

Melanoma

Version 1.2006

Continue

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Continue

Table of Contents

[NCCN Melanoma Panel Members](#)

[Clinical Presentation and Preliminary Workup \(ME-1\)](#)

[Stage 0 \(in situ\), Stage IA, Stage IB-II \(ME-2\)](#)

[Stage IIIA, Stage IIIB, IIIC, Stage III \(in-transit\) \(ME-3\)](#)

[Stage IV \(ME-4\)](#)

[Follow-up \(ME-5\)](#)

[True local scar recurrence, In-transit recurrence \(ME-6\)](#)

[Nodal recurrence \(ME-7\)](#)

[Distant disease \(ME-8\)](#)

[Guidelines Index](#)

[Print the Melanoma Guideline](#)

[Order the Patient Version of the Melanoma Guidelines](#)

[For help using these documents, please click here](#)

[Staging](#)

[Manuscript](#)

[References](#)

This manuscript is being updated to correspond with the newly updated algorithm.

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 Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Consensus](#)

[Summary of Guidelines Updates](#)

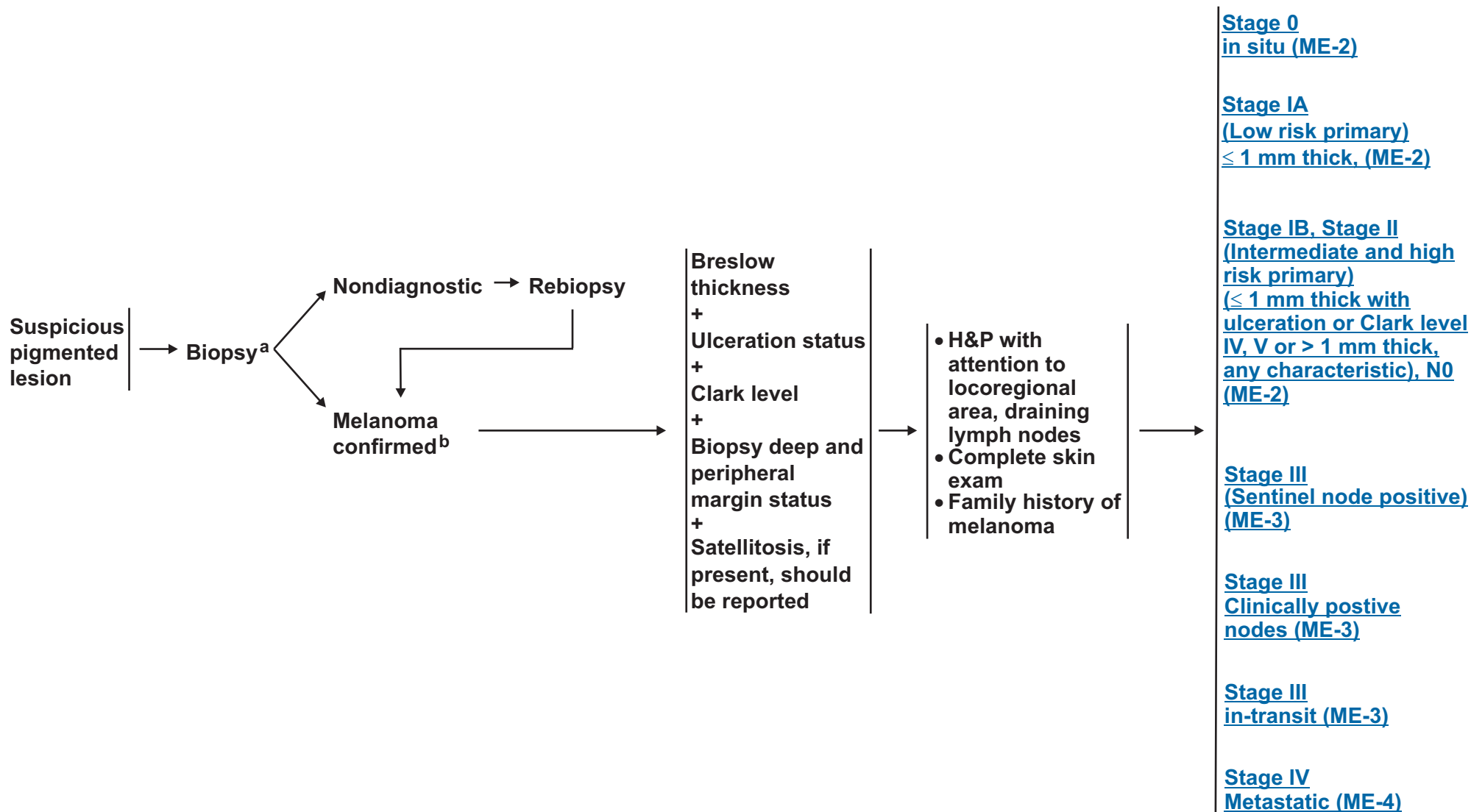
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**CLINICAL
PRESENTATION**

