



National
Comprehensive
Cancer
Network[®]

NCCN Clinical Practice Guidelines in Oncology™

Melanoma

V.2.2007

Continue

www.nccn.org

NCCN Melanoma Panel Members

* Alan N. Houghton, MD/Chair † ‡
Memorial Sloan-Kettering Cancer Center

Christopher K. Bichakjian, MD ☉
University of Michigan Comprehensive
Cancer Center

* Daniel G. Coit, MD ¶
Memorial Sloan-Kettering Cancer Center

Adil Daud, MD †
H. Lee Moffitt Cancer Center & Research
Institute at the University of South
Florida

Raza A. Dilawari, MD ¶
St. Jude Children's Research
Hospital/University of Tennessee Cancer
Institute

Dominick DiMaio, MD ≠
UNMC Eppley Cancer Center at The
Nebraska Medical Center

Jared A. Gollob, MD †
Duke Comprehensive Cancer Center

Naomi B. Haas, MD †
Fox Chase Cancer Center

Allan Halpern, MD ☉ ‡
Memorial Sloan-Kettering Cancer Center

Mohammed Kashani-Sabet, MD ☉
UCSF Comprehensive Cancer Center

William G. Kraybill, MD ¶
Roswell Park Cancer Institute

Julie R. Lange, MD ¶
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Anne Lind, MD ≠
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University
School of Medicine

Mary Martini, MD ☉
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Merrick I. Ross, MD ¶
The University of Texas M. D. Anderson
Cancer Center

* Wolfram E. Samlowski, MD †
Huntsman Cancer Institute at the
University of Utah

Stephen F. Sener, MD ¶
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Kenneth K. Tanabe, MD ¶
Dana-Farber/Partners CancerCare

* John A. Thompson, MD ‡
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Vijay Trisal, MD ¶
City of Hope Cancer Center

Marshall M. Urist, MD ¶
University of Alabama at Birmingham
Comprehensive Cancer Center

Michael J. Walker, MD ¶
Arthur G. James Cancer Hospital &
Richard J. Solove Research Institute at
The Ohio State University

† Medical oncology
‡ Internal medicine
☉ Dermatology
¶ Surgery/Surgical oncology
≠ Pathology
‡ Hematology/Hematology oncology
* Writing Committee member

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 \(ME-8\)](#)

[Biopsy \(ME-A\)](#)

[Surgery \(ME-B\)](#)

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

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

[Guidelines Index](#)

[Print the Melanoma Guideline](#)

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

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.

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

[Staging](#)

[Manuscript](#)

[References](#)

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](#)

Summary of the Guidelines Updates

The changes in the 2.2007 version of the Melanoma Guidelines from the 1.2007 version is the addition of the updated manuscript representing the changes to the algorithm.

Summary of changes in the 1.2007 version of the Melanoma guidelines from the 2.2006 version include:

- Stage IA now includes the same Workup as Stage IB, Stage II and is followed by new treatment pathways ([ME-2](#)).
- “Further imaging as clinically indicated” was changed to “Further imaging *to evaluate for specific signs or symptoms*” throughout the guideline ([ME-2](#)).
- Stage IB, Stage II pathway: After workup, changed to “Consider discussion of sentinel node biopsy” ([ME-2](#)).
- Stage III, Primary Treatment: Changed to “Lymph node dissection *or Clinical trial*” with new footnote “g” ([ME-3](#)).
- Stage 0, Follow-up: History and Physical added ([ME-5](#)).
- Removed the phrases “Definitive” and “Palliative” before “RT” ([ME-7](#)).
- The treatment option under “Consider adjuvant RT” was clarified with “and/or” ([ME-7](#)).
- Limited, Treatment of Recurrence: “Observe” pathway changed to “Observe then repeat scans” ([ME-8](#)).
- Disseminated, With Brain Metastases pathway ([ME-8](#)):
 - Removed “Temozolomide” as a single agent treatment option in the algorithm
 - “Consider resection for symptomatic patients” is a new treatment option
 - Footnote “n” is new to the page
- Adequacy of regional lymph node dissection: Second bullet changed to: “In general, removal and examination of *lymph node inclusive of sentinel and complete lymph node dissection samples*” ([ME-C](#)).
- First- or Second-Line Therapy: Dacarbazine changed to category 2B. Temozolomide is now a category 2B for use as a single or in combination therapy for Disseminated disease with brain metastases ([ME-D](#)).

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

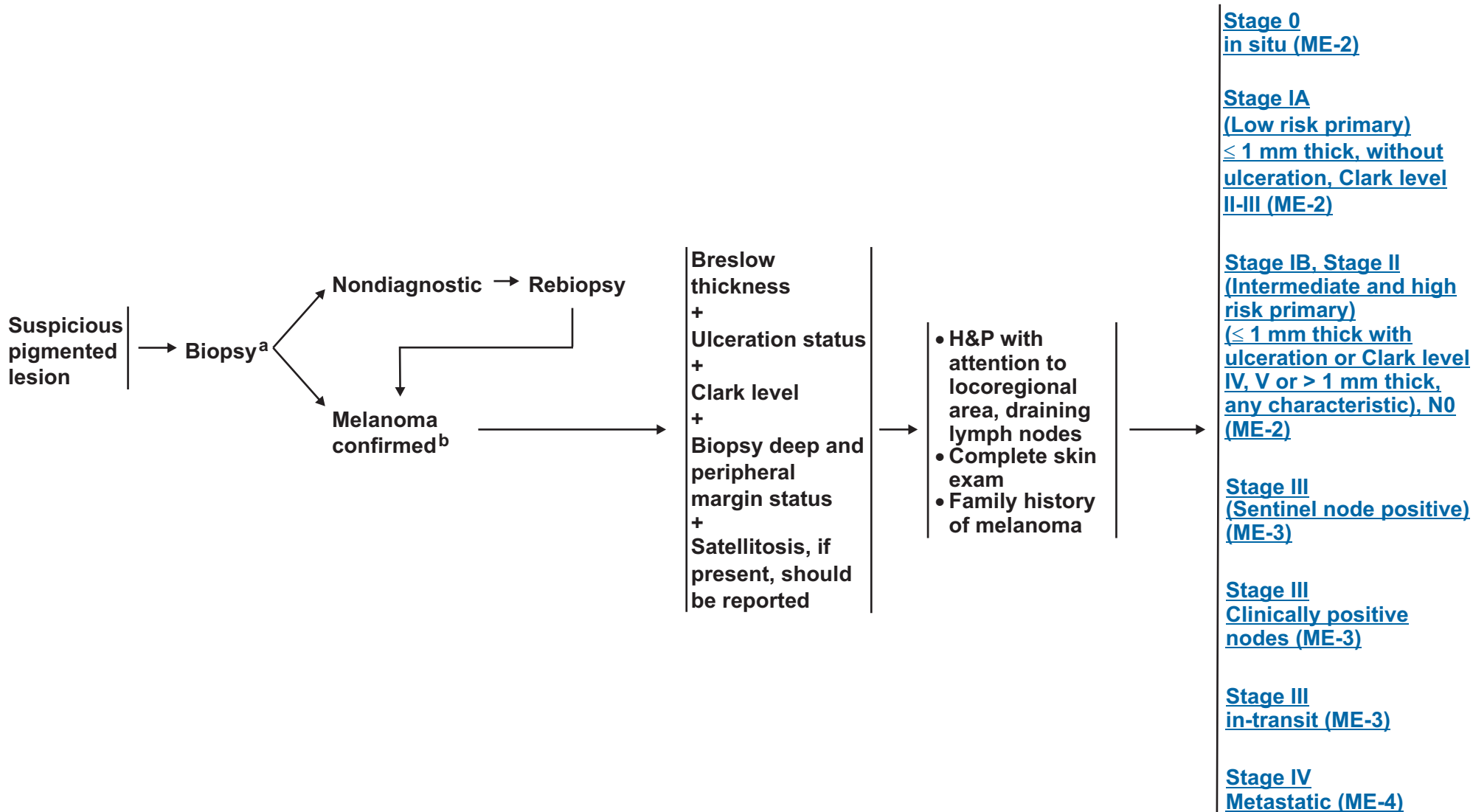
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL
PRESENTATION

