NCCN National Comprehensive Cancer Network®

The NCCN

Melanoma

Clinical Practice Guidelines in Oncology™

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In 2008, an estimated 62,480 new cases of melanoma will have been diagnosed and approximately 8420 patients will have died 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 more rapidly in women than any other malignancy except lung cancer. For someone born in the United States in 2005, the lifetime risk for developing melanoma may be as high as 1 in 55.[2] Melanoma ranks second to adult leukemia in terms of loss of years of potential life, per death. The median age at diagnosis is 59 years.

Melanoma Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, melanoma, skin cancer, biopsy, surgical excision, adjuvant therapy, metastases, radiation therapy, chemotherapy, interferon, sentinel lymph node, margin, lymph node dissection, pathology *(JNCCN* 2009;7:250–275)

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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.

Please Note

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 representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Melanoma Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and on-line. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Melanoma Guidelines Panel members can be found on page 275. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.nccn.org.

Risk factors for melanoma include family history, prior melanoma, multiple clinically atypical moles or dysplastic nevi,[3,4] inherited genetic mutations, and sun exposure.[5] Individuals unable to tan and those with fair skin that sunburns easily have a greater risk for developing melanoma.[6,7] However, melanoma can occur in any ethnic group and in areas of the body that have not had substantial sun exposure.

As with nearly all malignancies, the outcome of melanoma initially depends on the stage at presentation.[8] An estimated 82% to 85% of patients present with localized disease, 10% to 13% with regional disease, and 2% to 5% with distant metastatic disease. In general, the prognosis is excellent for patients who present with localized disease and primary tumors 1.0 mm or less in thickness, with 5-year survival achieved in more than 90% of patients. For patients with localized melanomas more than 1.0 mm in thickness, survival rates range from 50% to 90%. The likelihood of regional nodal involvement increases with increasing tumor thickness. When regional nodes are involved, survival rates are roughly halved. However, for stage III disease, 5-year survival rates range from 20% to 70%, depending primarily on the nodal tumor burden. Long-term survival in patients with distant metastatic melanoma, taken as a whole, is less than 10%. However, even within stage IV, some patients have a more indolent clinical course that is biologically distinct from most patients with advanced disease.

By definition, these guidelines cannot incorporate all possible clinical variations and are not intended

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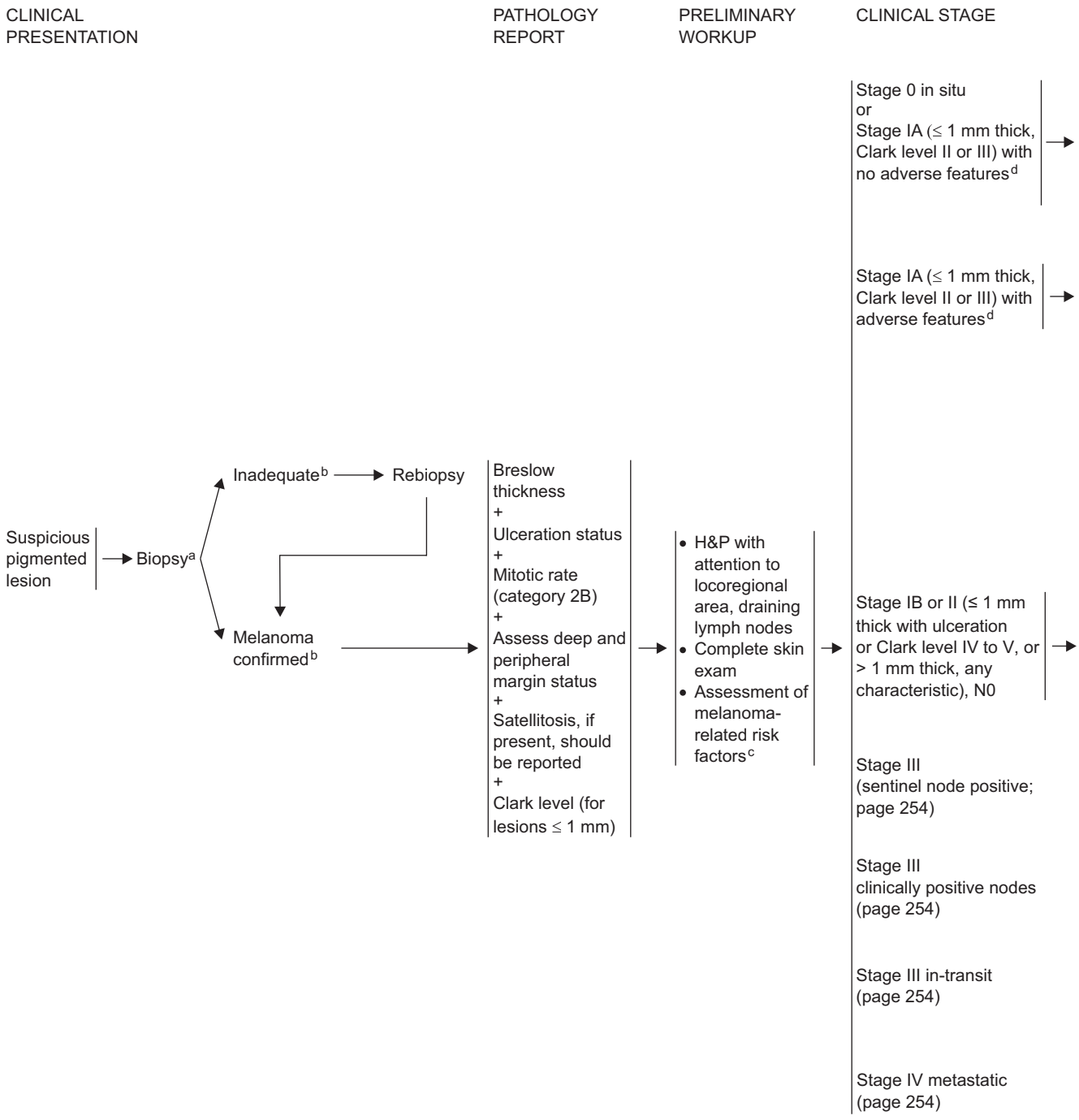