**PATHOLOGY
REPORT**

**PRELIMINARY
WORKUP**

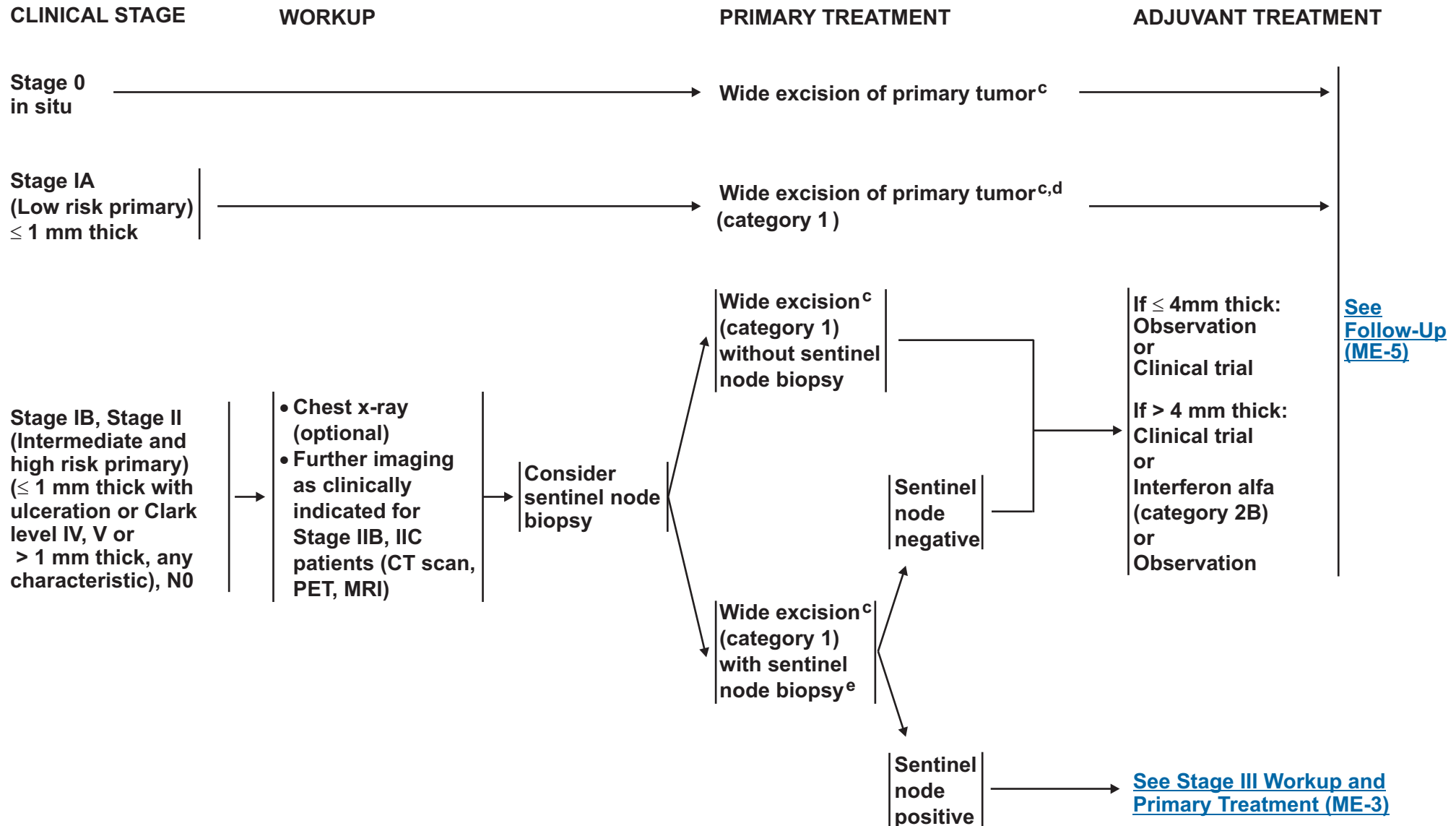
CLINICAL STAGE



^aSee Biopsy (ME-A).

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

Note: All recommendations are category 2A unless otherwise indicated.
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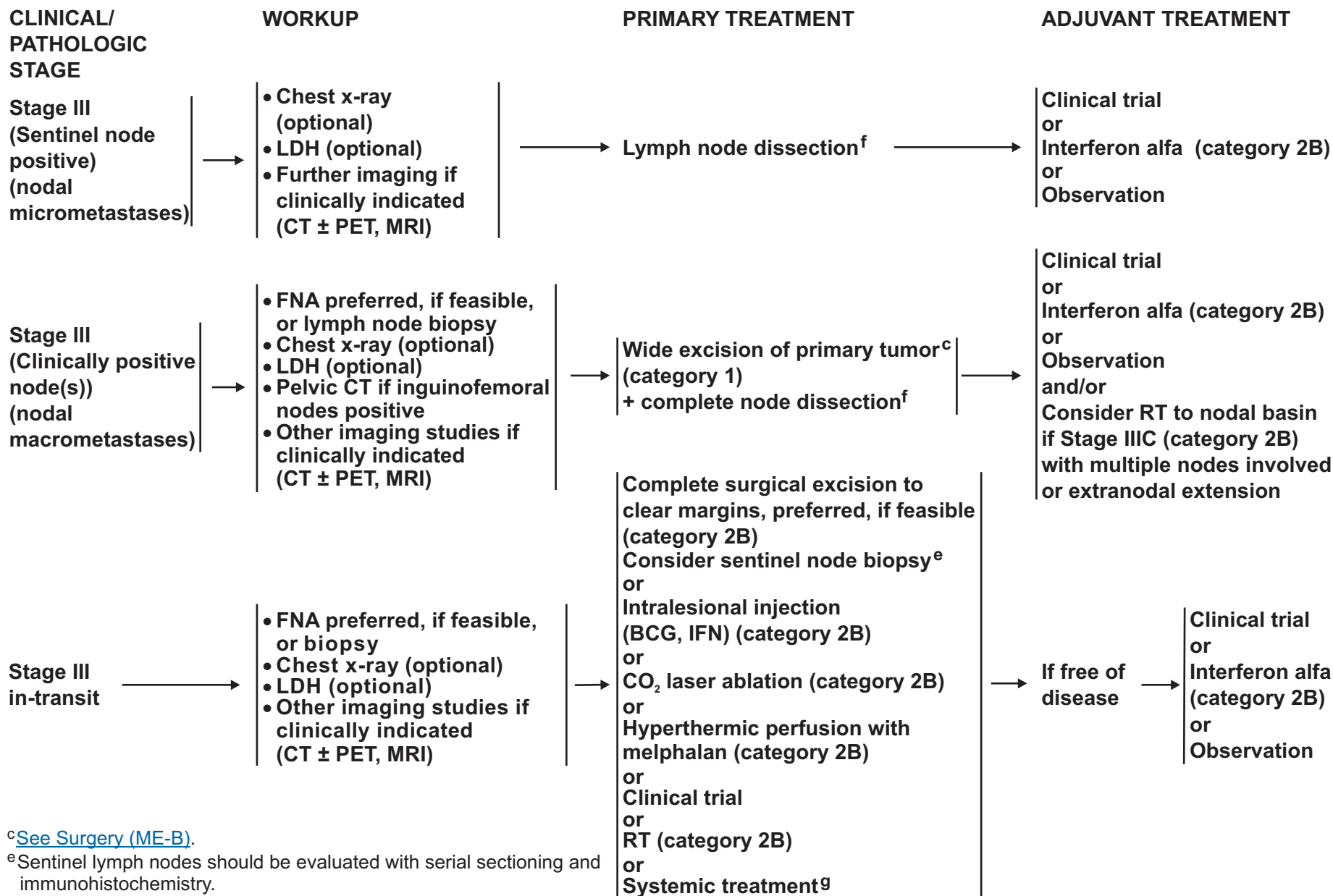
^cSee Surgery (ME-B).

^dIf ≤1 mm with positive deep margins, or with extensive regression, consider lymphatic mapping/SLNB.

^eSentinel lymph nodes should be evaluated with serial sectioning and immunohistochemistry.

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(See [Follow-up ME-5](#))

^cSee [Surgery \(ME-B\)](#).

^eSentinel lymph nodes should be evaluated with serial sectioning and immunohistochemistry.

^fSee [Complete Lymph Node Dissection \(ME-C\)](#).

^gSee [Principles of Systemic Therapy for Advanced or Metastatic Melanoma \(ME-D\)](#).