PATHOLOGY
REPORT

PRELIMINARY
WORKUP

CLINICAL STAGE

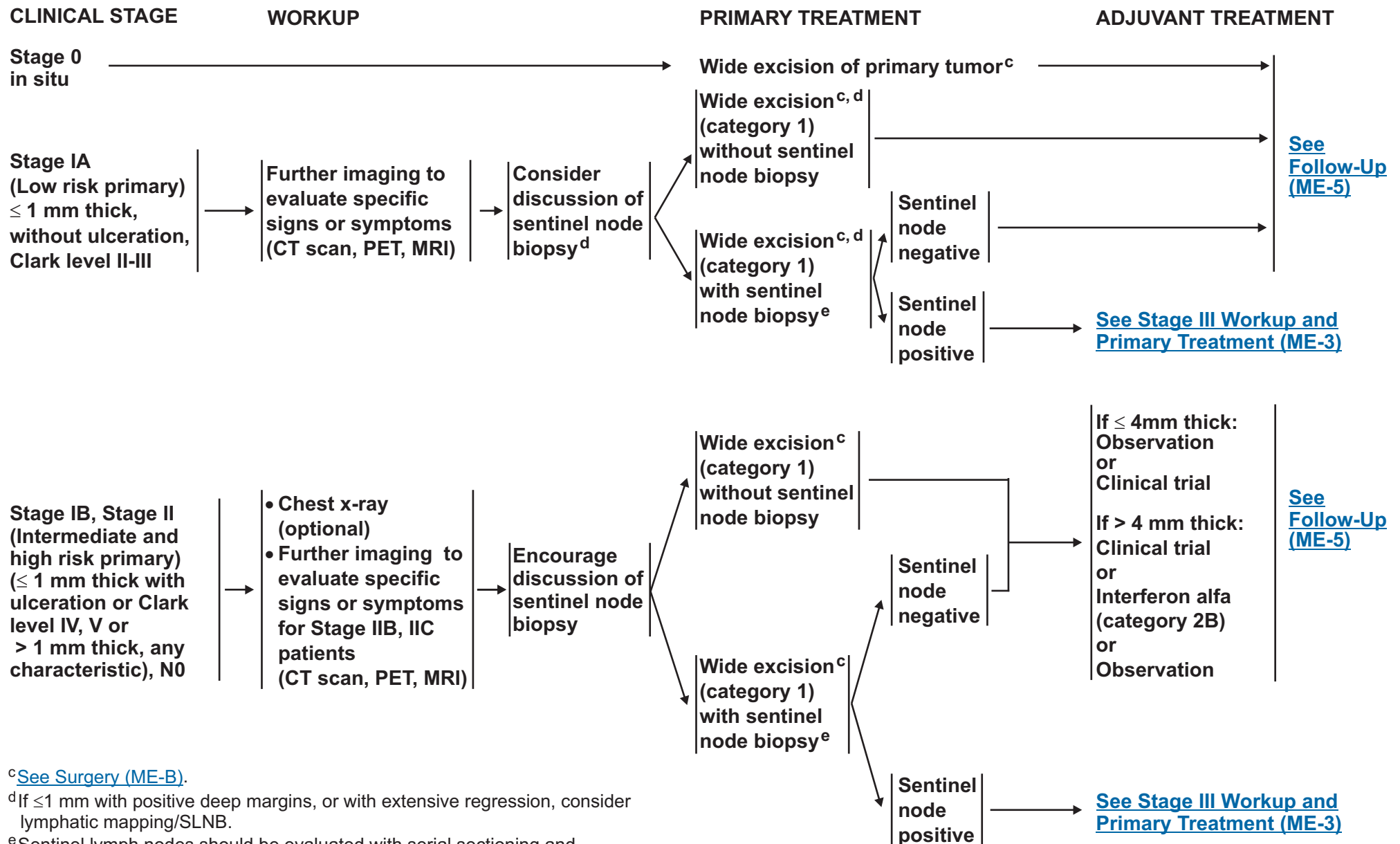


^aSee Biopsy (ME-A).

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

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

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



^cSee Surgery (ME-B).

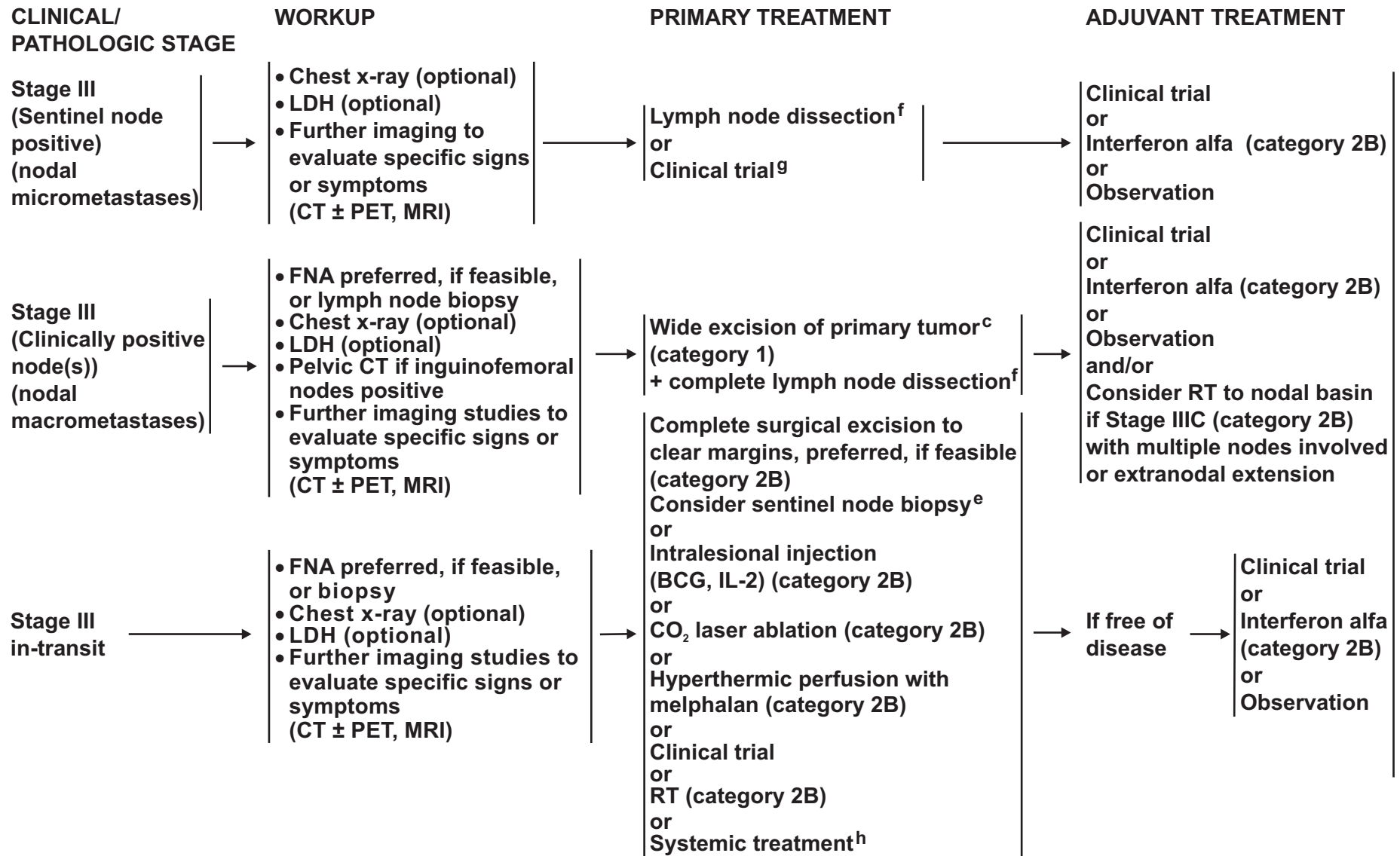
^dIf ≤1 mm with positive deep margins, or with extensive regression, consider lymphatic mapping/SLNB.

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

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.

Melanoma



(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 \(ME-C\)](#).

^gClinical trials assessing alternatives to complete lymph node dissection, such as careful observation.

