National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Melanoma

Version 1.2011

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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 1.2011 Updates
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Updates in Version 1.2011 of the NCCN Melanoma Guidelines from Version 1.2010 include:

Global Changes:

- **Principles of Radiation Therapy is a new page that provides specific recommendations and dosing for radiation therapy throughout the Melanoma Guidelines (ME-D).**

ME-1

- **Pathology report:**
  - **"Mitotic rate" changed to "Dermal mitotic rate".**
  - **"Satellitosis, if present..." changed to "Microsatellitosis, if present..."**
  - **"Pure desmoplasia if present" was added.**
- **Footnote "d": "Clark level IV" was added as an adverse feature. "younger age" was removed as an adverse feature.**

ME-2

- **Clinical Stage:**
  - **Stage 0 in situ or Stage IA: "no ulceration" was added. (Also for Stage IA)**
  - **Stage IA: Clarified as "Stage IA with one or more adverse features".**
- **Workup:**
  - **Under Stage IA: The statement, "Imaging only to evaluate specific signs or symptoms" was removed from the algorithm and became footnote "e".**
- **Footnote "h": "For lower risk patients, such as IA and IB lesions $\leq$ 0.5mm thick and mitotic rate < 2 per mm^2, SLNB should generally not be recommended, unless there are specific clinical indications (category 2B)," is new to the algorithm.**
- **Footnote "k" was clarified as "Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear".**

ME-3

- **Workup for all stages: "Consider baseline imaging for staging..." changed from category 2B to category 2A.**
- **Stage II (clinically positive nodes): The recommendation changed to "Consider RT to nodal basin if Stage IIIC with multiple nodes involved or macroscopic extranodal extension".**
- **Footnote "l" was revised.**

ME-5

- **Workup: Third bullet regarding imaging changed from "Encourage chest/abdominal/pelvic CT, MRI brain, and/or PET as clinically indicated (category 2B)" to "Encourage chest/abdominal/pelvic CT, MRI brain, and/or PET for baseline imaging and to evaluate specific signs and symptoms".**
- **Footnote "p" that states, "Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial" is new to the algorithm.**

ME-6

- **Stage IIB-IV, NED; Third bullet: Changed to "Consider chest x-ray, CT and/or PET-CT scans every 6-12 mo to screen..."**
- **Routine "lab testing/radiologic imaging..." changed to "Routine radiologic imaging..."**
- **Footnote "q" was revised and the following statement was added, "Routine blood tests are not recommended."**

ME-9

- **Workup; Third bullet: "as clinically indicated" changed to "...for baseline imaging and to evaluate specific signs or symptoms"**
- **Limited; Resect pathway: "Interferon alfa (category 2B)" was removed as an option.**
- **Disseminated; With brain metastases pathway: Recommendations changed to "Consider resection and/or radiation for asymptomatic patients or Consider palliative resection and/or radiation for symptomatic patients or Best supportive care".**

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NCCN Guidelines™ Version 1.2011 Updates Melanoma

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Updates in Version 1.2011 of the Melanoma NCCN Guidelines from Version 1.2010 include:

ME-A Principles of Biopsy and Pathology

- **Page title changed to Principles of Biopsy and Pathology.**
- **Principles of Pathology section**
  - **Second bullet:**
    - **After Clark level "(encouraged for lesions ≤ 1 mm, optional for lesions > 1 mm)" was added.**
    - **"After peripheral and deep margin status", "positive or negative)" was added.**
  - **Fourth bullet: "Pure desmoplasia, if present (specify pure vs. mixed)" was added.**
  - **New bullet was added "Consider use of fluorescent in situ hybridization (FISH) for histologically equivocol lesions"**
  - **Footnote "3" that states, "Mitotic rate should be determined using the "hot spot" technique and expressed as number of mitoses per square millimeter" is new to the page.**