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CLINICAL/
PATHOLOGIC
STAGE

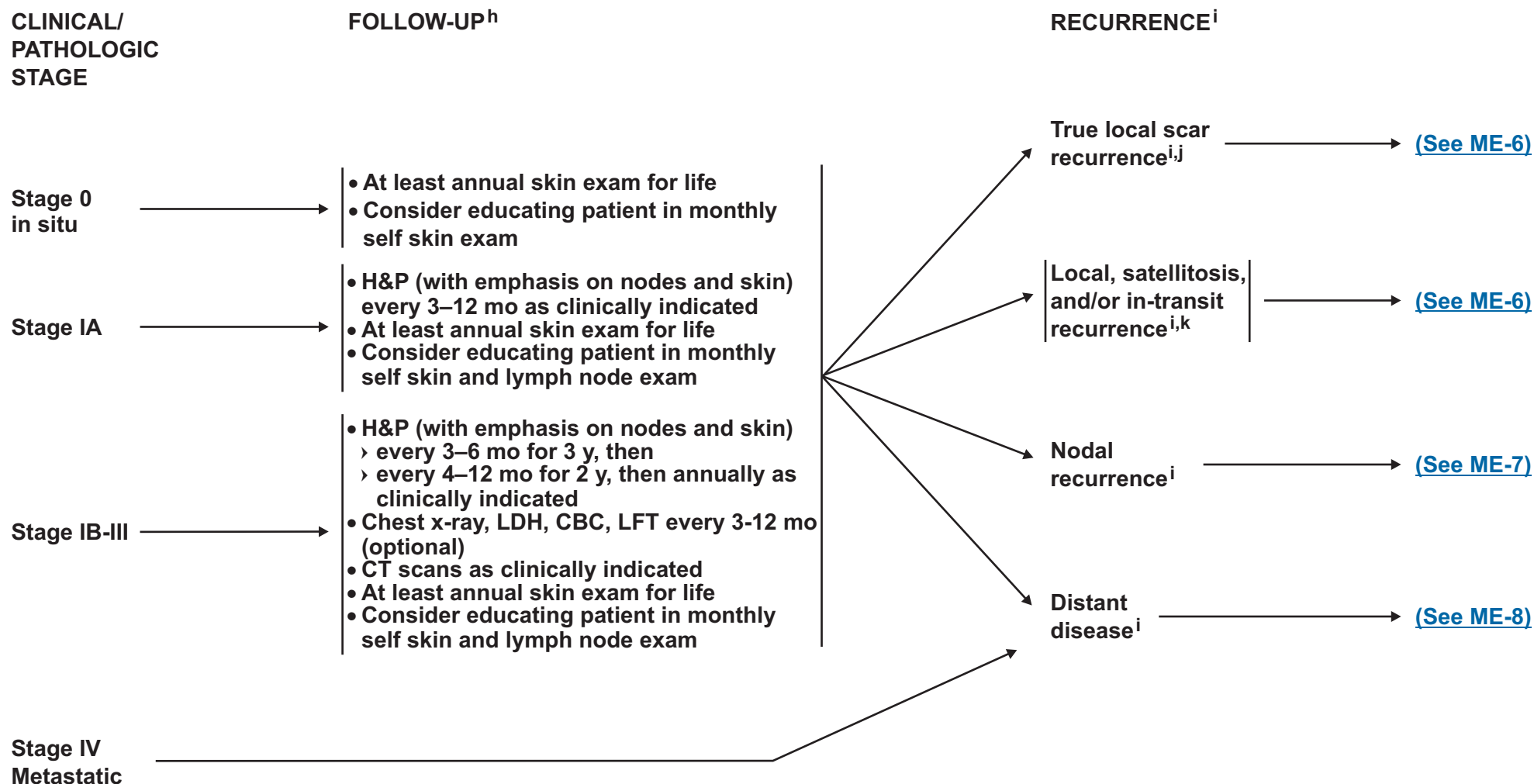
WORKUP

Stage IV
Metastatic

- FNA preferred, if feasible or biopsy
- Chest x-ray and/or chest CT
- LDH
- Consider abdominal/pelvic CT or head MRI, and/or PET (category 2B)
- Other imaging studies if clinically indicated

[See Treatment for Limited or Disseminated Disease \(ME-8\)](#)

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^hFollow-up schedule influenced by risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors, such as dysplastic nevus syndrome and patient anxiety.

ⁱInitial clinical recurrence should be confirmed pathologically by biopsy whenever possible.

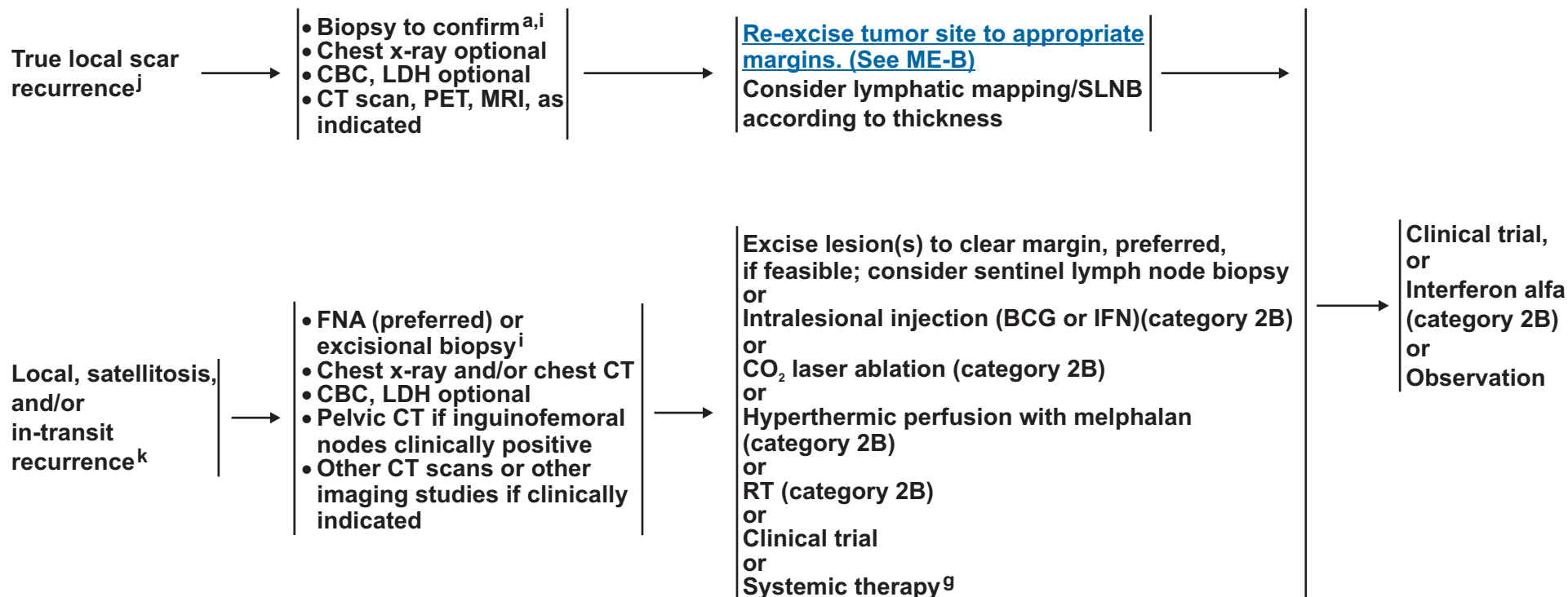
^jTrue local recurrence is defined by the presence of in situ and/or radial growth phase.

^k“Local recurrence” without in situ or radial growth phase.

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

TREATMENT OF RECURRENCEⁱ



^a See Biopsy (ME-A).

^g See Principles of Systemic Therapy for Advanced or Metastatic Melanoma (ME-D).

