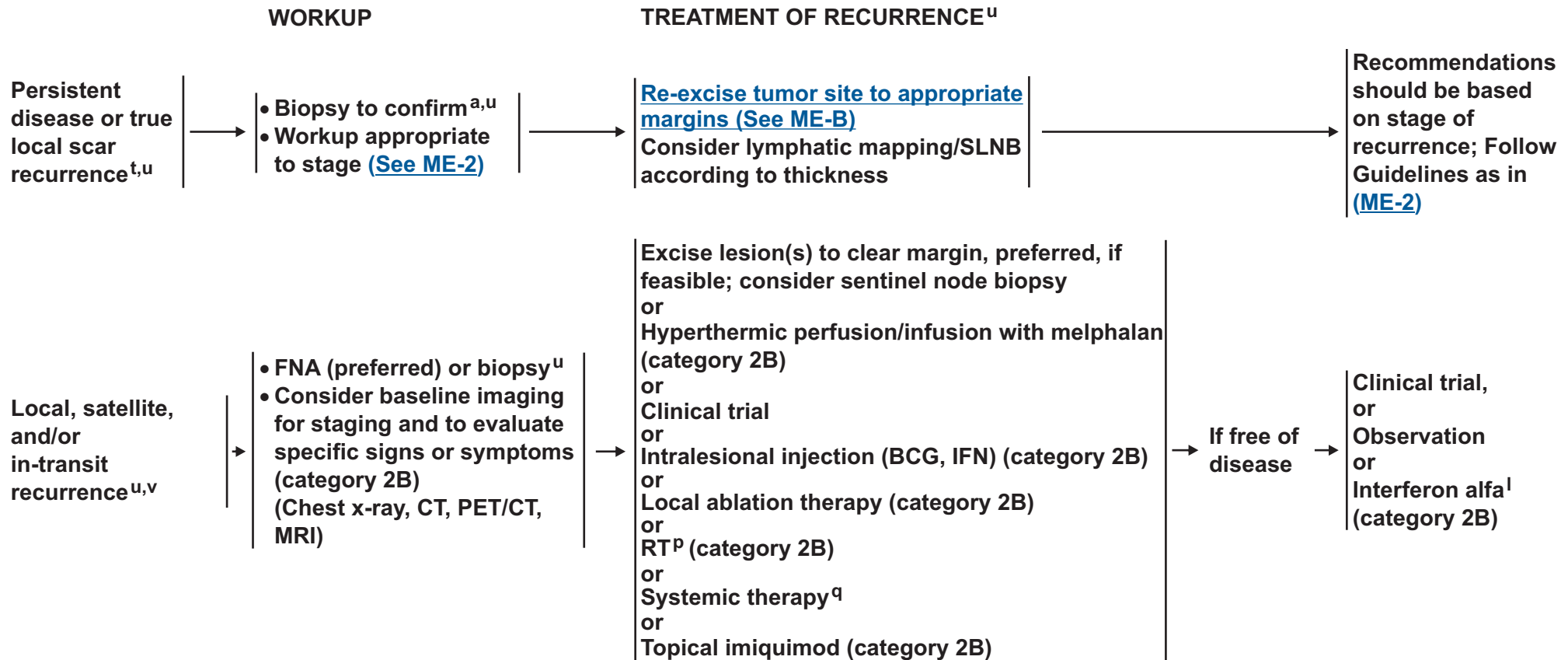
[†]Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.

^uInitial clinical recurrence should be confirmed pathologically whenever possible. Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.

^vLocal, 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).

^l Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.

^p See Principles of Radiation Therapy (ME-D).

^q See Systemic Therapy Options for Advanced or Metastatic Melanoma (ME-E).