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

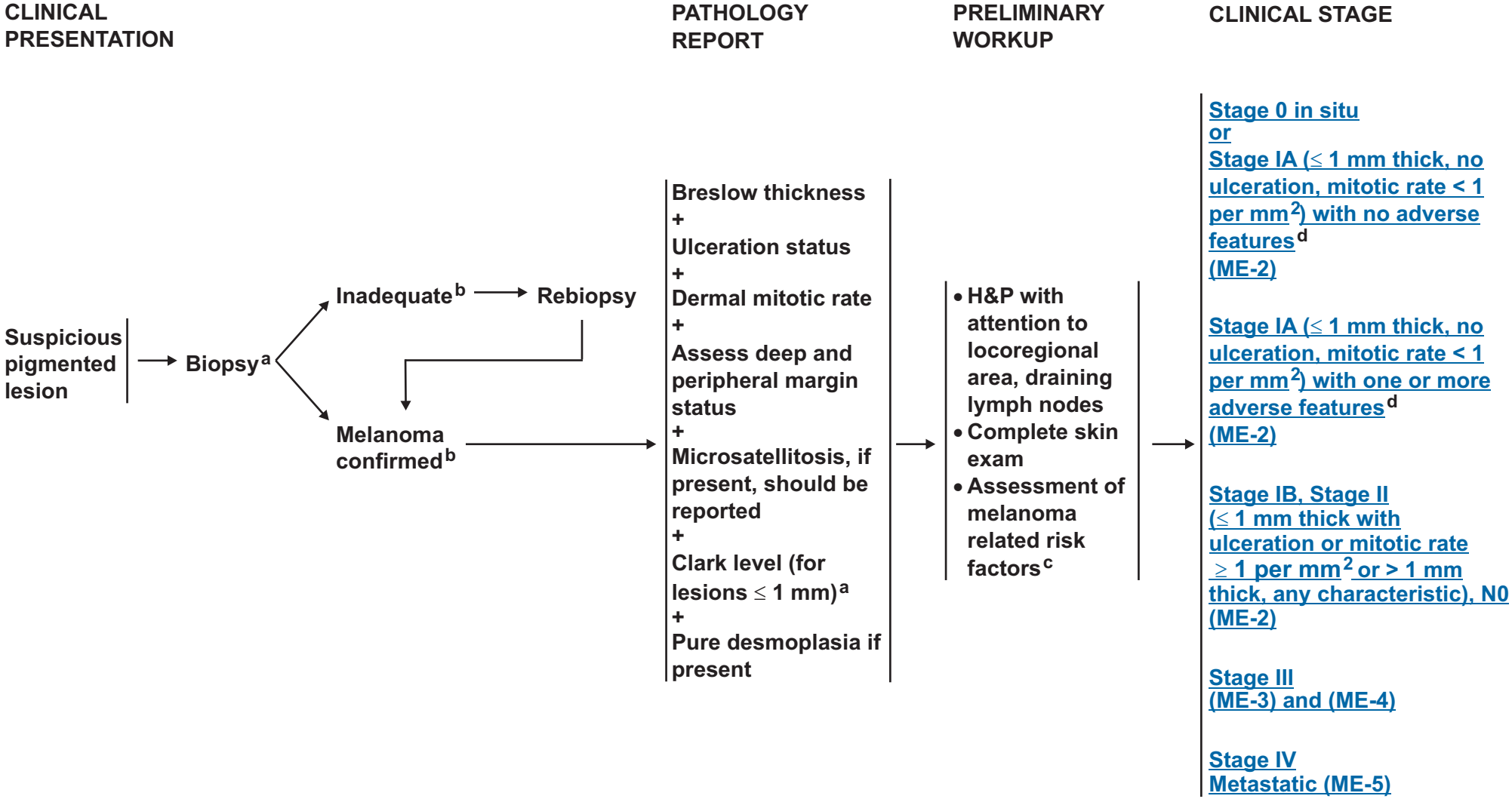
- **Footnote "1": The following sentence was added "For selected patients with positive margins after optimal surgery, consider topical imiquimod or RT (category 2B)".**
- **Footnote "2": "Clinical margins do not need to correlate with final histologic margins" changed to "Excision recommendations are based on clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist (category 1)".**

ME-E Systemic Therapy Options for Advanced or Metastatic Melanoma

- **Footnote "2" was revised to read "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)".**
- **Footnote "3" was revised to read: "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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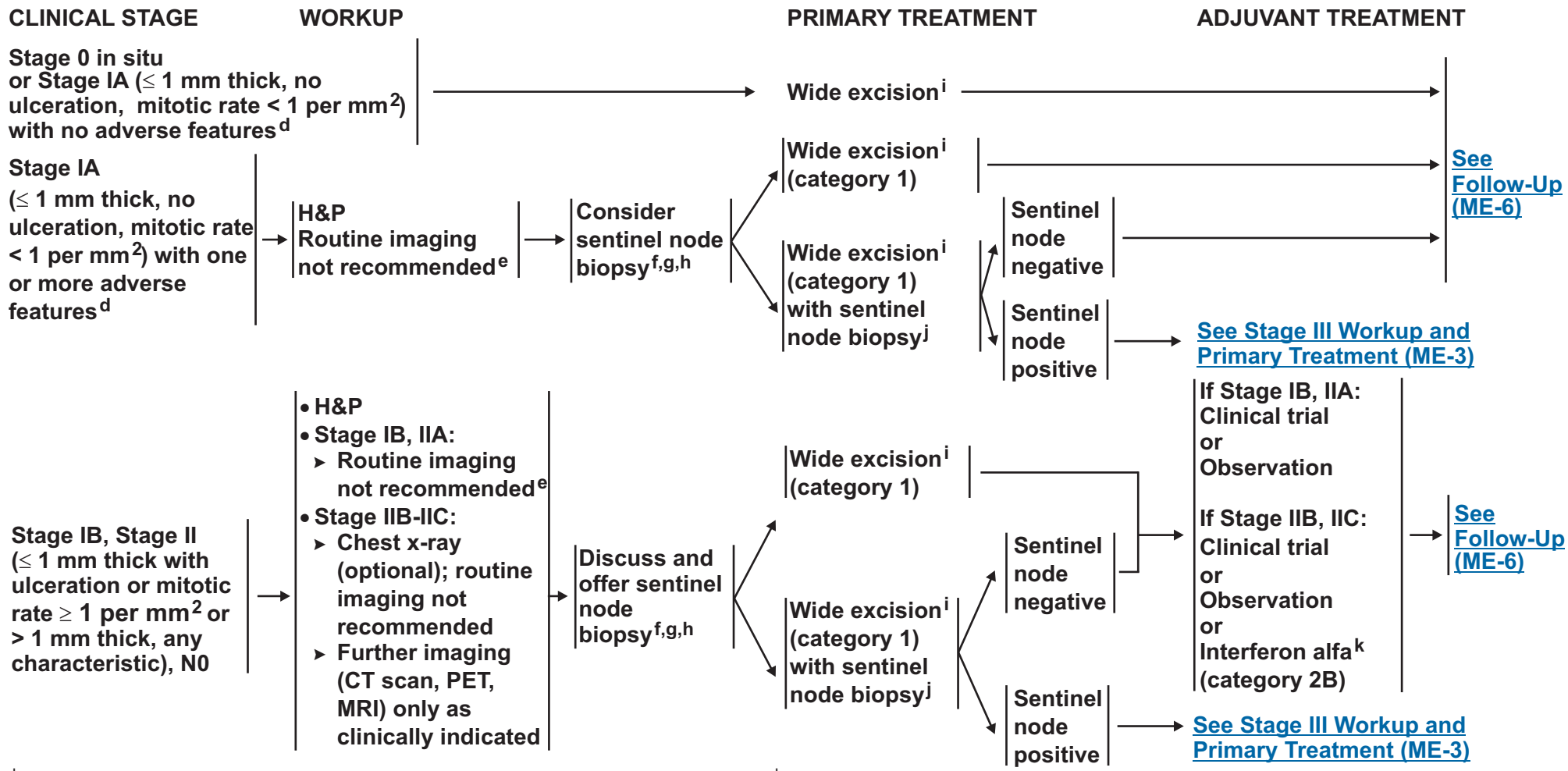