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

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

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

CLINICAL/
PATHOLOGIC
STAGE

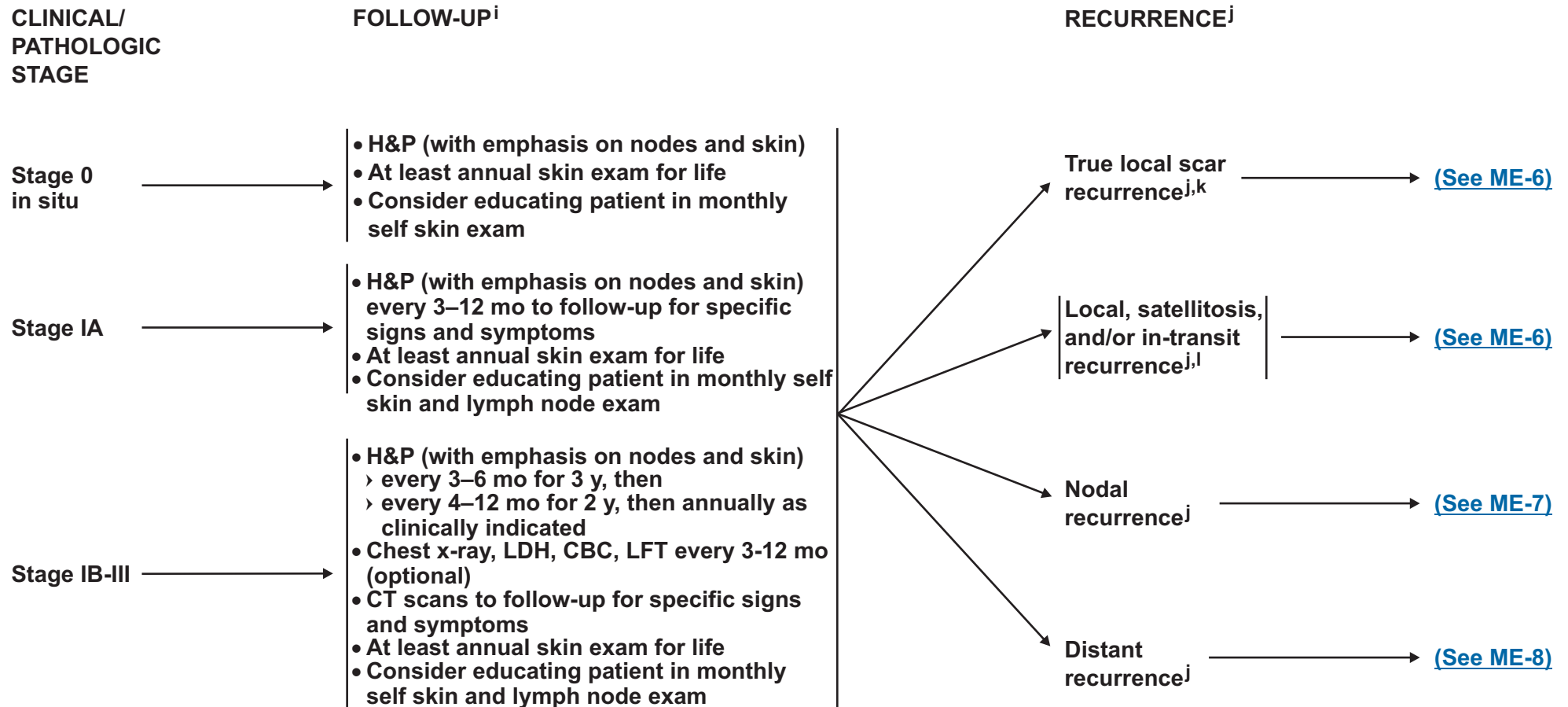
WORKUP

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)
- Further imaging studies to evaluate specific signs or symptoms

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

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.



ⁱ Follow-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.

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

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

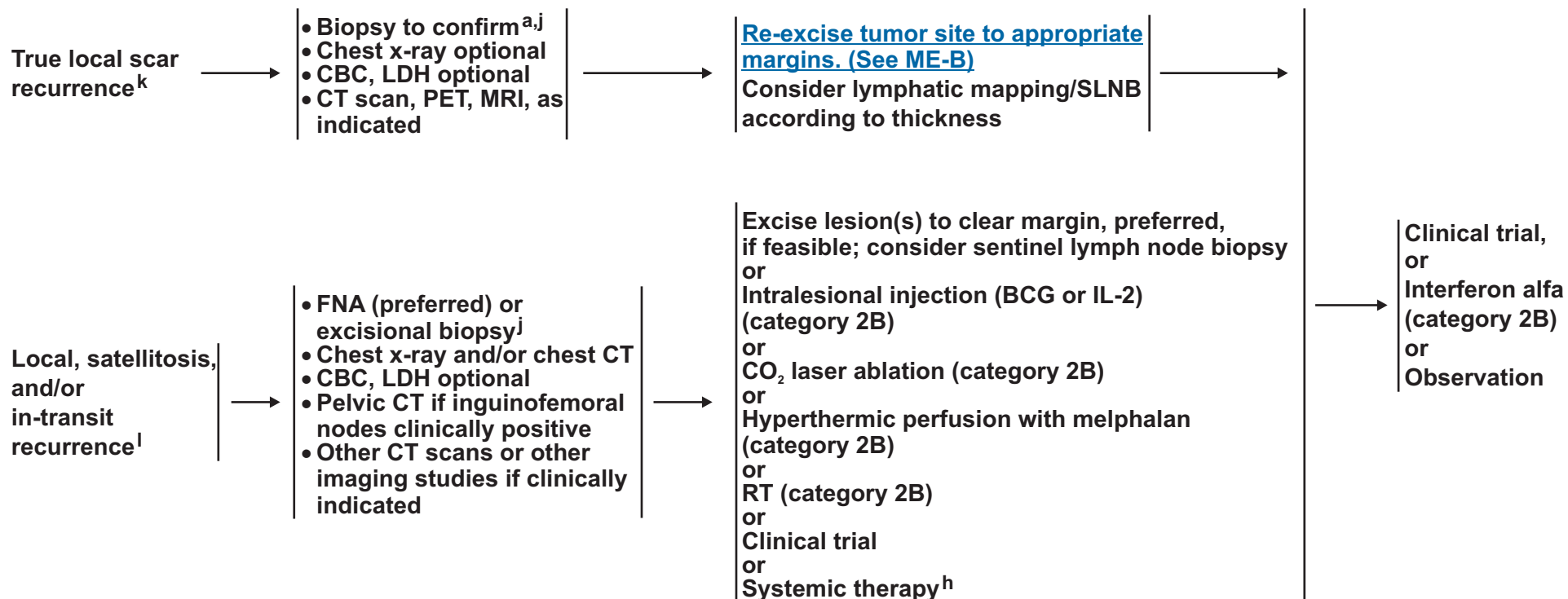
^l "Local recurrence" without in situ or radial growth phase.

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.

WORKUP

TREATMENT OF RECURRENCE^j



^a See Biopsy (ME-A).

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

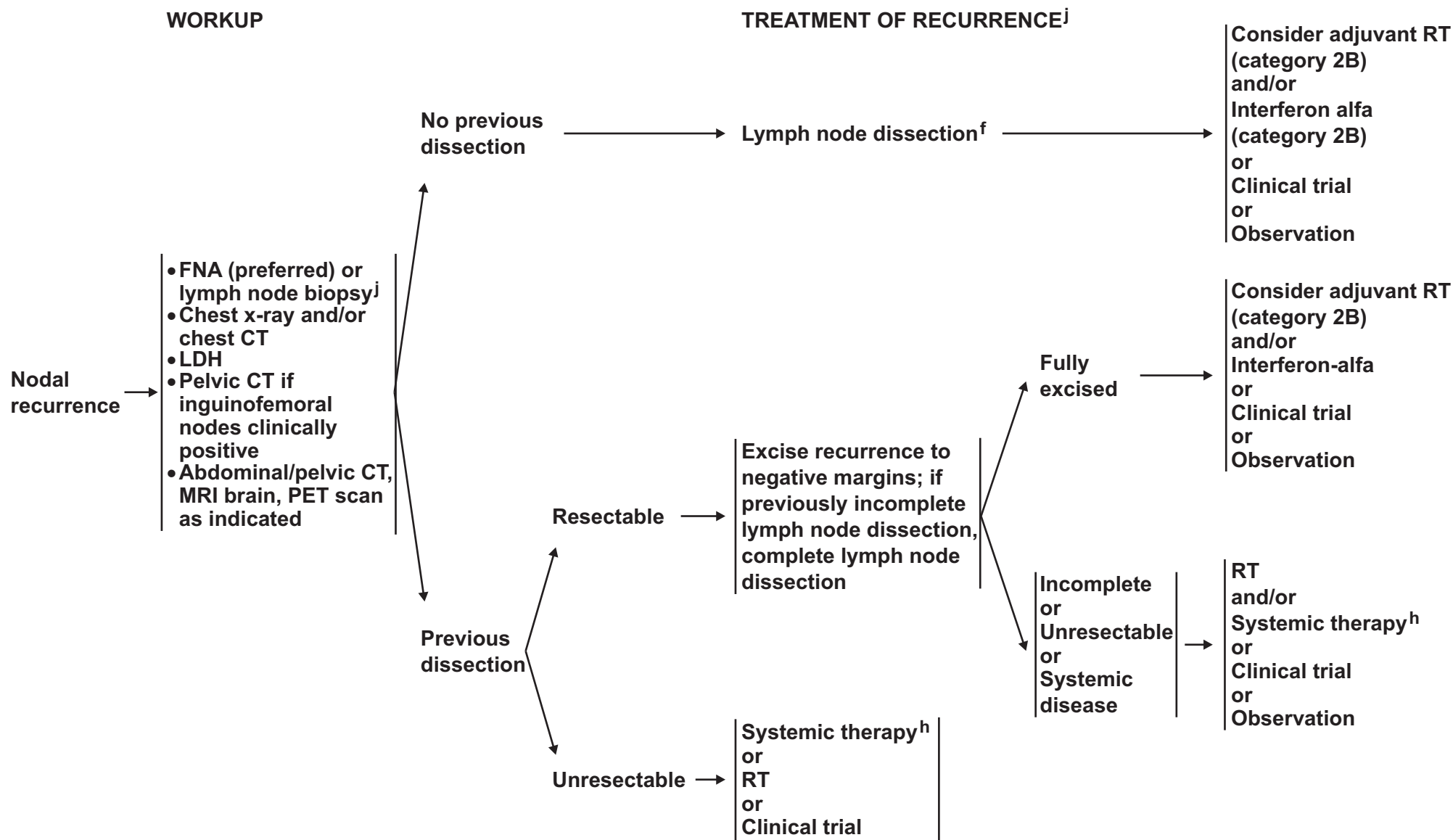
^j Initial clinical recurrence should be confirmed pathologically by biopsy whenever possible.