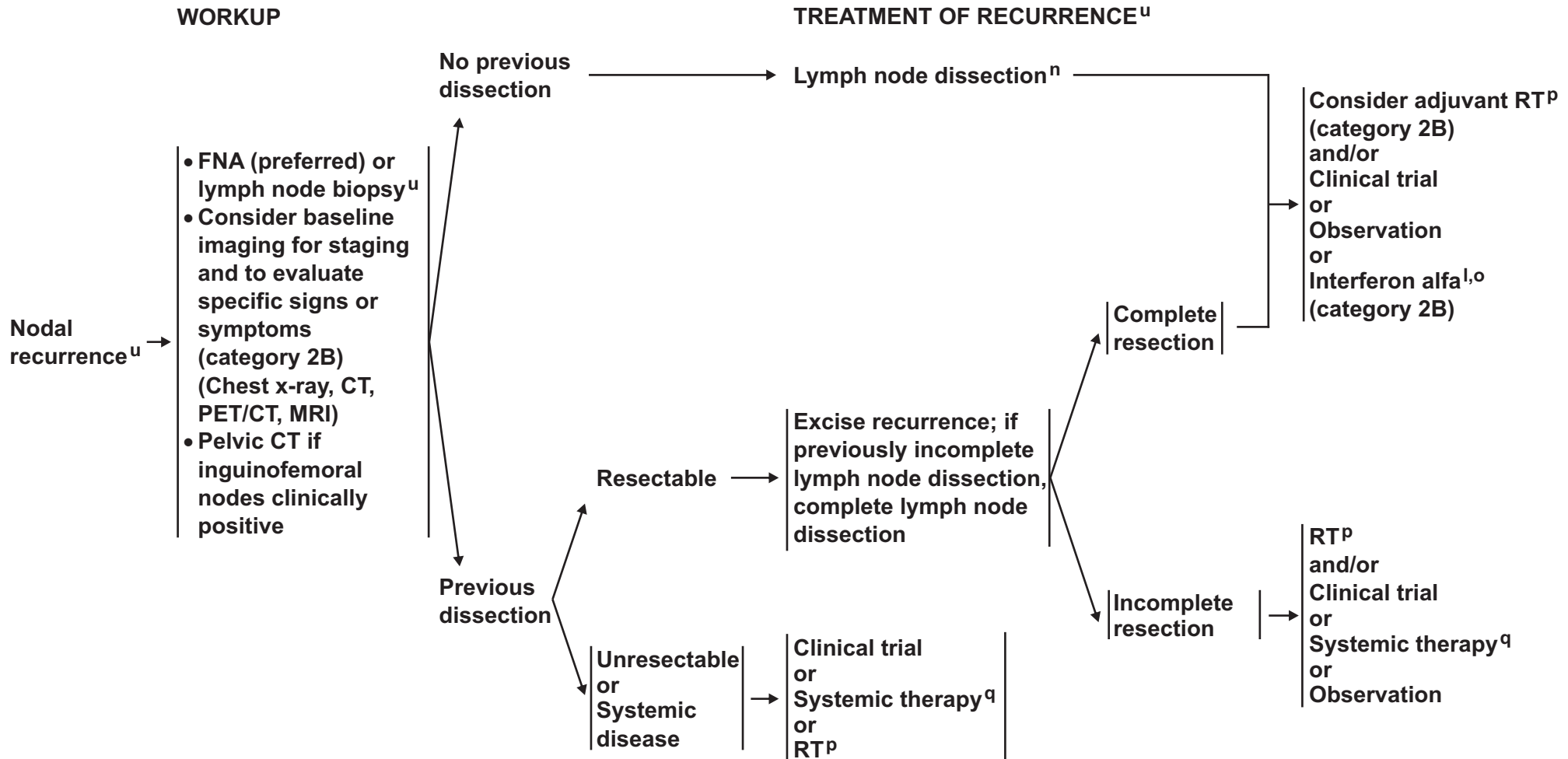
^t Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.

^u Initial clinical recurrence should be confirmed pathologically by biopsy whenever possible. Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.

^v 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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^lAdjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.

ⁿSee [Principles of Complete Lymph Node Dissection \(ME-C\)](#).

^oInterferon alfa can be given as high-dose interferon for one year or as peginterferon alfa-2b for up to 5 years.

^pSee [Principles of Radiation Therapy \(ME-D\)](#).

^qSee [Systemic Therapy Options for Advanced or Metastatic Melanoma \(ME-E\)](#).

^uInitial clinical recurrence should be confirmed pathologically by biopsy whenever possible. Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.