[a] See Principles of Biopsy and Pathology (ME-A).
[b] If diagnostic biopsy is inadequate for treatment decisions, rebiopsy may be appropriate.
[c] Risk factors for melanoma include family history of melanoma, prior primary melanoma, and other factors such as atypical moles/dysplastic nevi.
[d] Adverse features include ≥ 0.75 mm thick, positive deep margins, lymphovascular invasion (LVI), or Clark level IV.

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[d] Adverse features include ≥ 0.75 mm thick, positive deep margins, lymphovascular invasion (LVI), or Clark Level IV.

[e] Imaging only to evaluate specific signs or symptoms (CT scan, PET, MRI).

[f] Decision not 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] For lower risk patients, such as IA and IB lesions ≤ 0.5mm thick and mitotic rate < 2 per mm2, SLNB should generally not be recommended, unless there are specific clinical indications. (category 2B).

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

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

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

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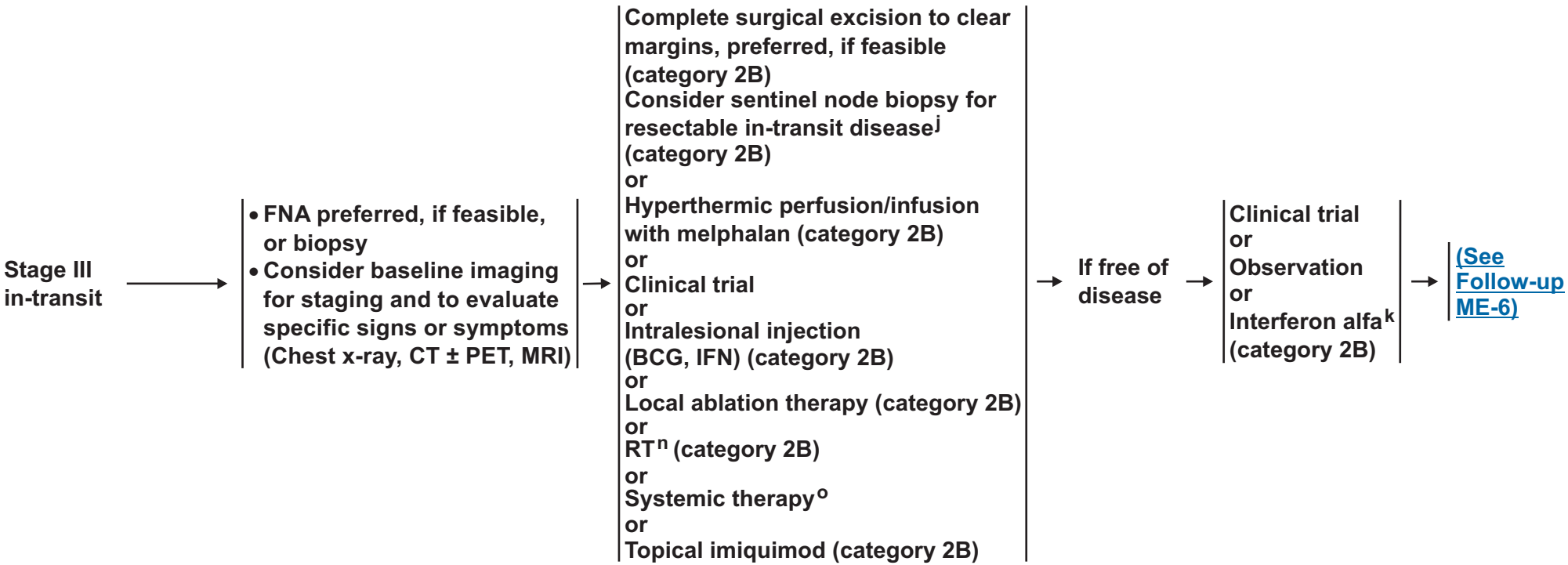
CLINICAL/ PATHOLOGIC STAGE	WORKUP	PRIMARY TREATMENT	ADJUVANT TREATMENT	
Stage III (Sentinel node positive)	Consider baseline imaging for staging and to evaluate specific signs or symptoms (Chest x-ray, CT ± PET, MRI)	Clinical trial[k] or Lymph node dissection[m]	Clinical trial or Observation or Interferon alfa[k] (category 2B)	(See Follow-up ME-6)
Stage III (Clinically positive node(s))	• FNA preferred, if feasible, or lymph node biopsy • Consider baseline imaging for staging and to evaluate specific signs or symptoms (Chest x-ray, CT ± PET, MRI) • Pelvic CT if inguinofemoral nodes positive	Wide excision of primary tumor[i] (category 1) + complete lymph node dissection[h]	Clinical trial or Observation or Interferon alfa[k] (category 2B) and/or Consider RT[n] to nodal basin if Stage IIIC with multiple nodes involved or macroscopic extranodal extension	

[i] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[j] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[k] 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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[j] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[k] 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] 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[p] • LDH • Encourage chest/abdominal/pelvic CT, MRI brain, and/or PET for baseline imaging and to evaluate specific signs and symptoms