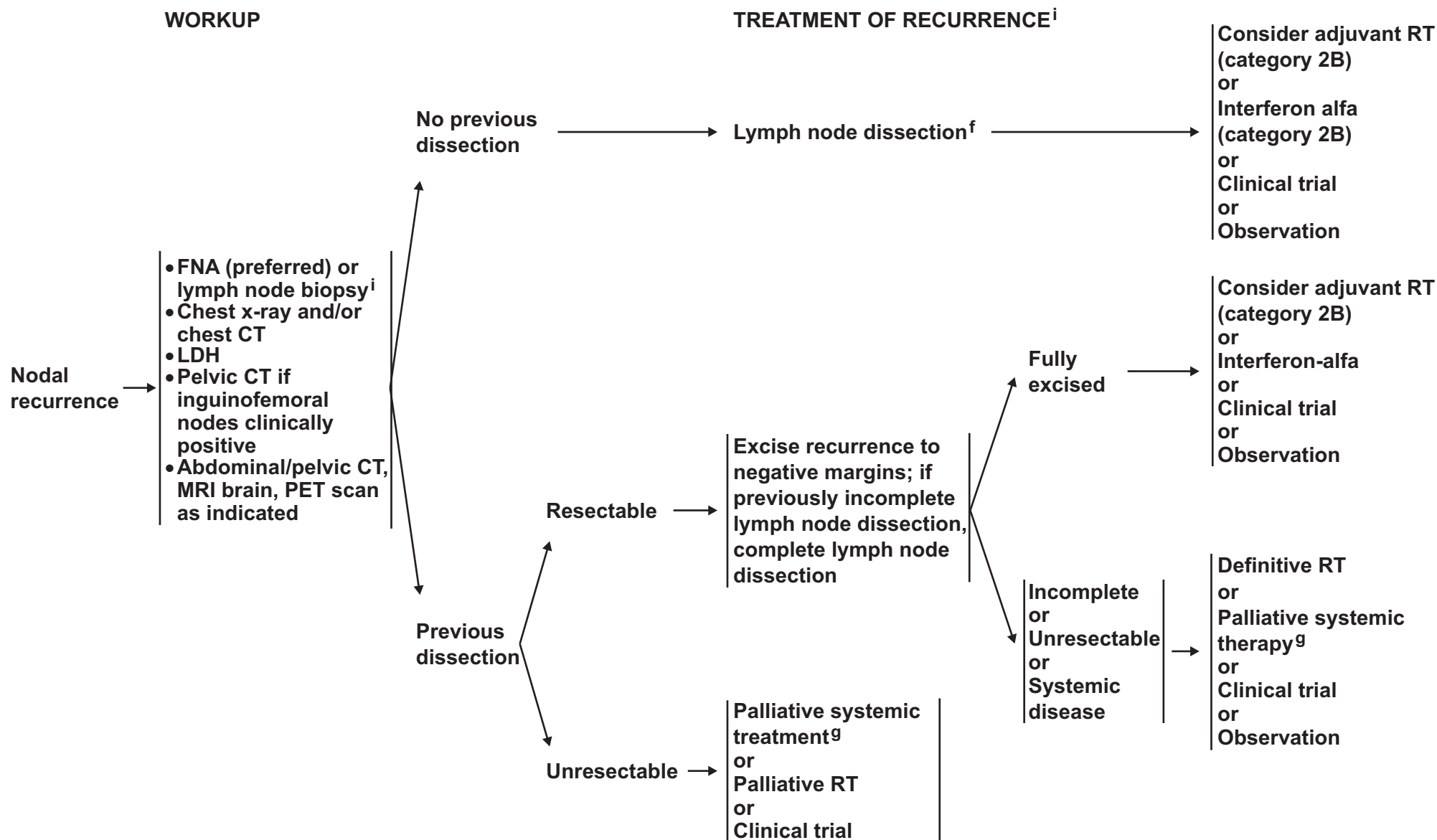
ⁱ Initial clinical recurrence should be confirmed pathologically by biopsy whenever possible.

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^fSee Complete Lymph Node Dissection (ME-C).

^gSee Principles of Systemic Therapy for Advanced or Metastatic Melanoma (ME-D).

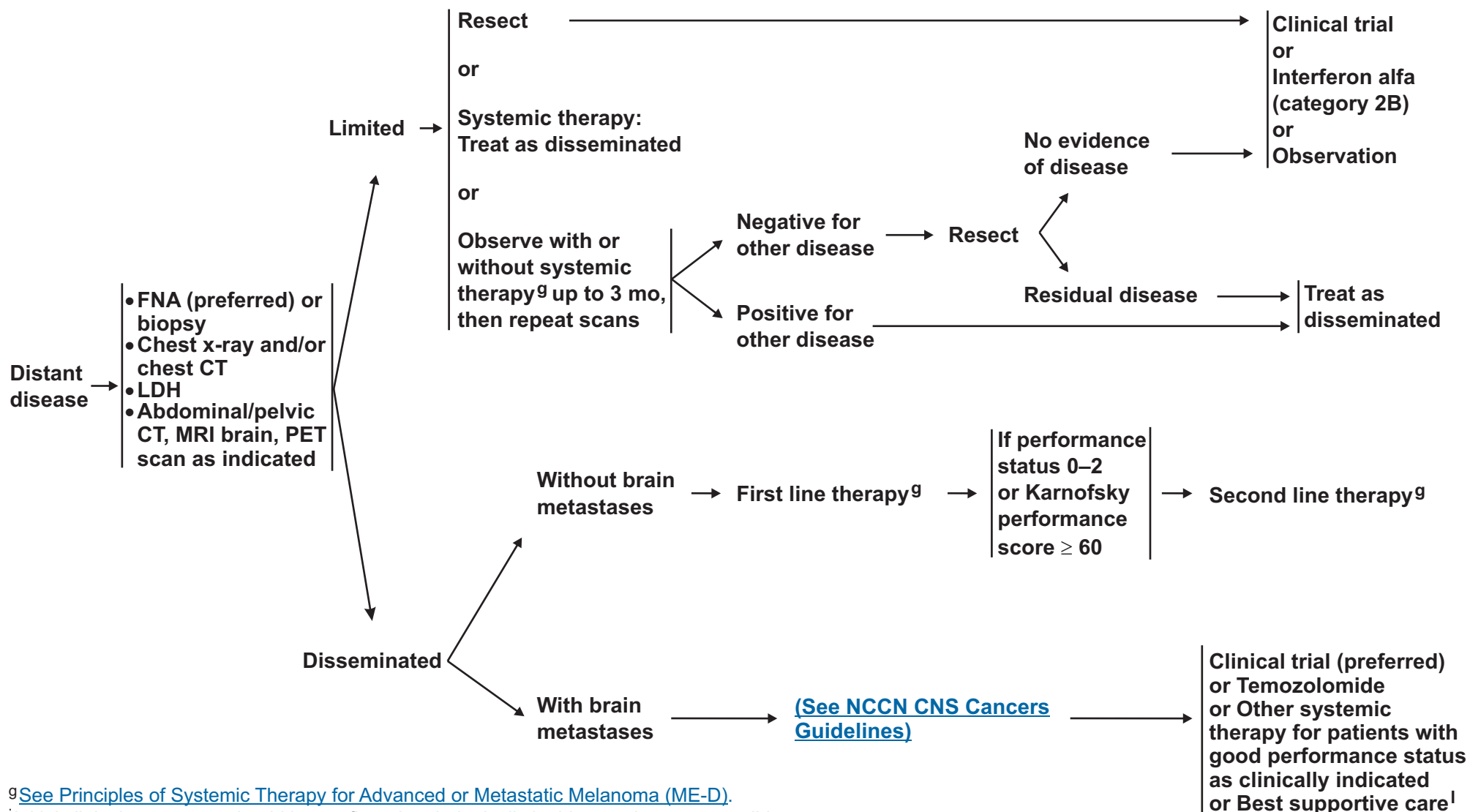
ⁱInitial clinical recurrence should be confirmed pathologically by biopsy whenever possible.

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WORKUP

TREATMENT OF RECURRENCEⁱ



^gSee Principles of Systemic Therapy for Advanced or Metastatic Melanoma (ME-D).

ⁱInitial clinical recurrence should be confirmed pathologically by biopsy whenever possible.

^lFor palliative purposes, management of symptoms due to local melanoma recurrences may include appropriate surgical resection or radiation therapy.

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

BIOPSY

- Excisional biopsy with 1-3 mm margins preferred. Avoid wider margins to permit accurate subsequent lymphatic mapping.
- Full thickness incisional or punch biopsy of clinically thickest portion of lesion acceptable, especially in certain anatomic areas (eg, palm/sole, digit, face, ear) or for very large lesions.
- Deep shave biopsy acceptable when index of suspicion for melanoma is low.
- Biopsy to be read by a pathologist experienced in pigmented lesions.
- Minimal elements to be reported should include Breslow thickness (mm), histologic ulceration, Clark level, and peripheral and deep margin status of biopsy.
- Satellitosis, if present, should be reported.
- Encourage consistent reporting of these additional factors (compatible with American Academy of Dermatology recommendations):
 - Location
 - Regression
 - Mitotic rate
 - Tumor infiltrating lymphocytes (TIL)
 - Vertical growth phase (VGP)
 - Angiolymphatic invasion
 - Neurotropism
 - Histologic subtype

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SURGERY

<u>Tumor Thickness</u>	<u>Recommended Clinical Margins</u>
In situ	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 cosmetic considerations.
- For in situ melanomas, pathologic confirmation of a negative peripheral margin is important (category 2B).