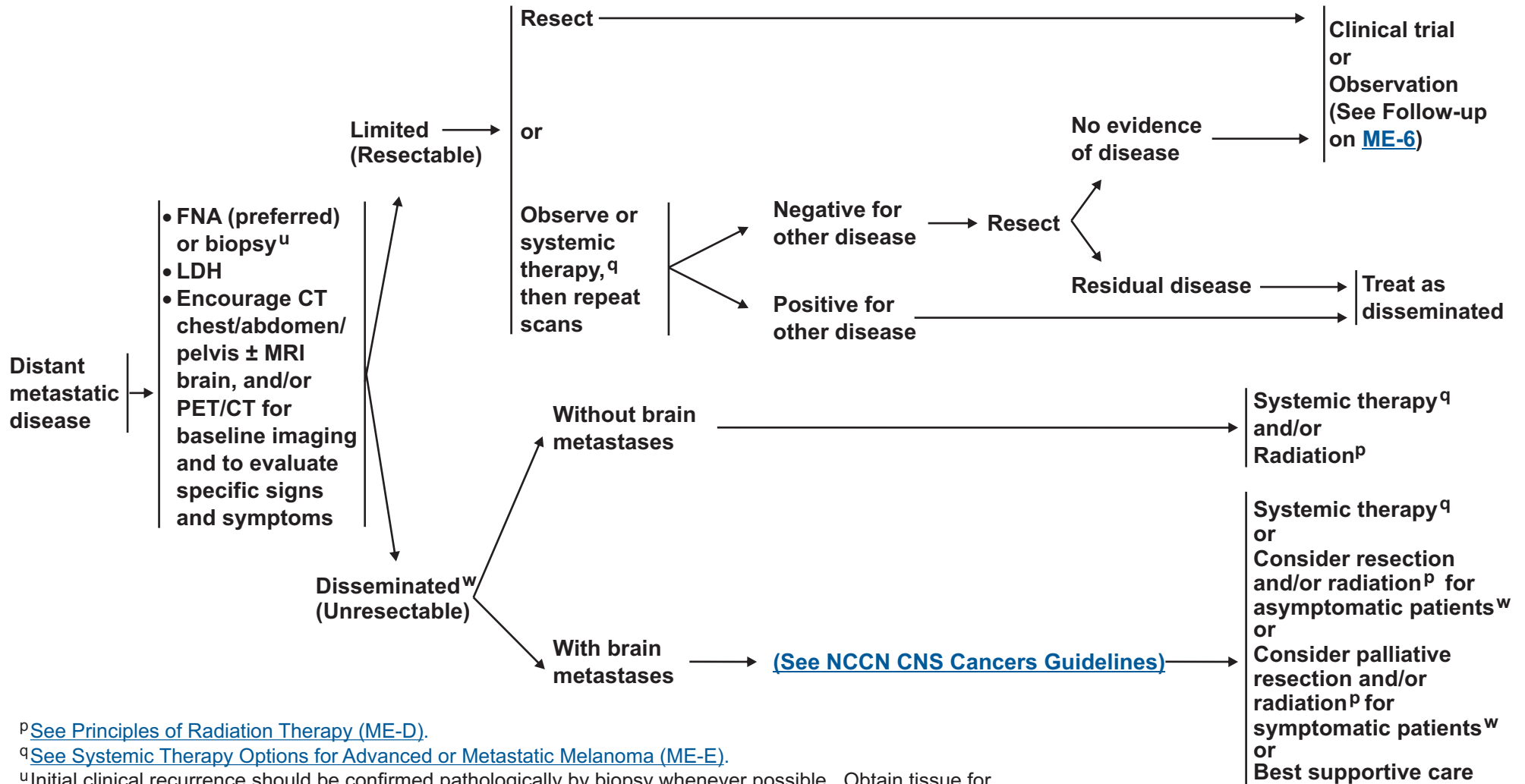
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WORKUP

TREATMENT OF METASTATIC DISEASE



^pSee Principles of Radiation Therapy (ME-D).

^qSee Systemic Therapy Options for Advanced or Metastatic Melanoma (ME-E).

^uInitial clinical recurrence should be confirmed pathologically by biopsy whenever possible. Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.

^wIn patients with disseminated metastases, resection or radiation may be indicated to palliate symptoms such as gastrointestinal bleeding or obstruction, ulcerated soft tissue cutaneous metastases, or bulky adenopathy.

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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 biopsy¹ 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, 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, if present, should be reported.**
- **Encourage consistent reporting of these additional factors (compatible with American Academy of Dermatology recommendations):**
 - ▶ **Location**
 - ▶ **Regression**
 - ▶ **Tumor infiltrating lymphocytes (TIL)**
 - ▶ **Vertical growth phase (VGP)**
 - ▶ **Angiolymphatic invasion**
 - ▶ **Neurotropism**
 - ▶ **Histologic subtype**
 - ▶ **Pure desmoplasia, if present (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.⁴**

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 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**

<u>Tumor Thickness</u>	<u>Recommended Clinical Margins²</u>
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

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

¹For 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).

²Excision 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).

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PRINCIPLES OF COMPLETE LYMPH NODE DISSECTION

Adequacy of regional lymph node dissection:

- An anatomically complete dissection¹ 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).

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

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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 extensive neurotrophism.

REGIONAL DISEASE

- Extracapsular extension
- ≥ 4 involved nodes
- Size ≥ 3 cm
- Cervical² > Axillary > Inguinal Location
- Recurrent disease after prior complete nodal dissection³

METASTATIC DISEASE

- Brain metastases (see [NCCN Central Nervous System Cancers Guidelines](#))
 - ▶ Definitive or palliative stereotactic radiosurgery and/or whole brain radiation therapy
 - ▶ Adjuvant radiation following resection of brain metastases.
- Other symptomatic or potentially symptomatic soft tissue and/or bone metastases

¹Most systemic treatments should be held during radiation.

²In the cervical location, consider adjuvant radiation if ≥ 2 lymph nodes are involved and for lymph nodes ≥ 2 cm.

³A wide range of radiation dose/fractionation schedules is effective. Hypofractionated regimens may increase the risk for long term complications such as lymphedema and small bowel obstruction.

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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA
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SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA¹

- **Clinical trial (preferred)**
- **Ipilimumab (category 1)^{2,3}**
- **Vemurafenib (category 1)^{4,5}**
- **Dacarbazine**
- **Temozolomide**
- **High-dose Interleukin-2^{6,7}**
- **Dacarbazine-or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2B)⁷**
- **Paclitaxel (category 2B)**
- **Paclitaxel/cisplatin (category 2B)**
- **Paclitaxel/carboplatin (category 2B)**

¹Patients who progress after initial therapy may be offered subsequent therapy if they maintain a performance status of ECOG 0-2 or Karnofsky score \geq 60.