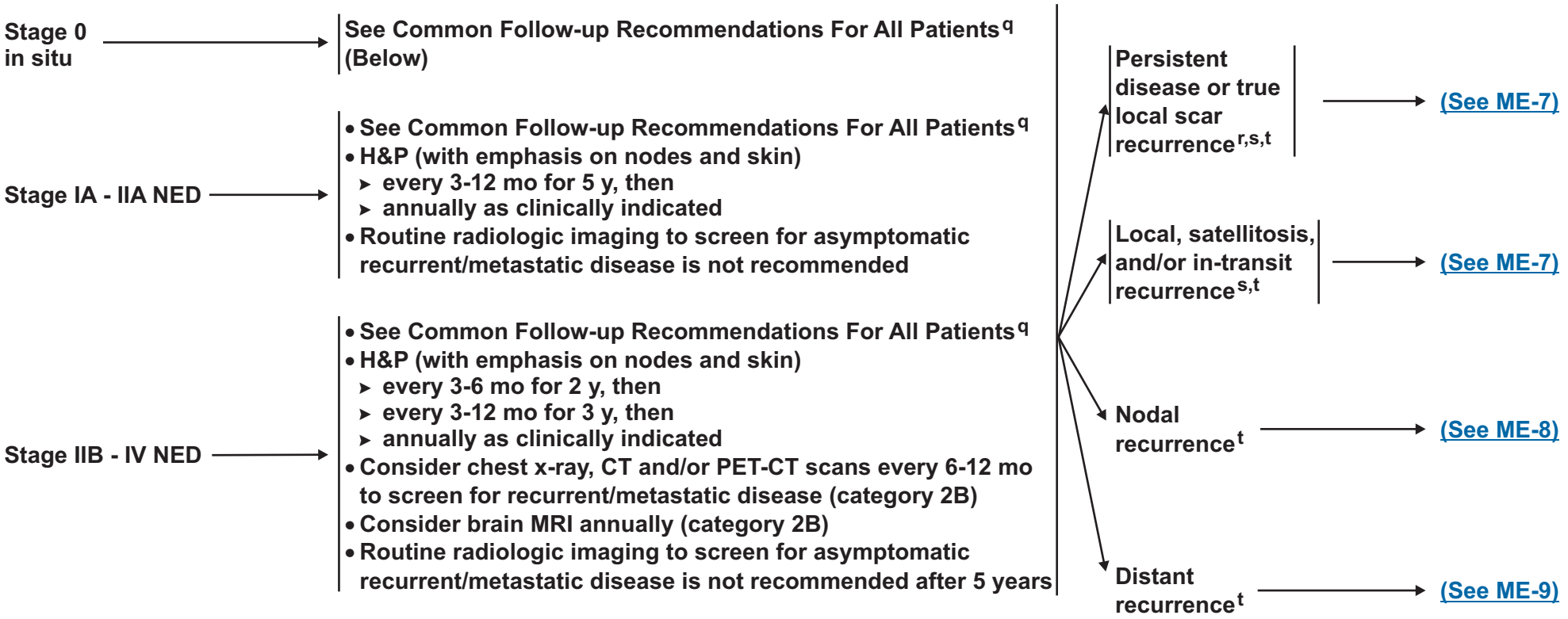
→ See Treatment for Limited (Resectable) or Disseminated Disease (Unresectable) ME-9)

[p]Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.

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[q] 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.

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

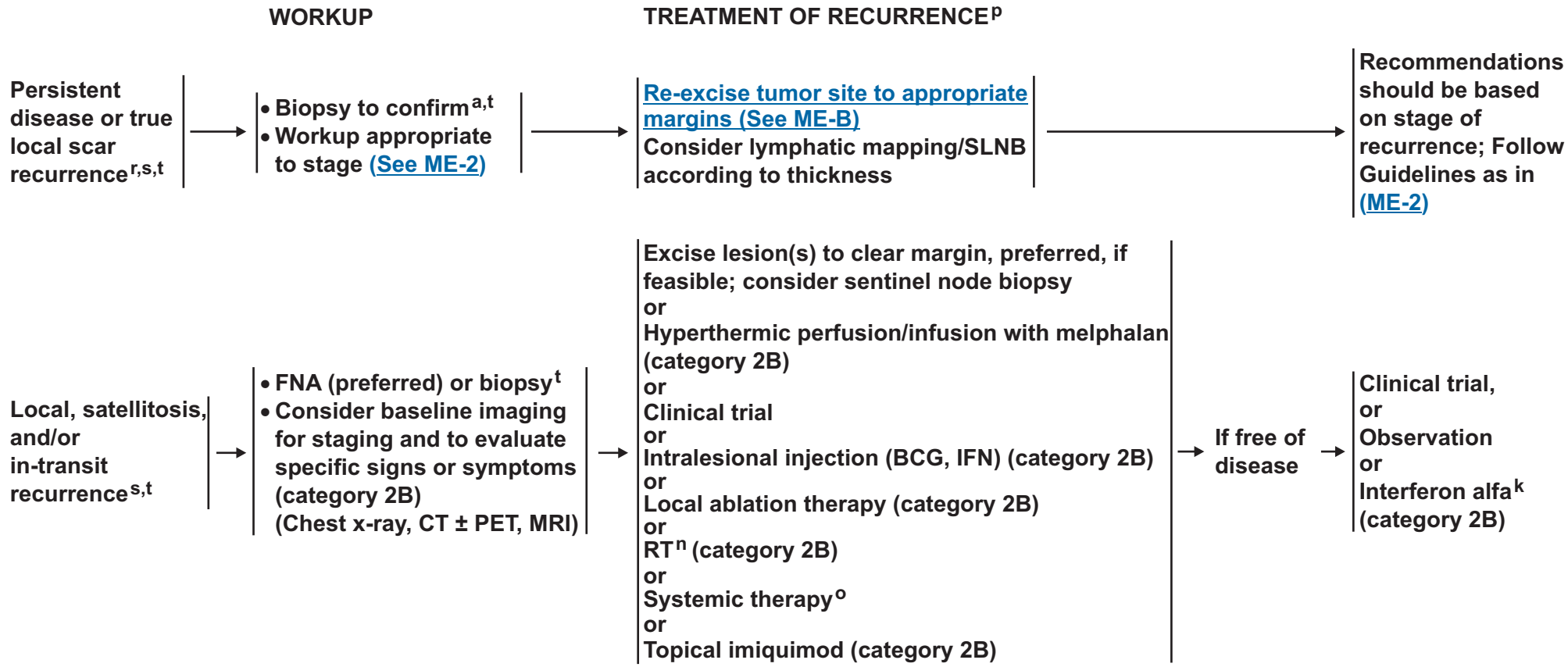
[s] Local recurrence without in situ or radial growth phase, with deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar.