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

^l "Local recurrence" without in situ or radial growth phase.

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.



^f See Complete Lymph Node Dissection (ME-C).

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

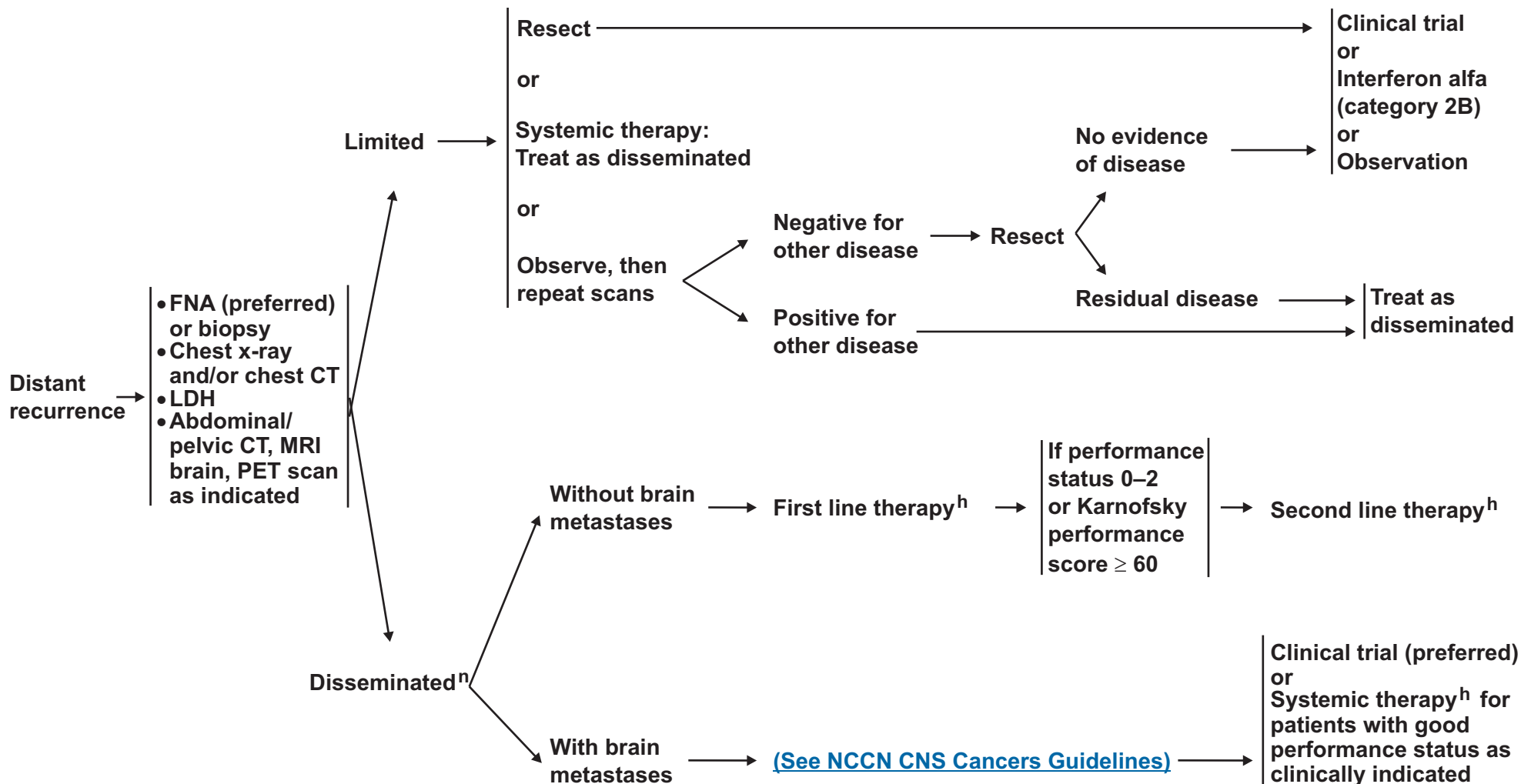
^j Initial clinical recurrence should be confirmed pathologically by biopsy whenever possible.

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.

WORKUP

TREATMENT OF RECURRENCE^j



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

^jInitial clinical recurrence should be confirmed pathologically by biopsy whenever possible.

^mFor palliative purposes, management of symptoms due to recurrences may include appropriate surgical resection and/or radiation therapy.

ⁿIn patients with disseminated metastases, resection or radiation may be indicated to palliate symptoms such as those caused by gastrointestinal bleeding, ulcerated cutaneous metastases, or bulky adenopathy.

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.

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 very 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

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.

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).

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.

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 lymph node inclusive of sentinel and complete lymph node dissection samples:
 - ▶ ≥ 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.

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

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

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

- Clinical trial (preferred)
- Dacarbazine (category 2B)
- Temozolomide (category 2B)
- High-dose Interleukin-2 (category 2B)
- Dacarbazine-or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without IL-2, 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.

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)

[Continue](#)

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.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.

Manuscript

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 2007, an estimated 59,940 new cases of melanoma will be diagnosed and about 8,110 patients will die of the disease in the United States.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 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 for someone born in the United States in the year 2000 may be as high as one in 58 for men and one in 82 for women.² Although melanoma is the fifth and sixth most common malignancy in men and women, respectively, melanoma ranks second to adult leukemia in terms of loss of years of potential life, per death. The median age at diagnosis is 45 to 55 years.

Risk factors for melanoma include strong family history, pigmented lesions, multiple clinically atypical moles or dysplastic nevi³ and inherited genetic mutations. Individuals with an inability to tan and a fair skin that sunburns easily have a greater risk of developing melanoma.^{4,5} Sun exposure may also play a contributing role in the development of melanoma in addition to genetic factors.⁶ However, melanoma can occur in any ethnic group and in those without substantial sun exposure.

It is estimated that 82-85% of melanoma patients present with localized disease (American Joint Committee on Cancer [AJCC] stage I or II), 10-13% present with regional disease (AJCC stage III), and 2-5% with distant metastatic disease (AJCC stage IV). In 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, prognostic factors include: (1) tumor burden (expressed as the number of positive nodes); (2) macroscopic (clinically apparent) or microscopic (clinically occult) nodal involvement; (3) the presence of extranodal soft-tissue extension; and (4) primary tumor ulceration.⁷ In patients with distant metastatic disease, the number of different organ sites involved tends to govern outcome.

As with nearly all malignancies, the outcome of melanoma initially depends on the stage at presentation. In general, the prognosis is excellent for patients with localized disease and primary tumors 1.0 mm or less in thickness, with long-term survival achieved in more than 90% of patients. For patients with 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 10-60%, 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%. However, even within stage IV, some patients have a more indolent clinical course that is quite distinct biologically from most patients with advanced disease.

By definition, the NCCN practice guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the panel during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The NCCN Melanoma Panel strongly recommends early diagnosis and appropriate treatment of melanoma.

Biopsy

Patients presenting with a suspicious pigmented lesion should undergo a biopsy, preferably a full-thickness excisional biopsy, with 1-3 mm margins ([ME-A](#)). 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 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 recommended. These procedures should provide accurate primary tumor microstaging, without interfering with definitive local therapy. If the biopsy is inadequate to make a diagnosis or to accurately microstage the tumor

(based on evaluation by a dermatopathologist), re-biopsy is recommended.

The pathology report should include Breslow thickness, ulceration status, Clark level as well as deep and peripheral biopsy margin status. Ulceration has been found to be an independent predictor of outcome for primary melanoma⁸ and has been incorporated into the 2002 AJCC staging system ([Table 1](#)).^{9,10} Satellitosis has also been incorporated into the 2002 AJCC staging system and should be reported if present. In accordance with American Academy of Dermatology recommendations, the pathology report should also consistently include the following additional factors ([ME-A](#)): location, regression, mitotic rate, tumor infiltrating lymphocytes (TIL), vertical growth phase (VGP), angiolymphatic invasion, neurotropism, and histologic subtype.¹¹

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 patient presenting with dysplastic nevi should include detailed personal and family history including any history of prior removal of dysplastic nevi¹². In the physical examination of patients with invasive melanoma, physicians should pay special attention to the locoregional area and lymph node drainage of the established melanoma.

Staging

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 those with invasive melanoma are categorized into the following five groups:

- Stage IA (low-risk primary), 1.0 mm thick or less without ulceration, Clark level II-III;

- Stage IB-II (intermediate- and high-risk primary), 1.0 mm thick or less with ulceration or Clark level IV-V; or greater than 1.0 mm thick, with any characteristic and clinically negative nodes;
- Stage III, sentinel node positive, or clinically positive nodes;
- Stage III, in-transit disease;
- Stage IV, distant metastatic disease.