²Ipilimumab 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.

³Re-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.

⁴Vemurafenib is recommended for patients with V600 mutation of the BRAF gene documented by an FDA-approved or Clinical Laboratory Improvement Amendments (CLIA)-approved facility.

⁵Vemurafenib has the potential for significant dermatologic complications including cutaneous squamous cell carcinoma and extreme photosensitivity. Regular dermatologic evaluation with referral to a dermatologist as clinically indicated. Patients should also be carefully monitored for the development of other adverse reactions such as joint pain and swelling.

⁶High-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).

⁷Administration 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 regimens.

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.

[References on next page](#)



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

Ipilimumab

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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

**ME-E
(2 of 3)**



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

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

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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.



NCCN Guidelines™ Version 2.2012 Staging Melanoma

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 mm² as shown below:

<i>T classification</i>	<i>Thickness (mm)</i>	<i>Ulceration Status/Mitoses</i>
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:

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

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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:

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

Anatomic Stage/Prognostic Groups

Clinical Staging*

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

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

Pathologic Staging**

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

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/03/11

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.

Overview

In the year 2010, an estimated 68,130 new cases of melanoma were diagnosed and about 8,700 patients died of the disease in the United States.¹ 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 55.² Melanoma ranks second to adult leukemia in terms of loss of years of potential life, per death. The median age at diagnosis is 59 years.

Risk factors for melanoma include a positive family history of melanoma, prior melanoma, multiple clinically atypical moles or dysplastic nevi,^{3,4} and rarely inherited genetic mutations. Genetic counselling 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.⁵ Individuals with an inability to tan and fair skin that sunburns easily have a greater risk of developing melanoma.⁶ 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.⁷ 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 50-90%. 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, rather than a shave biopsy, is an acceptable option. These procedures should provide accurate primary tumor microstaging, without interfering with definitive local therapy. If the incisional 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.

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).^{7,8} In patients with localized melanoma (stage I or II), Breslow tumor thickness, ulceration, and in patients with melanoma less than or equal to 1.0 mm in thickness, mitotic rate, are the three most important characteristics of the primary tumor predicting outcome.

Mitotic rate is an indicator of tumor proliferation and is measured as the number of mitoses per mm². The latest AJCC staging manual recommended the “hot spot” technique for calculating the mitotic rate.⁸ Barnhill et al⁹ 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, moderate mitotic rate (between 1 and 6) and mitotic rate greater than 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.¹⁰⁻¹² In the evidence-based derivation of the 2010 AJCC staging system, mitotic rate greater than or equal to 1 per mm² 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.^{13,14} In contrast to mitotic index, no threshold of age have 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).

The American Academy of Dermatology (AAD) Task Force recommends the inclusion of mitotic rate in the biopsy report as



optional along with other additional factors such as vertical growth phase (VGP), tumor-infiltrating lymphocytes (TIL) and regression.¹⁵ 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), as these have very low incidence of nodal involvement that does not support routine use of SLNB.¹⁶ Mixed desmoplasia has a similar rate of lymph node spread as that of conventional melanoma. Consider fluorescent in situ hybridization (FISH) for histologically equivocal lesions if the technique is available.

The NCCN melanoma panel recommends the inclusion of Breslow thickness, ulceration status, mitotic rate, deep and peripheral margin status (positive or negative), satellitosis if present and Clark level (especially for lesions 1.0 mm or less, optional for lesions over 1.0 mm thick) in the pathology report. Mitotic rate should be reported for all lesions, as it is emerging as an independent predictor of outcome. The panel agreed that recording of those parameters identified by the AAD task force would be helpful, but not mandatory.

Among patients with localized melanoma undergoing SLNB, the status of the sentinel node is the most important prognostic factor.¹⁷ 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, followed by the presence or absence of primary tumor ulceration. Other prognostically relevant factors include the presence of extranodal tumor extension and, in patients with positive sentinel nodes, the size and location of the metastatic melanoma in the sentinel nodes.

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.

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.^{17, 18}

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 dysplastic nevi should include a detailed personal and family history, including any history of prior removal of dysplastic nevi.³ 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, an H&P including examination of locoregional area and draining lymph nodes, and a complete skin examination. In accordance with the AJCC staging system, NCCN guidelines have categorized patients into the following clinical groups:



- Stage 0: melanoma in situ
- Stage IA: 1.0 mm thick or less, mitotic rate less than 1 per mm², no ulceration, with or without adverse prognostic features such as thickness over 0.75 mm, positive deep margins, lymphovascular invasion, or Clark level IV
- Stage IB-II: 1.0 mm thick or less with ulceration or mitotic rate greater than or equal to 1 per mm²; or greater than 1.0 mm thick, with any characteristic and clinically negative nodes
- Stage III: clinically positive nodes or in-transit disease
- Stage IV: distant metastatic disease

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 – 30% 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.^{17, 19} The AJCC staging system clearly recognizes this difference in prognosis among patients with pathologic stage III melanoma.⁷

Workup

There are several reasons to embark on an extent of disease workup in the melanoma patient. One would be to establish a set of baseline images against which to compare future studies in a patient at risk for relapse. Another would be to detect clinically occult disease that would affect immediate treatment decisions. A third reason would be 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.²⁰⁻²²

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%.²³⁻²⁵ 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%.²⁶⁻²⁸ 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 the majority of



clinical stage III patients will ultimately develop distant metastases, the inability of cross-sectional imaging studies to detect this 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.²⁹⁻³¹ In patients with more advanced stage III disease, PET scan may be more useful. In particular, PET 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).³²

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, the extent of workup is left to the discretion of the treating physician.