[t] Initial clinical recurrence should be confirmed pathologically whenever possible. Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.

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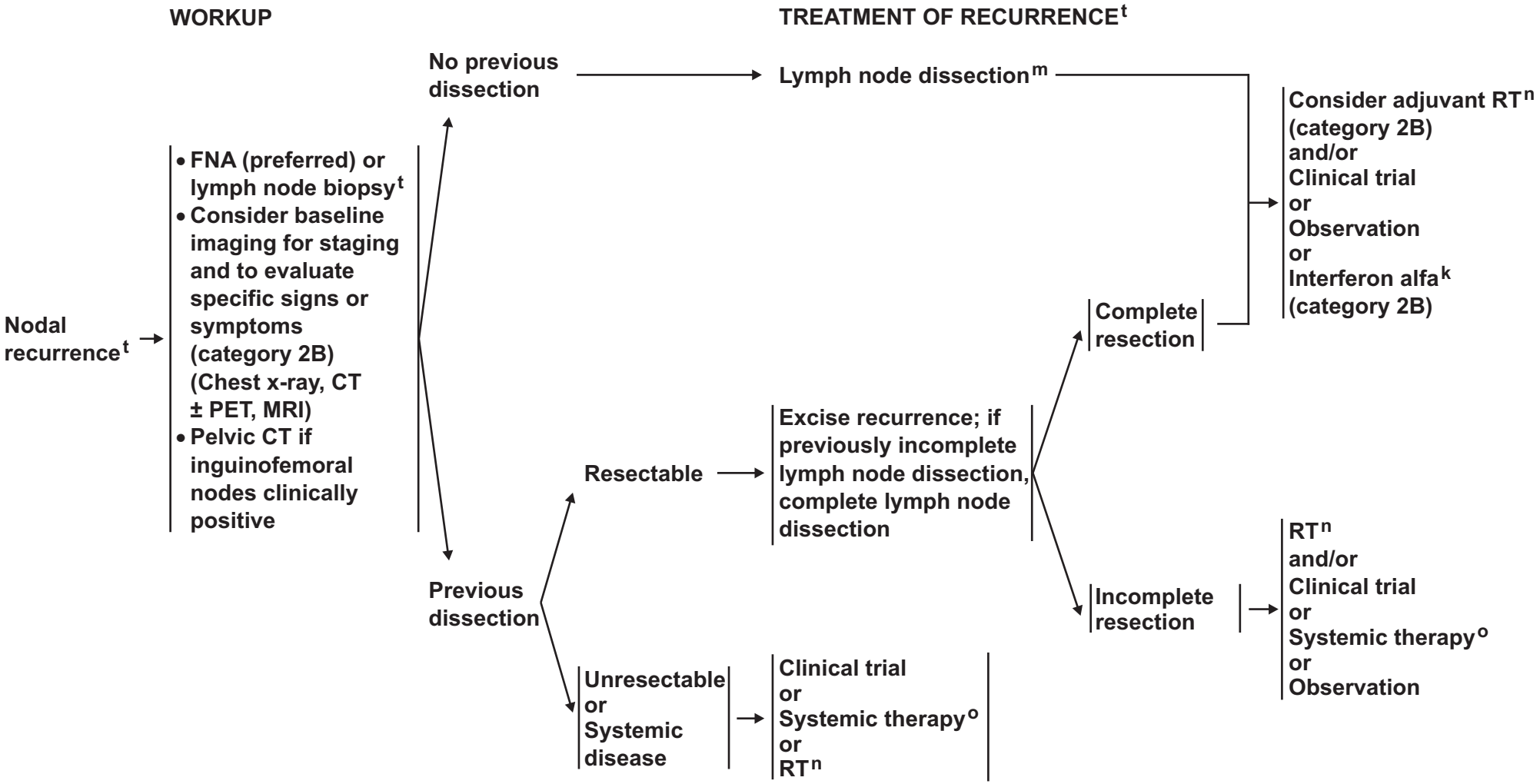


[a] See Principles of Biopsy and Pathology (ME-A).
[k] Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.
[n] See Principles of Radiation Therapy (ME-D).
[o] See Systemic Therapy Options for Advanced or Metastatic Melanoma (ME-E).
[r] Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.
[s] Local 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.
[t] 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.