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COMPLETE LYMPH NODE DISSECTION**Adequacy of regional lymph node dissection:**

- **A thorough dissection of involved nodal basin is required.**
- **In general, removal and examination of:**
 - ▶ **≥ 10 nodes in the groin,**
 - ▶ **≥ 15 nodes in the axilla (levels I-III as clinically indicated),**
 - ▶ **≥ 15 lymph nodes in the neck (levels I - V as clinically indicated).**
- **In the groin, consider elective iliac and obturator lymph node dissection if clinically positive superficial nodes or ≥ 3 superficial nodes positive.**
- **Iliac and obturator lymph node dissection indicated if pelvic CT is positive or if Cloquet's node is positive.**

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PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC MELANOMA**First- or Second- Line Therapy:**

- Clinical trial (preferred)
- DTIC
- Temozolomide (category 2B)
- High-dose IL-2 (category 2B)
- DTIC- or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without IL2, interferon alfa) (category 2B)
- Best supportive care¹

¹For palliative purposes, management of symptoms due to local melanoma recurrences may include appropriate surgical resection or radiation therapy.

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.

Summary of the Guidelines updates

Highlights of major changes in the 2006 version of the Melanoma guidelines from the 2.2005 version include:

- Under Stage IA, “no ulceration, Clark level II, III” were removed ([ME-1](#)) and ([ME-2](#)).
- Stage III categorizations on ([ME-1](#)) and ([ME-3](#)) are now listed as follows:
 - Stage III (Sentinel node positive) (nodal micrometastasis)
 - Stage III (Clinically node positive) (nodal macrometastasis)
- After workup of Stage I and Stage II patients, the panel now recommends to “Consider” sentinel node biopsy. ([ME-2](#)).
- Workup for all Stage III patients now lists LDH and Chest x-ray as “Optional” ([ME-3](#)).
- Primary Treatment for Stage III in-transit patients now includes the recommendation “Consider sentinel node biopsy” ([ME-3](#)).
- Follow-up for Stage 0 in situ, Stage IA, and Stage IB-III patients now recommends to “Consider educating patients in monthly self skin exam” ([ME-5](#)).
- Follow-up for Stage IB-III patients now includes LFT ([ME-5](#)).
- Under treatment for “Local, satellitosis, and/or in-transit recurrence” ([ME-6](#)):
 - “Intradermal injection” was changed to “Intralesional injection”
 - “BCG” was changed to “BCG or IFN”
- Workup for nodal recurrence now includes “Pelvic CT if inguinofemoral nodes clinically positive” ([ME-7](#)).
- The panel now includes the recommendation to “Consider adjuvant RT” after lymph node dissection for patients with no previous dissection ([ME-7](#)).
- First and Second line systemic therapy recommendations ([ME-8](#)) were moved to page ([ME-D](#)).
- The recommended clinical margins for “In situ” changed from “0.5 - 1.0 cm” to “0.5 cm” ([ME-B](#)).
- Second bullet: The panel changed “clinically ill defined lentigo maligna pattern lesions of the head and neck” to “in situ melanomas” ([ME-B](#)).
- The panel clarified the Clark levels for removal and examination of nodes in the axilla and lymph nodes in the neck ([ME-C](#)).
- The panel added a new page entitled, “Principles of Systemic Therapy for Advanced or Metastatic Melanoma” ([ME-D](#)).

Staging

Table 1

**2002 American Joint Committee on Cancer (AJCC)
TNM Staging System for Melanoma****Primary Tumor (T)**

- TX** Primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)
- T0** No evidence of primary tumor
- Tis** Melanoma *in situ*
- T1** Melanoma ≤ 1.0 mm in thickness with or without ulceration
- T1a** Melanoma ≤ 1.0 mm in thickness and level II or III, no ulceration
- T1b** Melanoma ≤ 1.0 mm in thickness and level IV or V or with ulceration
- T2** Melanoma 1.01 -- 2.0 mm in thickness with or without ulceration
- T2a** Melanoma 1.01 -- 2.0 mm in thickness, no ulceration
- T2b** Melanoma 1.01 -- 2.0 mm in thickness, with ulceration
- T3** Melanoma 2.01 -- 4.0 mm in thickness with or without ulceration
- T3a** Melanoma 2.01 -- 4.0 mm in thickness, no ulceration
- T3b** Melanoma 2.01 -- 4.0 mm in thickness, with ulceration
- T4** Melanoma > 4.0 mm in thickness with or without ulceration
- T4a** Melanoma > 4.0 mm in thickness, no ulceration
- T4b** Melanoma > 4.0 mm in thickness, with ulceration

Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- N1** Metastasis in one lymph node
- N1a** Clinically occult (microscopic) metastasis
- N1b** Clinically apparent (macroscopic) metastasis
- N2** Metastasis in two or three regional nodes or intralymphatic regional metastasis without nodal metastases
- N2a** Clinically occult (microscopic) metastasis
- N2b** Clinically apparent (macroscopic) metastasis
- N2c** Satellite or in-transit metastasis without nodal metastasis
- N3** Metastasis in four or more regional lymph nodes, or matted metastatic nodes, or in-transit metastasis or satellite(s) with metastasis in regional node(s)

Distant Metastasis (M)

- MX** Distant metastasis cannot be assessed
- M0** No distant metastasis
- M1** Distant metastases
- M1a** Metastasis to skin, subcutaneous tissue, or distant lymph nodes
- M1b** Metastasis to lung
- M1c** Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH)

Staging, continued

Clinical Stage Grouping

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
	Any T	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

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

Histopathologic Type

- Melanoma in situ
- Malignant melanoma, NOS
- Superficial spreading melanoma
- Nodular melanoma
- Lentigo maligna melanoma
- Acral lentiginous melanoma
- Desmoplastic melanoma
- Epithelioid cell melanoma
- Spindle cell melanoma
- Balloon cell melanoma
- Blue nevus, malignant
- Malignant melanoma in giant pigmented nevus

Pathologic Stage Grouping

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	T1–4a	N1a	M0
	T1–4a	N2a	M0
Stage IIIB	T1–4b	N1a	M0
	T1–4b	N2a	M0
	T1–4a	N1b	M0
	T1–4a	N2b	M0
	T1–4a/b	N2c	M0
Stage IIIC	T1–4b	N1b	M0
	T1–4b	N2b	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note: 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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Manuscript This manuscript is being updated to correspond with the newly updated algorithm.

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

In the year 2005, an estimated 59,580 new cases of melanoma will be diagnosed and about 7770 patients will die of the disease.¹ However, these projections 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 rise 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 for someone born in the United States in the year 2000 may be as high as 1 in 58 for men and 1 in 82 for women.² Although melanoma is the fifth and sixth most common malignancy in men and women, respectively, it is

important to realize that melanoma ranks second to adult leukemia in terms of loss of years of potential life. The median age at diagnosis is 45 to 55 years. Therefore, the NCCN Melanoma Panel cannot overemphasize the importance of early diagnosis and appropriate treatment.

It is estimated that 82% to 85% of melanoma patients present with localized disease (American Joint Committee on Cancer [AJCC] stage I or II), 10% to 13% present with regional disease (AJCC stage III), and the remaining 2% to 5% with distant metastatic disease (AJCC stage IV).³ In those patients with localized disease, major prognostic factors include Breslow thickness, ulceration, and Clark level. Primary tumor site and patient gender are other factors. In patients with regional disease, the following factors seem to be most predictive of outcome: (1) tumor burden (expressed as the number of positive nodes); (2) macroscopic (clinically apparent) versus microscopic (clinically occult) nodal involvement; (3) the presence of extranodal soft-tissue extension; and (4) primary tumor ulceration.⁴ However, among stage III patients, there are clearly subsets of patients in whom melanoma follows a more indolent natural history. In patients with metastatic disease, the sites and number of metastases tend to govern outcome. Again, even within stage IV, there are subsets of patients whose clinical course may be more indolent and quite distinct biologically from most patients with advanced disease.