Routine cross-sectional imaging (CT, PET, MRI) is not recommended for patients with localized melanoma. For patients with stage IA melanoma, this is consistent with the National Institutes of Health guideline.³³ For patients with stage IB to IIC, this recommendation is based on the very low yield of detection of subclinical disease. In patients with stage IIB-IIC, chest x-ray is optional. In any patient with localized melanoma, cross-sectional imaging should only be used to investigate specific signs or symptoms.

Most panel members acknowledged the low yield of screening CT or PET 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 scanning to the discretion of the treating physician. 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.

For the small group of patients presenting with stage III in-transit disease, the workup outlined above for 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 (preferred) or with open biopsy of the lesion. Sample tissue may be obtained during biopsy for genetic analysis (eg., BRAF or C-kit mutational status) if it potentially impacts enrollment in clinical trials of targeted therapy.³⁴ Chest abdominal/pelvic CT, with or without PET, and/or head MRI should be considered.

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 suggestions of symptoms or physical findings 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.

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.^{35, 36} At a median follow-up of 90 months, local recurrence, disease-free and overall survival rates were similar in both groups.

The National Intergroup Trial randomized 468 patients with melanomas 1.0-4.0 mm in thickness to wide excision with either two or four cm margins. At a median follow-up of ten years, there were no differences in local recurrence, disease-free, or overall survival.^{37, 38} Prospective randomized trials from Sweden have confirmed that satisfactory local control and melanoma specific survival are not compromised by narrower margins.^{39, 40}

In a more recent prospective randomized trial comparing 1 cm vs. 3 cm margins for melanomas thicker than 2 mm, wider margins were associated with a slightly lower rate of combined local/regional/nodal recurrence, but without improvement in local recurrence alone, or in melanoma specific survival.⁴¹ 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.⁴²

Management of lentigo maligna 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. Various approaches aimed at complete surgical excision with meticulous margin control, have demonstrated high local control rates and are used at some NCCN centers, although they are not universally accepted.^{43, 44}

NCCN Recommendations

The NCCN recommendations for surgical margins for wide excision are based on the results of clinical trials discussed above. In cases where there were no prospective data available (in situ and thick melanoma), recommendations were made based on consensus. Note that the clinical/surgical margins discussed here 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. 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 for tumors 4 mm or less in thickness; category 2A for tumors more than 4 mm in thickness).



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.

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.⁴⁵⁻⁴⁹ However, long-term, comparative studies are still needed. Radiotherapy has also been used for lentigo maligna.⁵⁰ If positive margins remain after optimal surgery, topical imiquimod or radiotherapy may be considered in selected patients (category 2B).

Sentinel Lymph Node Biopsy

SLNB is a minimally invasive procedure developed to identify patients with nodal metastases and who could be candidates for complete lymph node dissection.⁵¹ 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.⁵² 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.

Recently, Morton et al published data from the third interim analysis of results from the MSLT-I trial.⁵³ 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 at least in 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.

MSLT-II is an ongoing trial in which patients with sentinel node metastases are randomized to undergo either complete 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).

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.⁵⁴ A review by Andtbacka and Gershenwald⁵⁵ 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 mm to 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.⁵⁶ Larger series and longer term follow-up will be required to assess the prognostic value of the SLN in patients with thin melanoma.⁵⁷⁻⁵⁹

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.⁶⁰⁻⁶² 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.

NCCN Recommendations

Sentinel node biopsy may be offered to appropriate patients with localized melanoma for pathological staging. The NCCN melanoma panel does not recommend SLNB for patients with *in situ* melanoma (stage 0) or stage IA melanoma that is 1.0 mm or less with no adverse features. Discussion of SLNB should be considered for patients with stage IA thin melanomas (1.0 mm or less) with adverse prognostic features such as thickness over 0.75 mm, positive deep margins, lymphovascular invasion, or young patient age (although no threshold of young age alone is sufficient to recommend SLNB).⁶³⁻⁶⁶ The significance of tumor regression is debatable, with more recent studies reporting no association between the presence of regression incidence and the incidence of SLN positivity.^{67, 68} As the yield of a positive sentinel node biopsy 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 IB or stage II melanoma (1.0 mm

thick or less with ulceration or mitotic rate greater than or equal to 1 per mm²; 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. However, while SLNB is a useful staging tool, its impact on the overall survival of these patients is unclear. In patients who would be candidates for SLNB, the decision to not perform SLNB may be based on significant patient comorbidities or individual patient preference.