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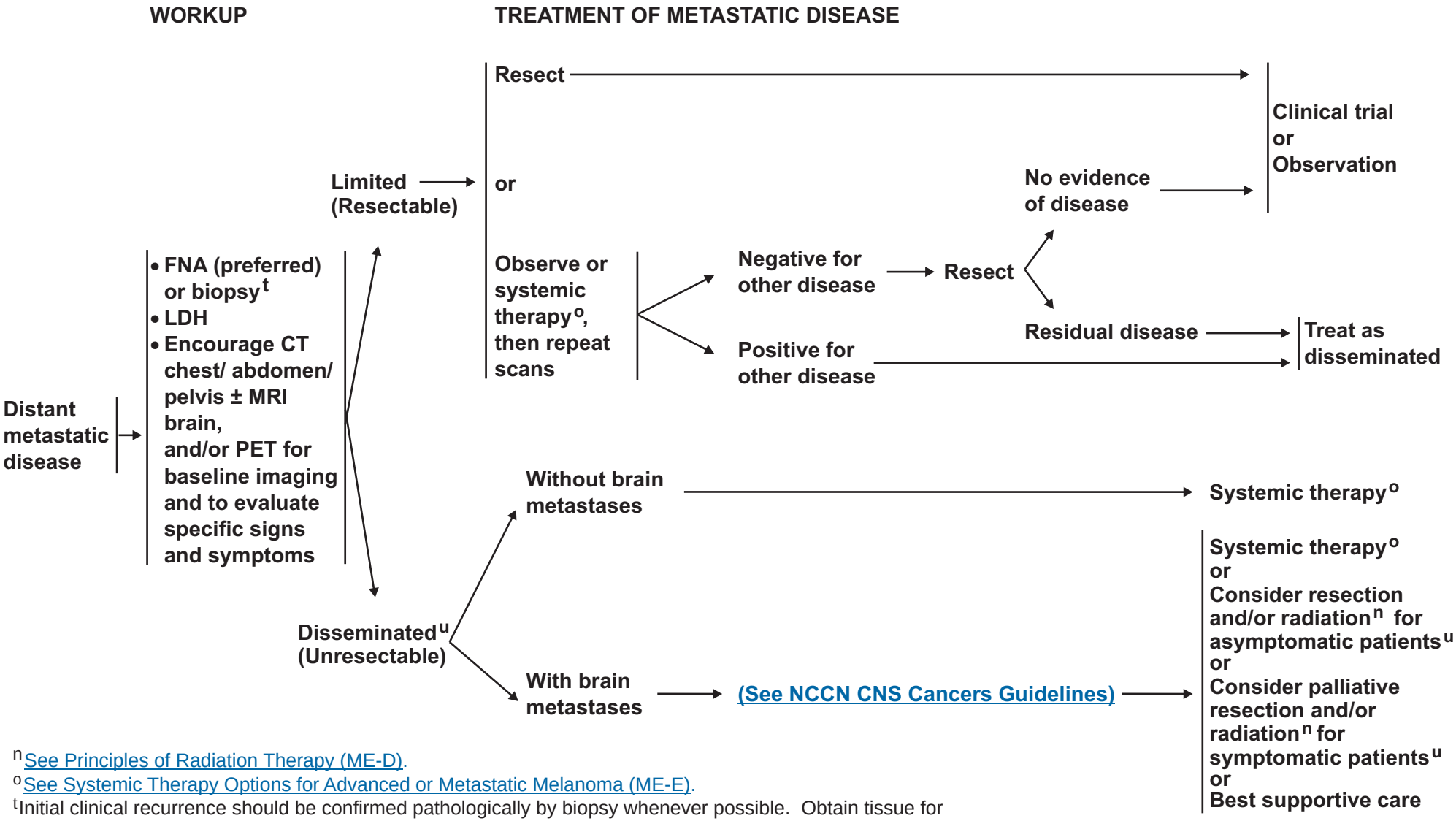


[k] Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.
[m] See Principles of Complete Lymph Node Dissection (ME-C).
[n] See Principles of Radiation Therapy (ME-D).
[o] See Systemic Therapy Options for Advanced or Metastatic Melanoma (ME-E).
[t] Initial 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.

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

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

[t] 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.

[u] In 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.
- 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, dermal mitotic rate per mm[2],[3] Clark level (encouraged for lesions $\leq$ 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)
- Consider use of fluorescent in situ hybridization (FISH) for histologically equivocol lesions.

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

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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

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

[1]For large melanoma in situ, 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 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).

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PRINCIPLES OF COMPLETE LYMPH NODE DISSECTION

Adequacy of regional lymph node dissection:

- **An anatomically complete dissection[1] of involved nodal basin is required.**
- **In the groin, consider elective iliac and obturator lymph node dissection if clinically positive 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.

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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Consider radiation therapy in the following situations:*

PRIMARY DISEASE

- **Gross total resection with appropriate negative margins (see ME-B) is the first-line treatment of primary melanoma lesions. Definitive or adjuvant radiation may be considered in special cases where adequate surgical treatment is not possible.[1-3]**
- **Adjuvant radiation therapy may be considered for selected patients with desmoplastic melanoma with extensive neurotrophism.**

REGIONAL DISEASE

- **Consider adjuvant radiation therapy for patients at significant risk of nodal basin relapse[4]**
  - **Lymph node risk factors[5]**
    - **Extracapsular extension**
    - **≥ 4 involved nodes**
    - **Size ≥ 3 cm**
    - **Cervical‡ > Axillary > Inguinal Location**
    - **Recurrent disease after prior complete nodal dissection**
  - **Suggested dose/Fractionation regimens**
    - **30 Gy in five fractions of 6 Gy over 2.5 weeks[6,#]**
      (Consider additional fraction to a total of 36 Gy to sites of microscopic residual disease.)[7,8]
    - **48 Gy in twenty fractions of 2.4 Gy over 4 weeks[4]**
    - **50 Gy in twenty fractions of 2.5 Gy over 4 weeks[9]**
    - **60 Gy in thirty fractions of 2 Gy over 6 weeks[10]**