Clinical Stage and 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 0 and IA melanoma. This NCCN recommendation is consistent with National Institutes of Health (NIH) consensus guidelines.¹³ Imaging studies such as a computed tomography (CT) scan, positron emission tomography (PET), and/or magnetic resonance imaging (MRI) may be performed for all patients to evaluate specific signs or symptoms.

For patients with stage IB-II melanomas, a baseline chest x-ray is optional, because this test is insensitive for detecting clinically occult distant disease in the lungs.¹⁴

For patients with stage III disease who have positive sentinel nodes, chest x-ray and measurement of serum LDH (lactic acid dehydrogenase) level are optional.¹⁴ 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 either 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. A pelvic CT scan is recommended in the setting of inguinofemoral lymphadenopathy to rule out associated pelvic lymphadenopathy.

Most panel members acknowledged the low yield of screening CT scans in patients with Stage III melanoma.¹⁵⁻¹⁸ but left the extent of scanning to the discretion of the physician because of the limited data; thus, screening practices vary widely among NCCN institutions. The highest yield of screening CT scans is in the body cavity adjacent to the clinically involved lymph nodes. The extent of disease workup in this patient population can help direct treatment decisions and define more homogenous patient populations for clinical trials. Another rationale for the initial extent of disease workup is that it provides a baseline against which future scans may be compared.

For the small group of patients presenting with stage III in-transit disease, the workup just outlined 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. LDH level plus chest x-ray and/or chest CT are recommended. Abdominal/pelvic CT, with or without PET, and/or head MRI should be considered (category 2B);

The panel had a 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 central nervous system (CNS) involvement, or if results of imaging would affect decisions about treatment.

LDH is an independent predictor of outcome in patients with stage IV melanoma,¹⁹ 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 physician.

Treatment of Primary Melanoma

Primary tumor

Surgical excision is the primary treatment for melanoma. Wide excision of primary tumor is recommended for in-situ melanoma, whereas wide excision (category 1) with or without sentinel node biopsy should be performed for stage IA, stage IB or stage II disease.

Surgical margins may be modified to accommodate individual anatomic or cosmetic considerations ([ME-B](#)). For in-situ melanoma, a measured margin of 0.5 cm around the visible lesion should be obtained (category 2A) with pathological confirmation of negative peripheral margins (category 2B). The recommended measured margin for invasive melanoma depends on the tumor thickness. For patients with stage IA melanoma, wide excision with a 1.0 cm margin is recommended (category 1), based on a World Health Organization (WHO) trial that revealed no local recurrences in this group of patients with sustained follow-up.²⁰

For patients with melanomas measuring 1.01-2.0 mm in thickness, a wide excision with a 1-2 cm margin is recommended (category 1).²¹ Wide excision with 2.0 cm margins is recommended for melanomas measuring more than 2.0 mm in thickness (category 1 for tumors 4 mm or less in thickness, category 2A for tumors more than 4 mm in thickness).¹⁵ These NCCN recommendations are based on the National Intergroup Trial, which suggested that for melanomas 1.0-4.0 mm in thickness, margins of 4 cm resulted in no further improvement in local control when compared with routine margins of 2 cm. A more recent

prospective randomized trial comparing 1 cm vs. 3 cm margins for melanomas over 2 mm thick reported that wider margins were associated with a slightly lower rate of combined local/regional/nodal recurrence, but without improvement in melanoma specific survival.²² Based on these results, the panel recognized that 1.0 cm to less than 2.0 cm margins might be acceptable in anatomically difficult areas where a full 2.0 cm margin would be difficult to achieve.

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,^{23,24} all 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 (category 3).

Sentinel Lymph Node Biopsy

Sentinel node status is the most important prognostic factor in primary melanoma. 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.²⁵ MSLT-1, 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.²⁶ In a preliminary publication, Morton and et al reported an initial sentinel node identification rate of 95.3%. SLNB was also associated with a low false negative rate (5.2% after 25 cases) and low complication rate (10.1%). Recently, Morton and et al published the data from third interim analysis of the results from the MSLT-1 trial.²⁷ In patients with primary melanoma (1.2-3.5 mm), the mean estimated 5-year disease-free survival was 78.3 ± 1.6% for the biopsy group and 73.1 ± 2.1% for the observation group (95% confidence interval, P = 0.0009). There was no

significant difference in melanoma-specific survival rates between the two groups. However, in patients with nodal metastases, those who had immediate lymph node dissection following lymphatic mapping and SLNB had higher survival rate than patients who had delayed lymphadenectomy for clinical disease ($72.3 \pm 4.6\%$ vs. $52.4 \pm 5.9\%$). This difference was largely attributed to a lower nodal tumor burden in the SLN positive patients than the clinically node positive patients. These results confirm that SLNB is of prognostic value and that the procedure can identify patients with low volume nodal metastases whose survival is superior to that of patients whose nodal metastases are detected on clinical examination.

MSLT-II is an ongoing trial in which patients with sentinel node metastases are randomized to undergo either complete lymph node dissection or observation. This trial should resolve the issue of whether complete lymph node dissection has therapeutic impact on outcome. (clinicaltrials.gov/show/NCT00297895).

Sentinel node biopsy may be offered to melanoma patients either as standard care or in the context of a clinical trial. Discussion of SLNB should be encouraged in patients with stage IB and stage II melanoma (ME-2).²⁸⁻³¹ There may be subsets of patients identified by deep Clark's level or high mitotic rate that may be candidates for sentinel lymph node biopsy.³² The yield and clinical significance of sentinel node biopsy in patients with Stage IA melanoma is unknown, and a discussion of the procedure in this patient population should reflect this fact. 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. If

sentinel node biopsy is not available, in the absence of trials showing improved survival, wide excision alone is an acceptable option.

If lymphatic mapping with sentinel node biopsy is available, this procedure should be considered for patients who have melanomas more than 1.0 mm thick, any characteristic.³³⁻³⁶ If the lesion is 1.0 mm or less, other characteristics may warrant consideration of sentinel lymph node biopsy, such as Clark level IV-V, high mitotic rate and/or presence of ulceration.³⁷ If the sentinel node is negative, regional lymph node dissection is not indicated. If the sentinel node contains micrometastatic melanoma, a complete lymph node dissection of the nodal basin is recommended, 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 20% of these complete lymph node dissection specimens.^{38,39}

The panel had a substantial discussion about the appropriate management of clinically negative lymph nodes in patients at risk for regional metastases, in the event that sentinel lymph node biopsy is unavailable. Based on the results of three prospective randomized trials, the panel does not recommend routine elective lymph node dissection for this group.^{40,41,42}

Lymph Node Dissection

Complete lymph node dissection consists of a thorough dissection of the involved nodal basin (ME-C). The extent of complete lymph node dissection is often modified according to the anatomic area of lymphadenopathy. In general, the number of lymph nodes examined reflects the adequacy of regional lymph node dissection and of pathologic evaluation. When possible, inguinal lymph node dissection should include at least 10 lymph nodes; axillary dissection, a minimum of 15 nodes (levels I-III as clinically indicated); and, for neck dissection, a minimum of 15 nodes, including levels I to V as clinically indicated. 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.^{43,44} Deep groin dissection also should be considered for clinically positive nodes or if more than 3 superficial nodes are involved.⁴⁵

For patients presenting with stage III disease with regional nodal micrometastases, lymph node dissection is recommended. Clinical trials assessing alternative options can be considered. Wide excision of the primary site is recommended for stage III disease with nodal macrometastases (category 1). In addition, complete lymph node dissection of the involved nodal basin should be performed ([ME-3](#)).

Management of Metastatic Melanoma

Metastatic melanoma is associated with a poor prognosis. Several chemotherapeutic agents have shown activity in patients with metastatic melanoma including dacarbazine and temozolomide as single agents as well as combination chemotherapy regimens.⁴⁶ However, little consensus currently exists regarding standard therapy for those approximately 8,000 patients diagnosed yearly in United States with metastatic melanoma, which most likely reflects the low level of activity of all available agents.^{47,48}

Dacarbazine still remains a standard of care in community practice, and has been used as a standard for comparing the efficacy of new regimens.⁴⁹ A small randomized trial has demonstrated similar response rates and survival for dacarbazine and temozolomide treatment of metastatic melanoma.⁵⁰ Both dacarbazine and temozolomide result in response rates of approximately 10-20%, with median response duration of 3-4 months.^{46,50,51}

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 12-21%. IL-2 was able to induce durable complete responses in approximately 6% of patients and partial responses in 10% of patients with metastatic melanoma, albeit with high levels of toxicity.⁵²

Initial reports of combination chemotherapy regimens such as CVD (dacarbazine plus cisplatin and vinblastine) or Dartmouth regimen (dacarbazine, carmustine, cisplatin and tamoxifen) suggested high response rates.^{53,54} Subsequent clinical trials have not replicated these high response rates. In phase III randomized trials, survival following treatment with either the standard CVD or Dartmouth regimen was not superior to dacarbazine alone.^{55,56}

Biochemotherapy is the combination of chemotherapy and biological agents.^{57,58} In initial single institutional phase II trials, CVD biochemotherapy (cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2) produced an overall response rate of 64% and a complete response rate of 21% in patients with metastatic melanoma.⁵⁸ 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.⁵⁹ Biochemotherapy was substantially more toxic than CVD. Additional attempts to decrease toxicity of biochemotherapy by administering subcutaneous outpatient IL-2 also have not shown a substantial benefit of biochemotherapy versus chemotherapy alone.^{60,61,62}

NCCN Recommendations

Stage III: In-transit metastases

Many different treatment options are available for patients presenting with stage III in-transit metastases ([ME-3](#)).