Sentinel nodes should be evaluated with serial sectioning and immunohistochemistry. The validity of sentinel node biopsy in accurately staging patients after prior wide excision is unknown. As such, wide excision before planned sentinel node biopsy is discouraged, although patients may be considered for sentinel node biopsy 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.

The panel discussed at length the absolute lower limit of probability of sentinel node positivity that should prompt a discussion of SLNB. As such, it was agreed that the procedure should be considered for patients with high risk stage IA melanoma, and discussed and offered to patients with stage IB-IIc melanomas. Included in the latter category will be patients with stage IA or IB melanoma at very low risk for either positive sentinel lymph node or melanoma recurrence (≤ 0.5 mm thick and mitotic rate <2 per mm²). In this case, there is non-uniform panel consensus that it would be appropriate to omit SLNB unless there are



other specific clinical indications (category 2B). In the absence of firm data, the decision about SLNB in this setting should be left to the patient and the treating physician.

Lymph Node Dissection

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 when there are more than three superficial nodes involved, when the nodes are clinically positive, or when Cloquet's node is positive.⁶⁹⁻⁷¹

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). Published studies have revealed additional positive non-sentinel nodes in approximately 15-20% of these complete lymph node dissection specimens.^{72, 73} However the impact of completion lymph node dissection on regional control and survival in this setting has not been clearly demonstrated. Participation in MSLT-II, assessing the option of nodal observation in patients with positive sentinel nodes, is encouraged where available. The option of nodal basin observation for these patients has not been thoroughly studied.

Patients presenting with clinical stage III and 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. Complete lymph node dissection is standard practice at most, but not all, NCCN member institutions. In the setting of inguinal lymphadenopathy, a deep groin dissection is recommended if the PET or pelvic CT scan reveals iliac and/or obturator lymphadenopathy or if a positive Cloquet's lymph node is found intraoperatively (category 2B).^{70, 71} Deep groin dissection also should be considered for clinically positive nodes or if more than three superficial nodes are involved (category 2B).⁶⁹

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. 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 conducted by WHO,⁷⁴ there was no significant improvement in the overall survival (35% for the interferon group vs. 37% for those assigned to observation alone). In the French Cooperative Group trial, after a median follow-up of 5 years, adjuvant interferon therapy showed a significant relapse-free survival benefit and also a trend towards an increase in overall survival.⁷⁵ In another prospective randomized study, adjuvant interferon prolonged disease-free survival for all patients at the median follow-up of 41 months.⁷⁶



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.⁷⁷ No significant improvement in progression-free survival was reported for intermediate-dose interferon alfa-2b in EORTC 18952.⁷⁸

High-Dose Interferon and pegylated interferon

High dose 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 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.⁷⁹ 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.⁸⁰ 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 1314 patients with stage II melanoma was closed early by the data monitoring committee because of inferior survival in the vaccine arm.⁸¹

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 survival (both relapse free and overall survival).⁸²

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.⁸³ 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.⁸⁴

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.⁸⁵

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%); there was no significant effect of pegylated interferon on overall survival.⁸⁶ Based on this data, pegylated interferon alfa received approval by the Food and Drug Administration (FDA) in 2011 as adjuvant therapy for melanoma 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 was observed primarily in patients with ulcerated primary melanomas.⁸⁷ The clinical and biologic significance of this observation remains unclear.

NCCN Recommendations

Most patients with in-situ or early-stage melanoma will be cured by primary excision alone. Adjuvant therapy is not recommended for patients with in situ or node-negative primary melanoma (stage IA, 1.0 mm thick or less with or without adverse features). 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 mm², 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.

Treatment with adjuvant high-dose or pegylated interferon alfa is 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.⁸⁸⁻⁹⁰

In a recent multicenter, randomized Phase III trial conducted in patients with stage III melanoma that had been completely resected, patients received either postoperative adjuvant radiation to the nodal basin or observation. Lymph node field recurrence was significantly less frequent in the adjuvant radiation group, but there was no improvement in overall survival.⁹¹ Adjuvant hypofractionated RT to the nodal bed should be considered for stage IIIC patients in the setting of multiple positive nodes or macroscopic extranodal soft-tissue extension, especially in the head and neck region.^{92, 93}

For all patients who have been rendered free of disease by surgery, following initial treatment for recurrent or metastatic disease (stage III in-transit metastases or stage IV), consideration of adjuvant treatment is appropriate. See sections “Treatment of metastatic melanoma” and “Treatment of recurrence”. Of note, 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.