As with nearly all malignancies, the outcome of melanoma initially depends on the stage at presentation. In general, the prognosis of patients with localized disease and primary tumors 1.0 mm or less in thickness is excellent, with long-term survival generally achieved in more than 90% of patients.⁵ For patients with melanomas more than 1.0 mm in thickness, a survival rate in the range of 50% to 90% is expected.

The likelihood of regional nodal involvement clearly rises with increasing tumor thickness. When regional nodes are involved, survival rates are roughly halved. However, within stage III, a large range of prognosis is included, with 5-year survival rates ranging from 10% to 60%, depending on factors such as nodal tumor burden. Long-term survival in patients with distant metastatic melanoma, taken as a whole, is less than 10%.

Treatment Guidelines

Presentation and Biopsy

Patients presenting with a suspicious pigmented lesion should undergo a biopsy. Whenever possible, this should be a full-thickness excisional biopsy 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 lymph node biopsy, biopsies should also be planned in such a way that they will not interfere with this procedure.

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 appropriate. These procedures should provide accurate primary tumor microstaging, without interfering with definitive local therapy.

If, on evaluation by an experienced dermatopathologist, the biopsy is believed to be inadequate to make a diagnosis or to accurately microstage the tumor, re-biopsy is appropriate. Once adequate material has been obtained, Breslow thickness (mm), ulceration

status, Clark level of the lesion, and deep and peripheral biopsy margin status should be reported. Ulceration has been found to be an independent predictor of outcome for primary melanoma⁶ and has been incorporated into the 2002 AJCC staging system.⁵ Satellitosis has also been incorporated into the 2002 AJCC staging system and should be recorded if present. Consistent reporting of the following additional factors in pathology reports is encouraged: location, regression, mitotic rate, tumor infiltrating lymphocytes (TIL), vertical growth phase, angiolymphatic invasion, neurotropism, and histologic subtype (consistent with American Academy of Dermatology recommendations).⁷

Once the diagnosis of melanoma has been confirmed, a history and physical examination (H&P) as well as a complete dermatologic examination are mandatory. In the physical examination of patients with invasive melanoma, physicians should pay special attention to the locoregional area of the established melanoma. The patient can be clinically staged after histopathologic microstaging, an H&P, and a complete dermatologic examination.

Patients with melanoma in situ are categorized as stage 0 and are treated with wide excision of the primary tumor. Patients with invasive melanoma are allocated to one of five treatment pathway groups: (1) stage IA (low-risk primary), 1.0 mm thick or less without ulceration, Clark level II-III; (2) stage IB-II (intermediate- and high-risk primary), 1.0 mm thick or less with ulceration or Clark level IV-V; or more than 1.0 mm thick, with clinically negative nodes; (3) stage III, regional nodal disease with or without a known primary; (4) stage III, in-transit disease; or (5) stage IV, distant metastatic disease.

Workup

The panel unanimously agreed that no specific search for occult visceral metastases with either chest x-ray or blood work is

necessary in patients with stage IA melanoma. This is consistent with National Institutes of Health (NIH) consensus guidelines.⁸

For patients with stage IB-II melanomas, the panel felt that a baseline chest x-ray and lactate dehydrogenase (LDH) level (which is a known prognostic indicator in patients with advanced disease) are optional, recognizing that these tests are very insensitive and nonspecific means of detecting clinically occult distant disease. If clinically indicated, further imaging studies (such as a computed tomography [CT] scan with or without positron emission tomography [PET] and/or magnetic resonance imaging [MRI]) should be performed for stage IIB or IIC patients to detect distant metastases.

For patients with stage IIIA disease diagnosed by positive sentinel lymph node biopsy, further evaluation should include chest x-ray and serum LDH level for detection of distant metastases. Further imaging studies (such as CT scan with or without PET scans and/or MRI) may be obtained as clinically indicated. For patients presenting with stage IIIB or IIIC disease (ie, clinically involved regional lymph nodes), all panel members believe it is appropriate to confirm the suspicion of regional metastatic disease with either fine-needle aspiration (preferred) or with 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. Further evaluation of extent of disease should include at least a chest x-ray and LDH level. A pelvic CT scan is recommended in the setting of inguinofemoral lymphadenopathy to rule out associated pelvic lymphadenopathy. Other scans should be performed, if clinically indicated, to evaluate symptoms or abnormalities in the LDH or chest x-ray. For the most part, the panel recognized the low, but finite, yield of screening CT scans⁹⁻¹¹ but left the extent of scanning to be done to the discretion of the treating physician. The highest

yield of screening CT scans is in the body cavity adjacent to the clinically involved lymph nodes. The value of the extent of disease workup in this patient population is in part to direct treatment decisions, and in part to define more homogenous patient populations for clinical trials. For the small group of patients presenting with stage III in-transit disease, the workup previously outlined for stage IIIB or IIIC nodal disease, including histologic confirmation of the in-transit metastasis, was recommended.

For patients presenting with stage IV distant metastatic disease, a workup similar to the one outlined for patients with stage IIIB or IIIC disease was also advised, together with consideration of chest/abdominal/pelvic CT with or without PET and/or MRI.

There was substantial discussion regarding the indications for CT scanning and MRI in patients with stage III and IV disease. Member institution practices range from routine scanning of the head, chest, abdomen, and pelvis for all patients to scanning only to investigate symptoms or abnormalities in the screening blood work and/or chest x-ray. Because patients with metastatic melanoma have a particularly 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 CNS involvement or if results of imaging would affect decisions about treatment. With respect to blood work, LDH is an independent predictor of outcomes in patients with stage IV melanoma,¹² and has been incorporated into the AJCC staging system. Although LDH is not a sensitive marker for detecting metastatic disease, the panel recognizes its prognostic role. Other blood work may be done at the discretion of the treating physician.

Treatment of the Primary

If the diagnosis is in-situ melanoma, a wide excision of 0.5-1.0 cm around the visible lesion should be performed with confirmation of histologically negative margins.

Management of lentigo maligna melanoma may present unique problems because of the characteristic, yet unpredictable, subclinical extension of atypical junctional melanocytic hyperplasia that may extend several centimeters beyond the visible margins. Various approaches,^{13,14} all aimed at complete surgical excision with meticulous margin control, have demonstrated high local control rates and are used at some NCCN centers, although this is not universally accepted at other centers (category 3).

The recommended surgical margin in the treatment of invasive melanoma depends on the tumor thickness. For patients with stage IA melanoma, wide excision with a 1.0 cm margin was deemed appropriate (category 1). This recommendation is based on a World Health Organization (WHO) trial that revealed no local recurrences in this group of patients with sustained follow-up.¹⁵

For patients with melanomas measuring 1.1-2.0 mm in thickness, a wide excision with a 1-2 cm margin is appropriate (category 1). A wide excision with 2.0 cm margins is deemed appropriate for melanomas measuring more than 2.0 mm in thickness (category 1 for tumors \leq 4 mm in thickness, category 2A for tumors $>$ 4 mm in thickness). These recommendations are based on the National Intergroup Trial, which suggested for melanomas 1.0-4.0 mm in thickness that margins of 4 cm resulted in no further improvement in local control when compared with routine margins of 2 cm.¹⁶ The panel recognized that 1.0-2.0 cm margins may be acceptable in anatomically difficult areas where a full 2.0 cm margin would be difficult to achieve.