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 can be considered because of the high probability of occult nodal involvement.⁶³ 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 finite number of in-transit metastases, particularly dermal lesions, which are not amenable to complete surgical excision, intralesional local injections with bacillus Calmette-Guérin (BCG)⁶⁴ or interleukin-2⁶⁵ can be considered (category 2B). CO₂ laser ablation (category 2B) may be used in selected patients.

Another treatment option for patients with unresectable in-transit metastases is hyperthermic isolated limb perfusion with melphalan (category 2B).^{66,67,68} Isolation limb infusion has been reported by Thompson et al to be a simpler technique with response rates comparable to limb perfusion.⁶⁹

Radiation therapy (RT) 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) or a clinical trial.

Distant metastases (Stage IV)

Treatment for stage IV metastatic melanoma depends on whether disease is limited or disseminated ([ME-8](#)).

Resection, if feasible, followed by adjuvant treatment is recommended for limited metastatic disease.⁷⁰ Appropriate adjuvant treatment options are discussed in the following section. Alternatively, limited metastatic disease can be treated with systemic therapy. First-line therapy options include ([ME-D](#)): (i) clinical trial (preferred); (ii) single-agent systemic therapy (category 2B) with dacarbazine or high-dose interleukin-2 or temozolomide; (3) dacarbazine or temozolomide-based combination chemotherapy or biochemotherapy (including cisplatin and vinblastine with or without interleukin-2, interferon alfa) (category 2B); or (4) best supportive care.

In selected patients with a solitary site of visceral metastatic melanoma, a short period of observation 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 similar to those treated with immediate resection. Disseminated disease is treated based on the presence or absence of brain metastases. First-line therapy is recommended for residual disease following incomplete resection for limited metastases or for disseminated disease without brain metastases.

Finally, for patients with unresectable distant metastatic disease that persists after first-line therapy, the following options may be offered as second-line therapy ([ME-8](#)) as clinically appropriate, based on the patient's performance status: (i) clinical trial (preferred); (ii) single-agent systemic therapy (category 2B) with dacarbazine or high-dose

interleukin-2 or temozolomide; (3) dacarbazine or temozolomide-based combination chemotherapy or biochemotherapy (including cisplatin and vinblastine with or without interleukin-2, interferon alfa) (category 2B); or (4) best supportive care.

For patients with brain metastases, surgery or RT may be considered based on symptoms, number of lesions present, and location of the lesions, as described in [NCCN Central Nervous System Cancers Guidelines](#). Other treatment options include a clinical trial (preferred), systemic therapy (first line or second-line therapy) for patients with good performance status as clinically indicated, or best supportive care ([NCCN Palliative Care Guidelines](#)).

In symptomatic patients, surgical resection or radiation of metastases may be considered for palliation and management of symptoms, for instance caused by gastrointestinal bleeding, ulcerated cutaneous metastases or bulky adenopathy.

Adjuvant Treatment for Melanoma

Low-Dose and Intermediate-Dose Interferon

In the first major randomized trial conducted by WHO Melanoma Programme,⁷¹ 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 and also a trend towards an increase in overall survival.⁷² In another prospective randomized study, adjuvant interferon prolonged disease-free survival for all patients at the median follow-up of 41 months.⁷³

Two other randomized clinical trials (AIM HIGH Study and EORTC 18952) have 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.⁷⁴ No significant improvement in progression-free survival was reported for intermediate-dose in EORTC 18952.⁷⁵

High-Dose Interferon

High dose interferon was evaluated in three randomized clinical trials. ECOG 1684 demonstrated an improvement in both disease-free and overall survival with 6.9 years median follow-up.⁷⁶ The results of a larger follow-up trial, ECOG 1690, showed a relapse-free survival advantage, but no overall survival advantage, for high-dose interferon alfa-2b.⁷⁷ E1694 compared high-dose interferon alfa-2b with an experimental vaccine. At approximately 2 years of median follow-up, the interferon alfa-2b group showed a statistically significant improvement in relapse-free survival and overall survival.⁷⁸

A recent study in 200 patients with melanoma (stage IIB, IIC, or III) reported that those who had auto antibodies or clinical manifestations of autoimmunity after treatment with high-dose interferon alfa-2b had improved survival (both relapse free and overall survival).⁷⁹

Review of 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.⁸⁰ A pooled analysis of E1684 and E1690 confirmed an improvement in relapse-free survival (two-sided log-rank *P* value = .006) but did not find a significant improvement in overall survival.⁸¹

Thus, the ultimate role of high-dose adjuvant interferon alfa on survival of patients with stage II or III melanoma remains incompletely defined. 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.^{82,83}

NCCN Recommendations

Most patients with in-situ or early-stage melanoma will be cured by primary excision alone. Thus, no standard adjuvant therapy is recommended for patients with in-situ or node-negative primary melanoma (1-4 mm thick or 1 mm thick or less with or without ulceration). For patients with node-negative melanoma who are at risk for recurrence (4.0 mm thick or less with ulceration, Clark level IV-V) adjuvant treatment options include a clinical trial or observation ([ME-2](#)).

The NCCN panel recommended that adjuvant treatment options include a clinical trial, high-dose adjuvant interferon alfa-2b (category 2B), and observation for patients with localized melanomas more than 4.0 mm thick or with stage III nodal metastases ([ME-3](#)). High-dose adjuvant interferon alfa-2b is a category 2B recommendation, because trial results have not consistently shown an increase in overall survival.

Adjuvant hypofractionated RT to the nodal bed should be considered (category 2B) for stage IIIC patients in the setting of multiple positive nodes or extranodal soft-tissue extension, especially in the head and neck region. However, this recommendation is based on retrospective, uncontrolled observations rather than on prospective, randomized data.⁸⁴

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, high-dose interferon alfa-2b (category 2B), or observation as adjuvant treatment options ([ME-8](#)).

Follow-up

Skin cancer preventive education including sun protection measures should be promoted for patients with melanoma and their families.⁸⁵

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 ([ME-5](#)). Frequency of dermatologic surveillance should be determined individually, based on risk factors, including skin type, family history, presence of dysplastic nevi, and history of nonmelanoma skin cancers. Clinicians should also consider educating patients about monthly self-exam of their skin and lymph nodes.

For patients with stage IA melanoma, comprehensive H&P (with specific emphasis on the regional nodes and skin) should be performed every 3-12 months as clinically indicated.⁸⁶ No specific radiologic investigations to detect occult distant disease are recommended, which is consistent with the NIH Consensus Panel statement.¹³

For patients with stage IB-III melanomas, a comprehensive H&P (with emphasis on the regional nodes and skin) should be performed every 3-6 months for 3 years; then every 4-12 months for 2 years; and annually (at least) thereafter, as clinically indicated. Chest x-ray, serum

LDH, liver function tests, and complete blood count may be performed every 3-12 months, at the discretion of the physician. The consensus of the panel was that routine follow-up CT scans were unnecessary; however, they certainly should be performed to follow-up specific signs and symptoms. The recommendations recognize the extremely low yield of routine screening chest X-rays and screening blood work in this population.⁸⁷

Consensus Panel Opinions

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;⁸⁸ it 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, late recurrence (more than 10 years later) is well documented for melanoma.⁸⁹ 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 4-8% 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 elective lymph node dissection. 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 nonmelanoma primary malignancies, patient education, and documentation of the results of treatment.⁹⁰⁻⁹²

Recurrence

Initial clinical recurrence should be confirmed pathologically by FNA 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 prognostically similar to recurrent regional disease.

For 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 is recommended, with or without lymphatic mapping and sentinel node biopsy, appropriate to the micro staging of the recurrence. For a local recurrence after an adequate prior wide excision, the workup (including H&P and laboratory investigation) is shown on [ME-6](#). In the absence of extra regional disease, surgical excision with negative margin is recommended for local recurrence and for limited recurrent in-transit disease ([ME-6](#)). Lymphatic mapping with sentinel node biopsy may be considered in these patients according to thickness or on an individual basis. After complete resection of a local recurrence following adequate primary therapy, adjuvant treatment options include clinical trial, high-dose interferon alfa-2b (category 2B), or observation.

In-Transit Recurrence

For patients with in-transit recurrence ([ME-6](#)), the workup is similar to the one previously outlined for patients presenting with in-transit disease. A surgically resectable recurrence should be re-excised with negative margins; sentinel node biopsy should be considered.

Unresectable recurrence could be treated with any one of the following options: intralesional injections with BCG or interleukin-2 (category 2B), CO₂ laser ablation (category 2B), hyperthermic limb perfusion with melphalan (category 2B), clinical trial or systemic therapy. In unusual circumstances, RT 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, high-dose interferon alfa-2b (category 2B), or observation.