Treatment of Metastatic Melanoma

Metastatic melanoma is associated with a poor prognosis. Common agents currently being used in community practice include dacarbazine,^{94, 95} temozolomide,⁹⁵ high-dose interleukin-2 (IL-2),⁹⁶⁻⁹⁹ and paclitaxel with or without cisplatin or carboplatin.¹⁰⁰⁻¹⁰⁴ These have demonstrated modest response rates under 20% in first-line and second-line settings. Little consensus exists regarding standard therapy for patients with metastatic melanoma, which most likely reflects the low level of activity of older FDA-approved agents.^{105, 106} However, the therapeutic landscape for metastatic melanoma is rapidly changing with



the recent development of novel agents. Ipilimumab, an immunotherapy with a monoclonal antibody directed to the immune checkpoint receptor termed “cytotoxic T lymphocyte antigen-4 (CTLA-4)”, received FDA approval in March 2011. Approval was based on a randomized phase III trial of 676 patients with unresectable metastatic disease that progressed during systemic therapy.¹⁰⁷ 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). The NCCN panel included ipilimumab as a category 1 recommendation for metastatic melanoma. Another promising therapy currently in clinical trial is inhibition of the protein kinase BRAF. Among patients whose melanoma has detectable mutations in BRAF, an 81% objective response was observed.³⁴ The pace of change underscores the importance of participating in a clinical trial whenever possible; this remains to be the preferred choice of management of unresectable metastatic disease in the NCCN guideline.

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 an overall response rate of 27-64% and a complete response rate of 15-21% in patients with metastatic melanoma.¹⁰⁸⁻¹¹⁰ A report of 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.¹¹¹ 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.¹¹² 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.¹¹³⁻¹¹⁵ A recent meta-analysis also showed that although biochemotherapy improved overall response rates, there was no survival benefit for patients with metastatic melanoma.¹¹⁶

NCCN Recommendations

Stage III: In-transit metastases

Many different treatment options are available for patients presenting with stage III in-transit metastases. For those with a one or a small number of in-transit metastases, complete surgical excision with histologically negative margins is preferred (category 2B), if feasible. In the patient undergoing curative resection of a solitary in-transit metastasis, sentinel node biopsy (category 2B) can be considered because of the high probability of occult nodal involvement.¹¹⁷ Although a positive sentinel node in the presence of in-transit metastasis portends a more ominous prognosis, the impact of sentinel node biopsy on outcome is unproven.

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 bacillus Calmette-Guérin (BCG)¹¹⁸ or interferon-alfa, or topical imiquimod¹¹⁹ can be considered (category 2B for all of the options). Imiquimod may have some activity for superficial



dermal lesions but not for subcutaneous disease.¹²⁰ Laser ablation may be used in selected patients (category 2B).

For patients with multiple, regional, in-transit metastases not suitable for local therapies, regional chemotherapy is an option. Isolation limb infusion has been reported by Thompson et al to be a simpler technique with response rates comparable to limb perfusion.¹²¹ The panel has included hyperthermic isolated limb perfusion or infusion as one of the treatment options for patients with unresectable in-transit metastases (category 2B).¹²²⁻¹²⁴

Radiation therapy is included as a treatment option (category 2B), recognizing its relative inefficiency in controlling regional disease and lack of effect on overall survival. Other alternatives include systemic therapy (particularly after failure of local and/or regional therapy) or treatment in the context of a clinical trial.

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.¹²⁵ 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, patients with resectable solitary sites of disease should be assessed for surgery. If resected, patients can be offered adjuvant treatment on clinical trial. There is unanimous panel consensus that adjuvant interferon alpha monotherapy 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 is treated based on the presence or absence of brain metastases. For patients without brain metastases, options for systemic therapy include:

- Clinical trial (preferred);
- Ipilimumab (category 1);
- Dacarbazine, temozolomide, or high-dose IL-2;
- Combination chemotherapy or biochemotherapy (dacarbazine or temozolomide-based including cisplatin and vinblastine, with or without IL-2, interferon alfa) (category 2B);
- Paclitaxel-based chemotherapy (single-agent or in combination with cisplatin or carboplatin) (category 2B)

Due to its activity on T-cells, ipilimumab is associated with substantial risk of immune-related reactions. Patients with underlying autoimmune disorders may be especially susceptible to serious reactions. In the pivotal trial, immune-related events were recorded in 60% of patients treated with the agent.¹⁰⁷ 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. Close monitoring of these potentially lethal events is essential, and panelists strongly recommend participation in the risk evaluation and mitigation strategy (REMS) program during the course of ipilimumab treatment.



Special caution is warranted in the administration of high-dose IL-2 or biochemotherapy due to the high degree of toxicity reported. Some patients may attempt biochemotherapy for palliation or to achieve a response that may render them eligible for other therapies. In any case, if such therapy is considered, the NCCN panel recommends patients to receive treatment at institutions with relevant expertise.

Contraindications for IL-2 include inadequate organ reserve, poor performance score, and untreated or active brain involvement. For patients who are intolerant to, or relapsing after first line systemic therapy, additional systemic therapy may be indicated if the patient has ECOG performance status 0-2 or Karnofsky score \geq 60. Options for second-line therapy include clinical trial (preferred) or treatment with a different agent from the list of first-line options indicated above.