There was substantial discussion about the appropriate management of clinically negative lymph nodes in patients at risk for regional metastases. Based on the results of three prospective randomized trials, the panel recognized that routine elective lymph node dissection should not be recommended for this group.¹⁷⁻¹⁹

If lymphatic mapping with sentinel lymph node biopsy²⁰ is available, this procedure should be discussed with patients who have melanomas 1.0 mm thick or more or have Clark IV, any thickness; sentinel lymph node biopsy should be performed either as a standard of care or within the context of a clinical trial.^{21,22} If the lesion is less than 1.0 mm with a positive deep margin or with adverse histologic features (including ulceration, vertical growth phase, or extensive regression), lymphatic mapping with sentinel node biopsy may be considered. Sentinel lymph nodes should be evaluated with serial sectioning and immunohistochemistry. If the sentinel node is negative, regional lymph node dissection is not indicated. If the sentinel node is found to contain micrometastatic melanoma, a completion lymphadenectomy of the nodal basin is appropriate, either as a standard of care or in the context of a clinical trial. In general, this completion lymph node dissection consists of a thorough dissection of the involved nodal basin. Series have revealed additional positive nonsentinel lymph nodes in 10% to 30% of these completion lymphadenectomy specimens. The validity of sentinel lymph 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. If sentinel lymph node biopsy is not available, in the absence of trials showing improved survival, wide excision alone is an acceptable option.

For patients presenting with regional nodal metastases (stage III), an appropriate wide excision of the primary site, according to the guideline previously outlined, is advised (category 1).^{15,16} In addition, therapeutic lymph node dissection of the involved nodal basin should be performed.

The panel recognized that the extent of therapeutic lymph node dissection is often modified according to the anatomic area of lymphadenopathy. The panel felt that a thorough dissection of the involved nodal basin is required. In general, the number of lymph nodes examined most consistently reflects the adequacy of regional lymph node dissection as well as the adequacy of pathologic evaluation. When possible, inguinal lymph node dissection should include at least 10 lymph nodes; axillary dissection, a minimum of 15 nodes; and, for neck dissection, a minimum of 15 nodes, including levels I to V as appropriate, with or without parotidectomy. In the setting of inguinal lymphadenopathy, a deep groin dissection is recommended if the pelvic CT scan reveals iliac and/or obturator lymphadenopathy or if a positive Cloquet's lymph node is found intraoperatively.²³ Deep groin dissection also should be considered in the setting of clinically positive nodes or if more than three superficial nodes are involved.²⁴

Many treatment options exist for patients presenting with metastatic in-transit melanoma. For those with a small, finite number of in-transit metastases, excision with histologically negative margins should be performed (category 2B). In the patient undergoing curative resection of a solitary in-transit metastasis, sentinel lymph node biopsy can be considered, because there is a high probability of occult nodal involvement.²⁵ However, the effect of sentinel lymph node biopsy on outcome is unproven, although a positive sentinel lymph node in the presence of in-transit metastasis portends a more

ominous prognosis. If the patient has a finite number of lesions, particularly dermal lesions, which are not amenable to complete surgical excision, intradermal local injections with bacillus Calmette-Guérin (BCG)²⁶ or with interferon alfa (category 2B) would be appropriate. CO₂ laser ablation (category 2B) may be used in selected patients with multiple small dermal in-transit metastases. Another standard option for patients with unresectable in-transit metastases is regional treatment with hyperthermic isolation limb perfusion with melphalan as a single agent (category 2B).²⁷ Melphalan may also be used in isolated limb infusion in the context of a clinical trial (category 2B).²⁸ Radiation therapy is included as a treatment option (category 2B), recognizing its relative inefficiency in controlling regional disease. Other alternatives include systemic therapy, particularly after failure of local and/or regional therapy, and/or participation in a clinical trial.

For patients presenting with stage IV metastatic melanoma, treatment recommendations are governed by several observations. If evaluation reveals a solitary focus of metastatic disease, options for treatment include resection, if feasible.²⁹ The panel recognized that in selected patients with a solitary site of visceral metastatic melanoma, a short observation period of up to 3 months or more, 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 help select patients who would be most appropriately treated by surgical intervention. If the solitary site is unresectable and/or the workup uncovers other sites of disease, treatment options (for patients without brain metastases) include (1) a clinical trial (preferred); (2) single-agent systemic therapy (ie, interleukin-2 [category 2B]), dacarbazine [DTIC], or temozolomide;³⁰ (3) DTIC-based combination therapy, chemotherapy, and/or immunotherapy

(category 2B); or (4) best supportive care, as described later in the discussion of systemic recurrence.

Adjuvant Therapy

Most patients with in-situ or early-stage melanoma will be cured by primary excision alone. For patients with either node-negative melanoma 1-4 mm thick or ≤ 1 mm thick with ulceration, no standard adjuvant therapy is recommended. For patients with node-negative invasive melanoma ≤ 4.0 mm thick who are at risk for recurrence (ie, ulcerated, Clark IV-V), participation in a clinical trial of adjuvant therapy (if available) or observation may be appropriate.

For patients with localized melanomas more than 4.0 mm thick who are at significant risk for recurrence, the panel felt it appropriate to offer participation in a clinical trial of adjuvant therapy, treatment with high-dose adjuvant interferon alfa-2b (category 2B), or observation (category 2B). This group of patients was included in the randomized trial of high-dose interferon alfa-2b versus observation (Eastern Cooperative Oncology Group [ECOG] trial 1684).³¹ A larger follow-up clinical trial (ECOG 1690 trial), which included this group, compared high-dose to low-dose interferon alfa-2b or to no treatment in a larger group of patients. The results showed a relapse-free survival advantage but no overall survival advantage for high-dose interferon alfa-2b.³² Thus, a determination of the survival benefits of interferon for node-negative patients awaits further data.

For patients found to have positive nodes, either microscopically (after lymphatic mapping with sentinel node biopsy) or clinically, appropriate options include participation in a clinical trial, adjuvant treatment with high-dose interferon alfa-2b (category 2B), or

observation (category 2B). The ECOG 1684 study³¹ initially demonstrated an improvement in both disease-free and overall survival in patients treated with adjuvant high-dose interferon alfa-2b when compared with observation; however, with longer follow-up, the difference in overall survival was not sustained. A subsequent trial, ECOG 1690, confirmed the improvement of relapse-free but not overall survival with high-dose interferon alfa-2b.³² A third trial (E1694) compared high-dose interferon alfa-2b with an experimental vaccine. At approximately 2 years median follow-up, the interferon alfa-2b treatment group had a statistically significant advantage in relapse-free survival and overall survival.³³ A recent review of randomized controlled trials found that adjuvant interferon alfa was not associated with improved overall survival in patients with melanoma who were at risk for recurrence.³⁴ However, a pooled analysis found that relapse-free survival was significantly prolonged (two-sided log-rank P value = .006) in patients receiving high-dose interferon alfa-2b.³⁵ 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 interferon results and side effects of therapy.

In addition, postoperative adjuvant hyperfractionated radiation therapy 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 (category 2B). This latter recommendation is based on retrospective, uncontrolled observations rather than on prospective, randomized data.³⁶

For patients either with metastatic in-transit melanoma or those with stage IV melanoma who have been rendered free of disease after treatment, further options include participation in a clinical trial, high-dose interferon alfa-2b (category 2B), or observation (category 2B).