Regional Nodal Recurrence

For patients presenting regional with nodal recurrence, the clinical diagnosis should be confirmed preferably by FNA biopsy. Workup of these patients includes FNA (preferred) or lymph node biopsy, chest x-ray and/or chest CT, LDH, pelvic CT if the inguinofemoral nodes are clinically positive, and abdominal/pelvic CT, MRI of the brain, and PET scan as indicated ([ME-7](#)).

For patients who have not undergone prior lymph node dissection, a complete lymph node dissection is appropriate ([ME-C](#)). 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 (category 2B) may decrease the likelihood of further regional nodal recurrences and can be considered in selected patients with completely

resected nodal recurrence, with risk factors such as multiple involved nodes or extranodal disease, especially in the head and neck region. Options for patients with incompletely resected nodal recurrence or those with unresectable recurrence are shown on [ME-7](#).

Distant Recurrence

For patients presenting with distant recurrence ([ME-8](#)), the workup and treatment options are similar to those outlined previously for patients presenting initially with stage IV metastatic disease.

Summary

The NCCN Melanoma Guidelines represent an effort to distill and simplify an enormous body of knowledge and experience into fairly simple management algorithms. In general, treatment recommendations for primary tumors are based on better data than the recommendations for treating recurrent disease. Few, if any, firm recommendations can be made about more controversial issues for the melanoma patient, such as the extent of workup or intensity of follow-up. These guidelines are intended as a point of departure, recognizing that all clinical decisions about individual patient management must be tempered by the clinician’s judgment and other factors, such as local resources and expertise as well as the individual patient’s needs, wishes, and expectations. Furthermore, the NCCN Melanoma Guidelines undergo annual revision and are continually revised as new data become available.

Disclosures for the NCCN Melanoma Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers’ bureau participation. Members of the panel indicated that they have received support from the following: Novartis Pharmaceuticals and Schering-Plough. Some panel members do not

accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer Statistics, 2007. *CA Cancer J Clin*. 2007;57(1):43-66.
2. Desmond RA, Soong SJ. Epidemiology of malignant melanoma. *Surg Clin North Am* 2003;83:1-29.
3. Rigel DS, Rivers JK, Kopf AW, et al. Dysplastic nevi - markers for increased risk for melanoma. *Cancer* 1989;63:386-389.
4. Tsao H, Atkins MB, Sober AJ. Management of Cutaneous Melanoma. *N Engl J Med*. 2004;351(10):998-1012.
5. Melanoma and other skin cancers. Eric H. Jensen, EH, Kim A. Margolin, KA, Vernon K. Sondak, VK. In: Pazdur R, Hoskins WJ, Coia LR, Wagman LD, eds. *Cancer Management: A Multidisciplinary Approach*. 9th edition, 2005:531-562.
6. Ivry GB, Ogle CA, Shim EK. Role of Sun Exposure in Melanoma. *Dermatologic Surgery*. 2006;32(4):481-492.
7. Balch CM, Soong S-J, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 2001;19:3622-3634.
8. Huang X, Soong S, McCarthy WH, et al. Classification of localized melanoma by the exponential survival trees method. *Cancer* 1997;79:1122-1128.
9. Balch CM, Buzaid AC, Soong S-J, et al. Final Version of the American Joint Committee on Cancer Staging System for Cutaneous Melanoma. *J Clin Oncol*. 2001;19(16):3635-3648).
10. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*, 6th ed. New York: Springer-Verlag, 2002.
11. AAD Practice Management. Guidelines of care for primary cutaneous melanoma. Task Force: Sober AJ, Chuang T-Y, Duvic M, et al. Available at: [AAD - Guidelines of Care for Primary Cutaneous Melanoma](#). Accessed on February 28th, 2007.
12. Naeyaert JM, Brochez L. Dysplastic Nevi. *N Engl J Med*. 2003;349(23):2233-2240.
13. National Institutes of Health. After treatment of early melanoma, should patients and family members be followed? Why and how? NIH Consensus Statement 1992;10:1-26.
14. Wang TS, Johnson TM, Cascade PN, et al. Evaluation of staging chest radiographs and serum lactate dehydrogenase for localized melanoma. *J Am Acad Dermatol* 2004;51:399-405.
15. Kuvshinoff BW, Kurtz C, Coit DG. Computed tomography in evaluation of patients with stage III melanoma. *Ann Surg Oncol* 1997;4:252-258.
16. Buzaid AC, Sandler AB, Mani S, et al. Role of computed tomography in the staging of primary melanoma. *J Clin Oncol* 1993;11:638-643.
17. Johnson TM, Fader DJ, Chang AE, et al. Computed tomography in staging patients with melanoma metastatic to regional nodes. *Ann Surg Oncol* 1997;4:396-402.
18. Aloia TA, Gershenwald JE, Andtbacka RH, et al. Utility of Computed Tomography and Magnetic Resonance Imaging Staging Before Completion Lymphadenectomy in Patients With Sentinel Lymph Node-Positive Melanoma. *J Clin Oncol*. 2006;24(18):2858-2865.
19. Sirott MN, Bajorin DF, Wong GY, et al. Prognostic factors in patients with metastatic malignant melanoma. A multivariate analysis. *Cancer* 1993;72:3091-3098.
20. Veronesi U, Cascinelli N. Narrow excision (1-cm margin): A safe procedure for thin cutaneous melanoma. *Arch Surg* 1991;126:438-441.
21. Balch CM, Urist MM, Karakousis CP, et al. Efficacy of 2-cm surgical margins for intermediate thickness melanomas (1 to 4 mm) - results of

- a multi-institutional randomized surgical trial. *Ann Surg* 1993;218:262-267.
22. Thomas JM, Newton-Bishop J, A'Hern R, et al. Excision Margins in High-Risk Malignant Melanoma. *N Engl J Med*. 2004;350(8):757-766.
23. Johnson TM, Headington JT, Baker SR, et al. Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the square procedure. *J Am Acad Dermatol* 1997;37:758-764.
24. Zitelli JA, Brown C, Hanusa BH. Mohs micrographic surgery for the treatment of primary cutaneous melanoma. *J Am Acad Dermatol* 1997;37:236-245.
25. Johnson, Sondak, Bichakjian, Sabel. The role of sentinel lymph node biopsy for melanoma: Evidence assessment. *Journal of the American Academy of Dermatology*. 2006;54(1):19-27.
26. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg* 2005;242:302-311; discussion 311-313.
27. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-Node Biopsy or Nodal Observation in Melanoma. *N Engl J Med*. 2006;355(13):1307-1317.
28. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. *Ann Surg* 1999;230:453-463.
29. Kang JC, Wanek LA, Essner R, et al. Sentinel lymphadenectomy does not increase the incidence of in-transit metastases in primary melanoma. *J Clin Oncol* 2005;23:4764-4770.
30. Edwards MJ, Matrin KD, McMasters KM. Lymphatic mapping and sentinel lymph node biopsy in the staging of melanoma. *Surg Oncol* 1998;7:51-57.
31. Glass FL, Cottam JA, Reintgen DS. Lymphatic mapping and sentinel node biopsy in the management of high-risk melanoma. *J Am Acad Dermatol* 1998;39:603-610.
32. Paek SC, Griffith KA, Johnson TM, et al. The impact of factors beyond Breslow depth on predicting sentinel lymph node positivity in melanoma. *Cancer*. 2007;109(1):100-108.
33. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. *Ann Surg* 1999;230:453-463.
34. Kang JC, Wanek LA, Essner R, et al. Sentinel lymphadenectomy does not increase the incidence of in-transit metastases in primary melanoma. *J Clin Oncol* 2005;23:4764-4770.
35. Edwards MJ, Matrin KD, McMasters KM. Lymphatic mapping and sentinel lymph node biopsy in the staging of melanoma. *Surg Oncol* 1998;7:51-57.
36. Glass FL, Cottam JA, Reintgen DS. Lymphatic mapping and sentinel node biopsy in the management of high-risk melanoma. *J Am Acad Dermatol* 1998;39:603-610.
37. Wong SL, Brady MS, Busam KJ, et al. Results of sentinel lymph node biopsy in patients with thin melanoma. *Ann Surg Oncol* 2006;13:302-309.
38. Cascinelli N, Bombardieri E, Bufalino R, et al. Sentinel and Nonsentinel Node Status in Stage IB and II Melanoma Patients: Two-Step Prognostic Indicators of Survival. *J Clin Oncol*. 2006;24(27):4464-4471.
39. Lee JH, Essner R, Torisu-Itakura H, Wanek L, Wang H, Morton DL. Factors Predictive of Tumor-Positive Nonsentinel Lymph Nodes After Tumor-Positive Sentinel Lymph Node Dissection for Melanoma. *J Clin Oncol*. 2004;22(18):3677-3684.