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 for patients with brain metastases is based on symptoms, number of lesions present, and location of the lesions, as described in [NCCN Central Nervous System Cancers Guidelines](#). In addition to systemic therapy, surgical resection and/or radiation may be considered for palliation or management of symptoms, such as gastrointestinal bleeding or obstruction, ulcerated soft tissue cutaneous metastases or bulky adenopathy. Best supportive care is an alternative for these patients.

In patients with both brain and extracranial metastases, therapy as outlined in the preceding paragraph 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.¹²⁶ 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; it includes other factors, such as dysplastic nevi and patient anxiety.¹²⁷ 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 for melanoma.¹²⁸ It is probably not cost effective to follow all patients intensively for metastatic disease beyond five to ten years (depending on relative risk for metastasis). 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 colleagues¹²⁹ 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 sentinel node biopsy, 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.¹³⁰⁻¹³²

Skin cancer preventive education including sun protection measures should be promoted for patients with melanoma and their families.¹³³ There is increasing evidence that regular sunscreen use may diminish the incidence of subsequent melanoma.¹³⁴ 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. (www.acpm.org/skinprot.htm).
- 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. 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.¹³⁵ 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.¹²⁹ Although not recommended at baseline, chest x-ray, CT, MRI, and/or PET/CT every 6-12 months can be considered to screen for recurrent or metastatic disease at the discretion of the physician. This is a category 2B recommendation given the low yield, false-positivity, and risks of cumulative radiation exposure from frequent medical imaging.¹³⁶⁻¹³⁹

Because most recurrences manifest within the first 5 years, routine blood tests and imaging are not recommended beyond this period.

Treatment of Recurrence

Initial clinical recurrence should be confirmed pathologically by FNA cytology or biopsy whenever possible.



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, 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 sentinel node biopsy, appropriate to the microstaging of the recurrence. For a local recurrence after adequate prior wide excision, baseline imaging (chest X-ray, CT and/or PET or MRI) should be considered for staging and to evaluate specific signs or symptoms. In the absence of extra regional disease, surgical excision with negative margin is recommended for local recurrence after initial adequate wide excision. Lymphatic mapping with sentinel node biopsy may be considered in these patients on an individual basis. After complete resection of a local recurrence following adequate primary therapy, adjuvant treatment options include clinical trial, observation, or interferon alfa (category 2B).

In-Transit Recurrence

For patients with in-transit recurrence, the clinical diagnosis should be confirmed by biopsy (FNA or excision). The workup is similar to the one previously outlined for patients presenting with in-transit disease. A surgically resectable recurrence should be excised with negative margins; sentinel node biopsy may be considered in these patients on an individual basis.

Unresectable in-transit recurrence could be treated with any one of the following options: intralesional injections with BCG or interferon-alfa, topical imiquimod (for dermal lesions), laser ablation therapy or hyperthermic limb perfusion or infusion. All of the local treatment options are category 2B recommendations. Alternatively, patients can be treated in the context of a clinical trial or with systemic therapy. In unusual circumstances, radiation therapy may be effective in achieving regional control (category 2B).

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

Regional Nodal Recurrence

For patients presenting with regional nodal recurrence, the clinical diagnosis should be confirmed preferably by biopsy (FNA or excision). 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, a complete lymph node dissection is appropriate. For patients who have had an incomplete prior lymph node dissection, complete lymph node dissection is recommended. If the patient underwent a previous “complete” lymph node dissection, excision of the recurrence to negative margins is recommended. Postoperative adjuvant RT may decrease the likelihood of further regional nodal recurrences and can be considered in selected patients with completely resected nodal recurrence, with risk factors such as multiple involved nodes or extranodal disease, especially in the head and neck region (category 2B).



After complete resection, options for adjuvant treatment include a clinical trial, observation, or high-dose or pegylated interferon alfa (category 2B). Options for patients with incompletely resected nodal recurrence or those with unresectable recurrence are shown in the algorithm.

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 revised as new data become available.

Discussion
update in
progress



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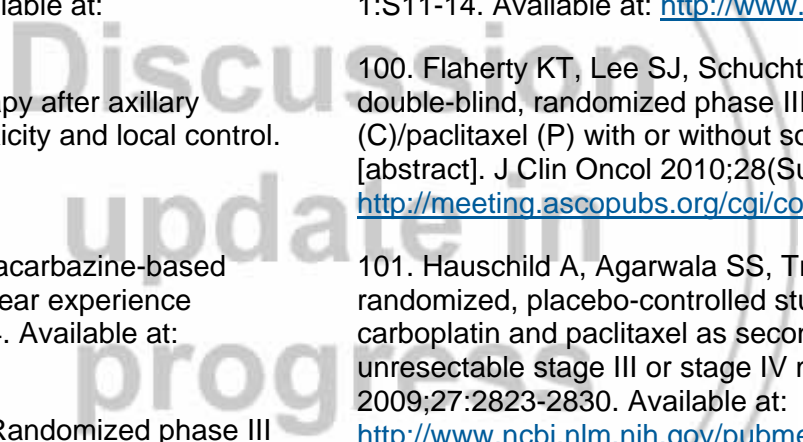
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