METASTATIC DISEASE

- **Brain metastases**
  - **Consider definitive or palliative stereotactic radiosurgery and/or whole brain radiation therapy[11] as described in the NCCN Central Nervous System Cancers Guidelines**
  - **Consider adjuvant radiation following resection of brain metastases.**
- **Other symptomatic or potentially symptomatic metastases**
  - **Studies show a 62 - 84% incidence of significant symptom relief,[12-13] and a 17 - 69% incidence of complete clinical tumor response (49 - 97% with either partial or complete response).[9,14,15]**
  - **A wide range of radiation dose/fractionation schedules is effective.[9,12-15]**

*Most systemic treatments should be held during radiation.
‡In the cervical location, consider adjuvant radiation if ≥ 2 lymph nodes are involved and for lymph nodes ≥ 2 cm. (See reference 16)
#Hypofractionated regimens may increase the risk for long term complications such as lymphedema and small bowel obstruction. (See reference 6).

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SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA

First- or Second- Line Therapy:[1]

- **Clinical trial (preferred)**
- **Dacarbazine**
- **Temozolomide**
- **High-dose Interleukin-2**[2,3]
- **Dacarbazine-or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2B)**[3]
- **Paclitaxel (category 2B)**
- **Paclitaxel/cisplatin (category 2B)**
- **Paclitaxel/carboplatin (category 2B)**

References on next page

[1] In general, second line therapy is offered to patients who progress or are intolerant to first line therapy with performance status ECOG 0-2 or Karnofsky score ≥ 60.

[2] 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).

[3] 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 regimens.

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Continued

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

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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* 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:

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

Anatomic Stage/Prognostic Groups

Clinical Staging*

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

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

Pathologic Staging**

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

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 03/17/10

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

In the year 2009, an estimated 68,720 new cases of melanoma will be diagnosed and about 8,650 patients will die 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 inherited genetic mutations. 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

Discussion update in progress

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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.

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 mm^2. Barnhill et al compared the relative importance of mitotic rate vs. ulceration as major prognostic factors in localized melanoma.[9] 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 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.[13, 14]

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 also be recorded, as this defines a patient subgroup at high risk for regional and systemic failure, prognostically similar to Stage III.

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For Stage I-II patients, the NCCN melanoma panel recommends the inclusion of Breslow thickness, ulceration status, mitotic rate, deep and peripheral margin status, satellitosis if present and Clark level (especially for lesions 1.0 mm or less, if mitotic rate is unknown) 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 sentinel lymph node biopsy (SLNB), the status of the sentinel node is the most important prognostic factor.[16] 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.[16, 17]

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 with mitotic rate less than 1 per mm^2, with or without adverse prognostic features such as thickness over 0.75 mm, positive deep margins, lymphovascular invasion, or younger age
- Stage IB-II: 1.0 mm thick or less with ulceration or mitotic rate greater than or equal to 1 per mm^2; 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

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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.[16, 18] 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.[19-21]

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%.[22-24] 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%.[25-27] 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 computed tomography (CT) scans 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.[28-30] In patients with more advanced stage III disease, PET scan may be more useful. In particular, PET scans can help to further

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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).[31]

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.[32] 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 is appropriate to investigate 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. Chest abdominal/pelvic CT, with or without PET, and/or head MRI should be considered (category 2B).

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.

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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. [33, 34] 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 that are 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.[35, 36] Prospective randomized trials from Sweden have confirmed that satisfactory local control and melanoma specific survival are not compromised by narrower margins.[37, 38]

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.[39] 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.[40]

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.[41, 42]

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 do not necessarily correlate with gross pathological/histological margins.

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.[43-46] However, long-term, comparative studies are still needed and the panel currently did not include specific recommendations for this treatment option for in situ melanoma.

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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.[47] 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.[48] 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.[49] 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 rates 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 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).

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. Three recent retrospective reviews have shown that, for patients with melanomas less than or equal to 1 mm thick, the incidence of positive SLN is 2-5%.[50] Factors predicting an increased probability of a positive SLN in patients with thin melanomas include increasing Breslow thickness and 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.[51] Larger series and longer term follow-up will be required to assess the prognostic value of the SLN in patients with thin melanoma.[52-54]

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.[55-57] 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.

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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.[58-61] The significance of tumor regression is debatable, with more recent studies reporting no association of regression incidence to increased SLN positivity.[62, 63] 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 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. 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 committee could not define 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 IB melanoma at very low risk for either positive sentinel lymph node or melanoma recurrence (eg., 0.4 mm thick, non-ulcerated, mitotic rate 1 per mm^2). In this case, it might be clinically appropriate to omit the biopsy. 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.[64-66]

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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 a standard of care or in the context of a clinical trial. Published studies have revealed additional positive non-sentinel nodes in approximately 15-20% of these complete lymph node dissection specimens.[67, 68] 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. 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.[65, 66] Deep groin dissection also should be considered for clinically positive nodes or if more than three superficial nodes are involved.[64]

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,[69] 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.[70] In another prospective randomized study, adjuvant interferon prolonged disease-free survival for all patients at the median follow-up of 41 months.[71]

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.[72] No significant improvement in progression-free survival was reported for intermediate-dose interferon alfa-2b in EORTC 18952.[73]

High-Dose 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.[74] The results of a larger

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follow-up trial, ECOG 1690, also showed a relapse-free survival advantage, but no overall survival advantage, for high-dose interferon alfa-2b.[75] 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.[76]

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).[77]

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.[78] 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.[79]

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.[80]

The EORTC protocol 18991 randomized 1256 patients with stage III melanoma that had been completely resected to either observation or treatment with pegylated interferon alfa 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.[81]

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.[82] The clinical and biologic significance of this observation remains unclear.