40. Sim FH, Taylor WF, Pritchard DJ, et al. Lymphadenectomy in the management of stage I malignant melanoma: A prospective randomized study. *Mayo Clin Proc* 1986;61:697-705.
41. Veronesi U, Cascinelli N, Adamus J, et al. Thin stage I primary cutaneous malignant melanoma: Comparison of excision with margins of 1 or 3 cm. *N Engl J Med* 1988;318:1159-1162 [published erratum appears in *N Engl J Med* 1991;325:292].
42. Balch CM, Soong SJ, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg* 1996;224:255-263.
43. Coit DG, Brennan MF. Extent of lymph node dissection in melanoma of the trunk or lower extremity. *Arch Surg* 1989;124:162-166.
44. Shen P, Conforti AM, Essner R, et al. Is the node of Cloquet the sentinel node for the iliac/obturator node group? *Cancer J* 2000;6:93-97.
45. Coit DG. Extent of groin dissection for melanoma. *Surg Oncol Clin N Am* 1992;1:271-280.
46. Atallah E, Flaherty L. Treatment of metastatic malignant melanoma. *Curr Treat Options Oncol* 2005;6:185-93.
47. Houghton AN, Coit DG, Daud A, et al. Melanoma. *J Natl Compr Canc Netw* 2006;4:666-84.
48. Eigentler TK, Caroli UM, Radny P, et al. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomized clinical trials. *Lancet Oncol* 2003;4:748-59.
49. Serrone L, Zeuli M, Sega FM, et al. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. *J Exp Clin Cancer Res* 2000;19:21-34.
50. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000;18:158-166.
51. Bajetta E, Del Vecchio M, Bernard-Marty C, et al. Metastatic melanoma: chemotherapy. *Semin Oncol* 2002;29:427-45.
52. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999;17:2105-16.
53. Legha SS, Ring S, Papadopoulos N, Plager C, Chawla S, Benjamin R. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. *Cancer* 1989;64(10):2024-2029.
54. Mc Clay EF, Mastrangelo MJ, Bellet RE, et al. Combination chemotherapy and hormonal therapy in the treatment of malignant melanoma. *Cancer Treat Rep* 1987;71:465-69.
55. Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 1999;17:2745-2751.
56. Atkins MB, Lee S, Flaherty LE, et al. A prospective randomized phase III trial of concurrent biochemotherapy (BCT) with cisplatin, vinblastine, dacarbazine (CVD), IL-2 and interferon alpha-2b (IFN) versus CVD alone in patients with metastatic melanoma (E3695): an ECOG-coordinated intergroup trial. [Abstract] *Proceedings of the American Society of Clinical Oncology* 22: A-2847, 2003.
57. Legha SS, Ring S, Bedikian A, et al. Treatment of metastatic melanoma with combined chemotherapy containing cisplatin, vinblastine and dacarbazine (CVD) and biotherapy using interleukin-2 and interferon-alpha. *Ann Oncol* 1996;7:827-35.
58. Legha SS, Ring S, Eton O, et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. *J Clin Oncol* 1998;16:1752-1759.

59. Eton O, Legha SS, Bedikian AY, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. *J Clin Oncol* 2002;20:2045-52.
60. Ridolfi R, Chiarion-Sileni V, Guida M, et al. Cisplatin, dacarbazine with or without subcutaneous interleukin-2, and interferon alpha-2b in advanced melanoma outpatients: results from an Italian multicenter phase III randomized clinical trial. *J Clin Oncol* 2002;20:1600-7.
61. Keilholz U, Punt CJ, Gore M, et al. Dacarbazine, cisplatin, and interferon-alfa-2b with or without interleukin-2 in metastatic melanoma: a randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. *J Clin Oncol* 2005;23:6747-55.
62. Bajetta E, Del Vecchio M, Nova P, et al. Multicenter phase III randomized trial of polychemotherapy (CVD regimen) versus the same chemotherapy (CT) plus subcutaneous interleukin-2 and interferon-alpha2b in metastatic melanoma. *Ann Oncol* 2006; 17:571-7.
63. Yao KA, Hsueh EC, Essner R, et al. Is sentinel lymph node mapping indicated for isolated local and in-transit recurrent melanoma? *Ann Surg* 2003;238:743-747.
64. Tan JK, Ho VC. Pooled analysis of the efficacy of bacille Calmette-Guerin (BCG) immunotherapy in malignant melanoma. *J Dermatol Surg Oncol* 1993;19:985-990.
65. Radny P, Caroli UM, Bauer J, et al. Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. *British Journal of Cancer* 2003;89:1620-1626.
66. Fraker DL, Coit DG. Isolated perfusion of extremity tumors. In: Lotze MT, Rubin JT, eds. *Regional Therapy of Advanced Cancer*. Philadelphia, Lippincott-Raven, 1997: 333-350.
67. Lindner P, Doubrovsky A, Kam PC, et al. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. *Ann Surg Oncol* 2002;9:127-136.
68. Lens MB, Dawes M. Isolated limb perfusion with melphalan in the treatment of malignant melanoma of the extremities: a systematic review of randomized controlled trials. *Lancet Oncology*. 2003;4:359-364.
69. Thompson JF, Kam PC. Isolated limb infusion for melanoma: A simple but effective alternative to isolated limb perfusion. *Journal of Surgical Oncology*. 2004;88(1):1-3.
70. Allen PJ, Coit DG. The surgical management of metastatic melanoma. *Ann Surg Oncol*, 2002;9:762-770.
71. Cascinelli N, Belli F, MacKie RM, Santinami M, Bufalino R, Morabito A. Effect of long-term adjuvant therapy with interferon alpha-2a in patients with regional node metastases from cutaneous melanoma: a randomized trial. *Lancet*. 2001;358(9285):866-869.
72. Grob JJ, Dreno B, de la Salmoniere P, et al. Randomized trial of interferon alpha-2a as adjuvant therapy in resected primary melanoma thicker than 1.5 mm without clinically detectable node metastases. French Cooperative Group on Melanoma. *Lancet*. 1998;351(9120):1905-1910.
73. Pehamberger H, Soyer H, Steiner A, et al. Adjuvant interferon alfa-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. *J Clin Oncol*. 1998;16(4):1425-1429.
74. Hancock BW, Wheatley K, Harris S, et al. Adjuvant interferon in high-risk melanoma: the AIM HIGH Study--United Kingdom Coordinating Committee on Cancer Research randomized study of adjuvant low-dose extended-duration interferon alfa-2a in high-risk resected malignant melanoma. *J Clin Oncol* 2004;22:53-61.
75. Eggermont AM, Suci S, MacKie R, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomized controlled trial. *The Lancet* 2005;366:1189-1196.

76. Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: The Eastern Cooperative Oncology Group Trial EST-1684. *J Clin Oncol* 1996;14:7-17.
77. Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E 1690/S9111/C9190. *J Clin Oncol* 2000;18:2444-2458.
78. Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2- KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol* 2001;19:2370-2380.
79. Gogas H, Ioannovich J, Dafni U, et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. *N Engl J Med* 2006;354:709-718.
80. Lens MB, Dawes M. Interferon alpha therapy for malignant melanoma: A systematic review of randomized clinical trials. *J Clin Oncol* 2002;20:1818-1825.
81. Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res* 2004;10:1670-1677.
82. Hurley KE, Chapman PB. Helping Melanoma Patients Decide Whether to Choose Adjuvant High-Dose Interferon-alpha 2b. *Oncologist*. 2005;10(9):739-742.
83. Gray RJ, Pockaj BA, Kirkwood JM. An Update on Adjuvant Interferon for Melanoma. *Cancer Control*. 2002;9(1):16-21.
84. Strom EA, Ross MI. Adjuvant radiation therapy after axillary lymphadenectomy for metastatic melanoma: Toxicity and local control. *Ann Surg Oncol* 1995;2:445-449.
85. Rhodes AR. Public education and cancer of the skin. What do people need to know about melanoma and nonmelanoma skin cancer? *Cancer*. 1995;75(S2):613-636.
86. Basseres N, Grob JJ, Richard MA, et al. Cost-effectiveness of surveillance of stage I melanoma. *Dermatology* 1995;191:199-203.
87. Weiss M, Loprinzi CL, Greagan ET, et al. Utility of follow-up tests for detecting recurrent disease in patients with malignant melanoma. *JAMA* 1995;274:1703-1705.
88. Ferrone CR, Ben Porat L, Panageas KS, et al. Clinicopathological features of and risk factors for multiple primary melanomas. *JAMA* 2005;294:1647-1654.
89. Crowley NJ, Seigler HF. Late recurrence of malignant melanoma. Analysis of 168 patients. *Ann Surg* 1990;212:173-177.
90. Kang S, Barnhill R, Mihm MC, et al. Multiple primary cutaneous melanoma. *Cancer* 1992;70:1911-1916.
91. Fawzy FI, Fawzy NW, Hyun CS, et al. Malignant melanoma: Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. *Arch Gen Psychiatr* 1993;50:681-689.
92. Gutman M, Cnaan A, Inbar M, et al. Are malignant melanoma patients at higher risk for a second cancer? *Cancer* 1991;68:660-665.