Follow-up

In the absence of any clear data, there was a wide range of opinion regarding the appropriate follow-up of patients with melanoma.^{37,38} It is difficult, if not impossible, to document the effect of intensive surveillance on the outcome of patients with melanoma. Such a program may permit the earlier detection of recurrent disease at a time when it may be more amenable to potentially curative surgical resection. This is particularly appropriate for patients at risk for regional nodal recurrence who have not undergone sentinel lymph node biopsy or elective lymph node dissection. There are several other reasons for a structured follow-up program. These reasons include detection of a subsequent second primary melanoma,³⁹ provision of ongoing psychosocial support,⁴⁰ identification of familial kindreds,⁴¹ screening for second nonmelanoma primary malignancies,⁴² patient education, and documentation of the end results of treatment. The follow-up schedule is influenced by risk of recurrence and subsequent primary melanoma and includes other factors, such as dysplastic nevus syndrome and patient anxiety. The optimal duration of follow-up remains controversial. Although most patients who are going to have recurrent disease will present in the first 5 years after treatment, the phenomenon of late recurrence (> 10 years later) is well documented for melanoma. It is probably not cost effective to follow all patients intensively for metastatic disease beyond 5 to 10 years (depending on relative risk for metastasis). However, because the lifetime risk of developing a second primary melanoma is 4% to 6%, the panel felt that a recommendation for lifetime dermatologic surveillance for melanoma patients was justified.

Annual (at least) skin examinations for life are recommended for patients with stage 0, in-situ melanoma. The frequency of dermatologic surveillance should be determined individually, based

on risk factors, including skin type, family history, presence of dysplastic nevi, and presence of nonmelanoma skin cancers. Clinicians should also consider educating patients how to examine their skin and lymph nodes (every month).

For patients with stage IA melanoma, a comprehensive H&P (with specific emphasis on the locoregional area) should be performed every 3 to 12 months as clinically indicated. The panel also recommended at least an annual skin examination for life or more often, based on individual patient risk factors. Clinicians should also consider educating patients how to examine their skin and lymph nodes (every month). No specific investigations to detect occult distant disease are recommended. This is consistent with the NIH consensus statement.⁸

For patients with stage IB-III melanomas, a comprehensive H&P (with emphasis on the locoregional area) should be performed every 3 to 6 months for 3 years; then every 4 to 12 months for 2 years; and annually (at least) thereafter, as clinically indicated. The panel also recommended an annual (at least) skin examination for life or more often, based on individual patient risk factors. Clinicians should also consider educating patients how to examine their skin and lymph nodes (every month). A chest x-ray, LDH, and complete blood count may be performed every 3 to 12 months, at the discretion of the treating physician. The consensus of the panel was that routine follow-up CT scans were unnecessary; however, they certainly should be performed as clinically indicated. The recommendations recognize the extremely low yield of routine screening chest x-rays and screening blood work in this population.⁴³ For patients with stage IV melanoma who are rendered free of disease by any modality, a follow-up schedule similar to stage III disease was felt to be appropriate.

Recurrence

Initial clinical recurrence should be confirmed pathologically by fine-needle aspiration cytology or biopsy whenever possible.

Local Scar Recurrence

The panel recognized the distinction between 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 recognized as prognostically similar to recurrent regional disease.³

In the presence of local recurrence after inadequate primary therapy, the workup should be similar to that of the primary tumor (ie, based on lesion thickness). A wide excision, with or without lymphatic mapping and sentinel lymph node biopsy, appropriate to the microstaging of the recurrence, should be performed. In the presence of a local recurrence after an adequate prior wide excision, the workup (including H&P and laboratory investigation) should be comparable to the workup for patients with stage III disease. In the absence of extraregional disease, these patients should be treated in the same manner as those with limited recurrent in-transit disease, namely, by surgical excision with negative margins if possible. Lymphatic mapping with sentinel lymph node biopsy may be considered in these patients or on an individual basis. Adjuvant treatment options after complete resection of a local recurrence after adequate primary therapy include clinical trial, high-dose interferon alfa-2b (category 2B), or observation (category 2B).

In-Transit Recurrence

For patients with in-transit recurrence, the workup is similar to the one previously outlined for patients presenting with in-transit disease. In the case of a surgically resectable recurrence, the disease should be re-excised with negative margins; sentinel lymph node biopsy should be considered. For unresectable disease, the treatment options include intradermal local injections (with BCG/interferon [category 2B]), CO₂ laser ablation (category 2B), hyperthermic isolation limb perfusion/infusion with melphalan (category 2B), radiation therapy (category 2B), clinical trial, or systemic therapy. In unusual circumstances, radiation therapy may be effective in achieving regional control (category 2B). Adjuvant treatment after complete response to any of these modalities may be followed by participation in a clinical trial, high-dose interferon alfa-2b (category 2B), or observation (category 2B).

Nodal Recurrence

For patients presenting with nodal recurrence, the clinical diagnosis should be confirmed preferably by fine-needle aspiration biopsy. Workup of these patients is similar to that previously outlined for patients presenting with lymph node metastases.

For patients who have not undergone prior lymph node dissection, a complete therapeutic lymphadenectomy is appropriate, again following the guideline previously outlined for patients presenting initially with lymph node metastases. For patients who have had a prior lymphadenectomy, complete lymph node dissection is recommended if the previous lymph node dissection was incomplete. If the patient underwent a previous “complete” lymph node dissection, excision of the recurrence to negative margins is appropriate. Postoperative adjuvant radiation therapy may decrease the likelihood of further regional nodal recurrences and is an option in selected cases of patients with completely resected nodal

recurrence (category 2B) with risk factors, such as multiple involved nodes or extranodal disease, especially in the head and neck region. Systemic therapy and/or radiation therapy can also be considered for selected patients with incompletely resected nodal recurrence. Options for patients with unresectable recurrence include palliative systemic treatment, palliative radiation therapy, or clinical trial.

Systemic Recurrence

For patients presenting with systemic recurrence, the workup and treatment are similar to those previously outlined for patients presenting initially with stage IV disease. After an appropriate workup, patients with resectable solitary sites of disease should be assessed for surgery,²⁹ followed by participation in a clinical trial, high-dose interferon alfa-2b (category 2B), or observation (category 2B).

In patients with a solitary, asymptomatic visceral recurrence (eg, in the lung), an interval of observation up to 3 months or more followed by repeat scans (to help exclude the possibility of other foci of metastatic disease) may be appropriate before surgical resection. If resected, patients should be offered adjuvant therapy similar to those treated with immediate resection. Patients with symptomatic visceral recurrences (eg, bowel obstruction from a gastrointestinal metastasis) should undergo an appropriate palliative procedure (resection or bypass). For patients with a surgically unresectable recurrence and/or multiple sites of disease but without brain metastases, options include: (1) clinical trial (preferred); (2) standard therapy with single-agent DTIC; (3) interleukin-2 (category 2B); (4) DTIC-based combination therapy, chemotherapy, and/or other immunotherapy (category 2B); (5) temozolomide;³⁰ or (6) best supportive care may be offered as clinically appropriate, based on the patient's performance status.^{44,45}

For patients with brain metastasis, surgery or radiation therapy may be considered based on symptoms, the number of lesions present, and the location of the lesions (see [NCCN Central Nervous System Cancers Guidelines](#)). Other treatment options would include participation in a clinical trial (preferred), temozolomide,³⁰ other systemic therapy for patients with good performance status as clinically indicated, or best supportive care (see [NCCN Palliative Care Guidelines](#)). For palliative purposes, management of symptoms due to local melanoma recurrences may include appropriate surgical resection or radiation therapy.

For any patient with recurrent disease who is rendered free of disease by surgery, consideration of postoperative adjuvant therapy is appropriate. Clinical trial participation is preferred. High-dose interferon alfa-2b is a treatment option for any patient who has not previously received it (category 2B); otherwise, the patient may be followed with observation alone.

Finally, for patients with unresectable distant metastatic disease that persists after first-line therapy, the following options may be offered as clinically appropriate, based on the patient's performance status: (1) a clinical trial (preferred); (2) single-agent DTIC; (3) interleukin-2 (category 2B); (4) DTIC-based combination therapy, chemotherapy, and/or immunotherapy (category 2B); (5) temozolomide;³⁰ or (6) best supportive care.

Summary

It should be emphasized that the NCCN Guidelines contain suggestions, not absolute recommendations, for treatment. 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 (see www.nccn.org).



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