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NCCN Recommendations

Most patients with in-situ or early-stage melanoma will be cured by primary excision alone. For patients with in-situ or node-negative primary melanoma (stage IA, 1 mm thick or less with or without adverse features), no standard adjuvant therapy is recommended. 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 interferon alfa. For patients with stage III melanoma, adjuvant treatment options include clinical trial, observation, or interferon alfa.

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Treatment with adjuvant interferon alfa is a category 2B recommendation in all of the above cases. 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.[83-85]

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.[86] Adjuvant hypofractionated RT to the nodal bed should be considered for stage IIIC patients in the setting of multiple positive nodes or extranodal soft-tissue extension, especially in the head and neck region.[87, 88]

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. The guidelines recommend clinical trial, interferon alfa (category 2B), or observation as adjuvant treatment options.

Treatment of Metastatic Melanoma

Metastatic melanoma is associated with a poor prognosis. Several chemotherapeutic agents, including dacarbazine and temozolomide, have shown activity in patients with metastatic melanoma when used as single agents or in combination chemotherapy regimens.[89] However, little consensus currently exists regarding standard therapy for patients with metastatic melanoma, which most likely reflects the low level of activity of all available agents.[90, 91]

Dacarbazine remains a standard of care in community practice, and has been used as a standard for comparing the efficacy of new regimens.[92] A small randomized trial has demonstrated similar response rates and survival for dacarbazine and temozolomide treatment of metastatic melanoma.[93] Both dacarbazine and temozolomide result in response rates of approximately 10-20%, with median response duration of 3-4 months.[89, 93]

Initial reports of combination chemotherapy regimens such as CVD (dacarbazine plus cisplatin and vinblastine) or Dartmouth regimen (dacarbazine, carmustine, cisplatin and tamoxifen) suggested higher response rates.[94, 95] Subsequent clinical trials have not replicated these high response rates. In a phase III randomized trial, survival following treatment with Dartmouth regimen was not superior to dacarbazine alone.[96]

Paclitaxel alone or in combination with carboplatin may provide clinical benefit to some patients with metastatic melanoma; however, the duration of clinical benefit is short (2-7 months).[97, 98]

Interleukin-2 (IL-2) was approved by the Food and Drug administration (FDA) for treatment of metastatic melanoma in 1998. High dose intravenous bolus IL-2 treatment resulted in overall objective response rates of about 17%.[99] In a highly selected patient population (n = 270), IL-2 was able to induce durable complete responses (median response duration over 59 months) in approximately 6% of patients and partial responses in 10% of patients with metastatic melanoma, albeit with high levels of toxicity.[100, 101] A recent study demonstrated increased response rate in metastatic melanoma when IL-2 was given with the 210M peptide vaccine (22%) compared to IL-2 (13%) alone.[102]

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Biochemotherapy is the combination of chemotherapy and biological agents. In single institutional phase II trials, biochemotherapy (cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2) produced an overall response rate of 27-64% and a complete response rate of 15-21% in patients with metastatic melanoma.[103-105] A report of a small phase III randomized trial comparing sequential biochemotherapy (dacarbazine, cisplatin, vinblastine with interleukin-2 and interferon alfa administered on a distinct schedule) with 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.[106] In a phase III randomized intergroup trial (E3695), biochemotherapy (cisplatin, vinblastine, dacarbazine, interleukin-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 in patients with metastatic melanoma.[107] 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.[108-110] Recent report from a meta-analysis also showed that although biochemotherapy improved overall response rates, there was no survival benefit for patients with metastatic melanoma.[111]

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.[112] 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)[113] or interferon-alfa, or topical imiquimod[114] can be considered (category 2B for all of the options). 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.[115] 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).[116-118]

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. Clinical trial is the preferred treatment option for patients with distant metastatic disease.

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Resection, if feasible, is recommended for limited metastatic disease.[119] 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 or with interferon alfa (category IIB). 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. Systemic therapy options are listed in the following paragraph.

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 due to the low effectiveness of available agents);
dacarbazine, temozolomide, or high-dose interleukin-2;
combination chemotherapy or biochemotherapy (dacarbazine or temozolomide-based including cisplatin and vinblastine, with or without interleukin-2, interferon alfa) (category 2B);
paclitaxel-based chemotherapy (single-agent or in combination with cisplatin or carboplatin) (category 2B)

Special caution is warranted in the administration of high-dose interleukin-2 or biochemotherapy due to the high degree of toxicity reported. If such therapy is considered, the NCCN panel recommends patients to receive treatment only at institutions with relevant expertise. For patients with disseminated melanoma that is 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 ≥ 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.

In addition to systemic therapy, surgical resection or radiation may be considered for palliation and management of symptoms, such as gastrointestinal bleeding or obstruction, ulcerated soft tissue cutaneous metastases or bulky adenopathy.

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 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 interleukin-2, which has low efficacy in patients with previously untreated brain metastases and which may worsen edema surrounding the untreated metastases.[120]

Follow-up

In the absence of any 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.[121] The optimal duration of follow-up remains controversial. Although most patients who are going to have recurrent disease will present in the first five years after treatment, late recurrence (more than ten years later) is well

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documented for melanoma.[122] 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.

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.[123-125]

Skin cancer preventive education including sun protection measures should be promoted for patients with melanoma and their families.[126] 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 and symptoms are indications for additional lab tests and/or 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.[127] The consensus of the panel is that routine lab 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. Chest x-ray, CT, MRI, and/or PET/CT 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 medical imaging.[128-131]

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

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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 should be 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, 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

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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 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.

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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.

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