[a] See Principles of Biopsy (page 258).
[b] If diagnostic biopsy is inadequate for treatment decisions, rebiopsy may be appropriate.
[c] Risk factors for melanoma include family history of melanoma, prior primary melanoma, and other factors such as atypical moles/dysplastic nevi.
[d] Adverse features include positive deep margins, lymphovascular invasion (LVI), or mitotic rate ≥ 1 per mm^2.

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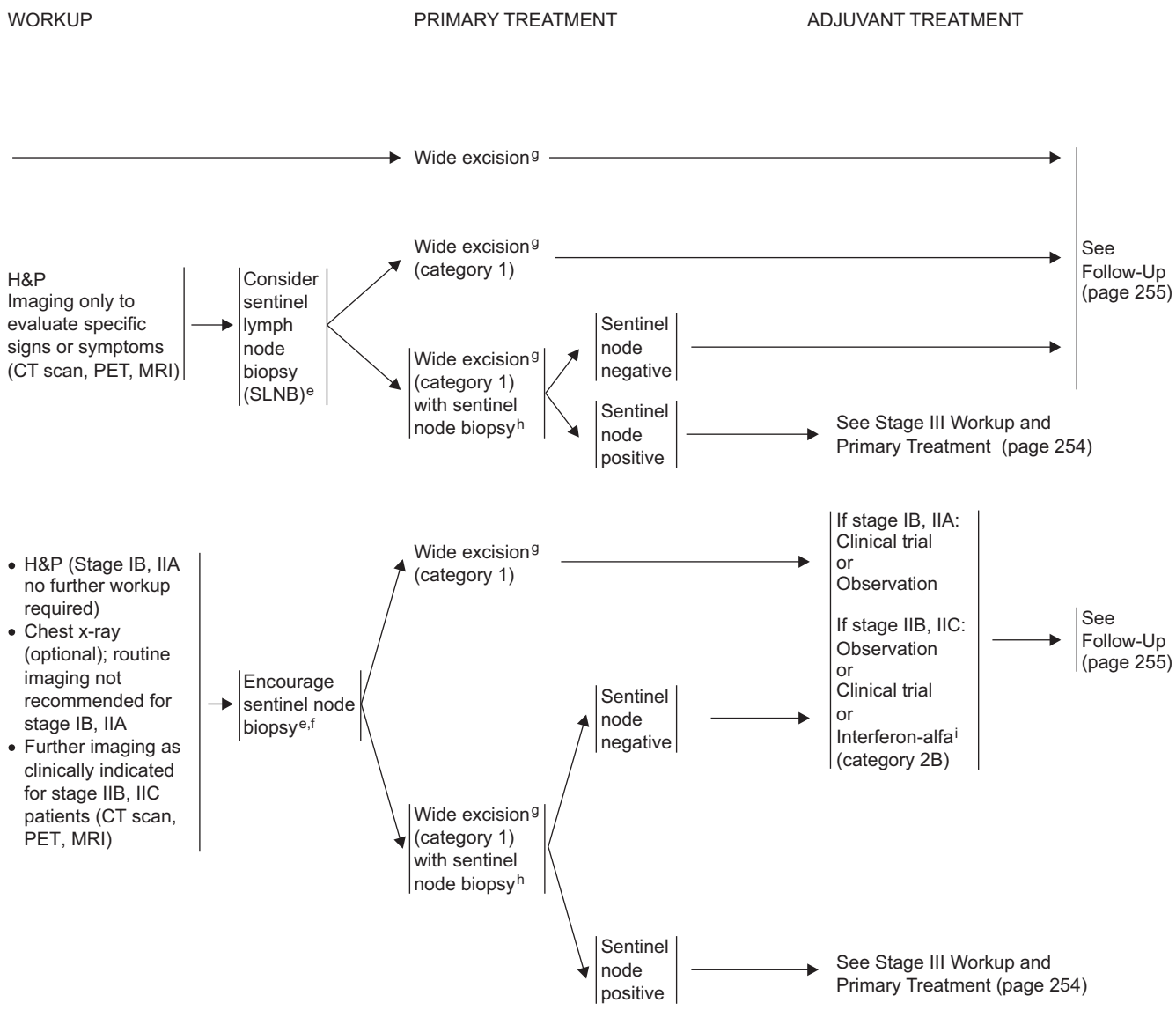
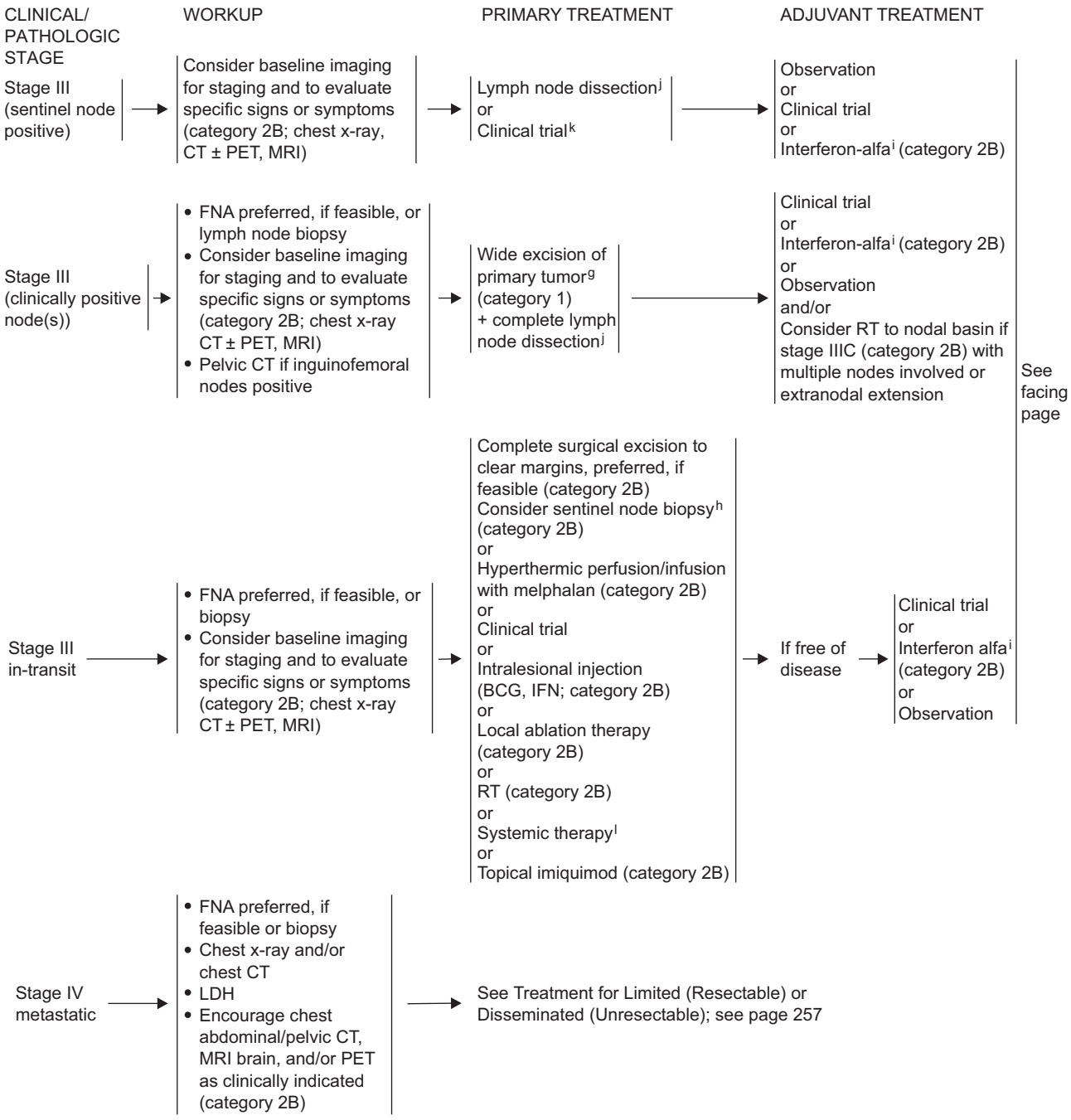


[e] Decision to not perform SLNB may be based on significant patient comorbidities, patient preference, or other factors.
[f] Sentinel node biopsy is an important staging tool, but its impact on overall survival is unclear.
[g] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (page 258).
[h] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[i] Interferon (IFN) has been associated with improved disease-free survival; however, its impact on overall survival is unclear.



[g] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (page 258).
[h] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[i] IFN has been associated with improved disease-free survival; however, its impact on overall survival is unclear.
[j] See Principles of Complete Lymph Node Dissection (page 259).
[k] Clinical trials assessing alternatives to complete lymph node dissection, such as careful observation.
[l] See Principles of Systemic Therapy for Advanced or Metastatic Melanoma (pages 259 and 260).

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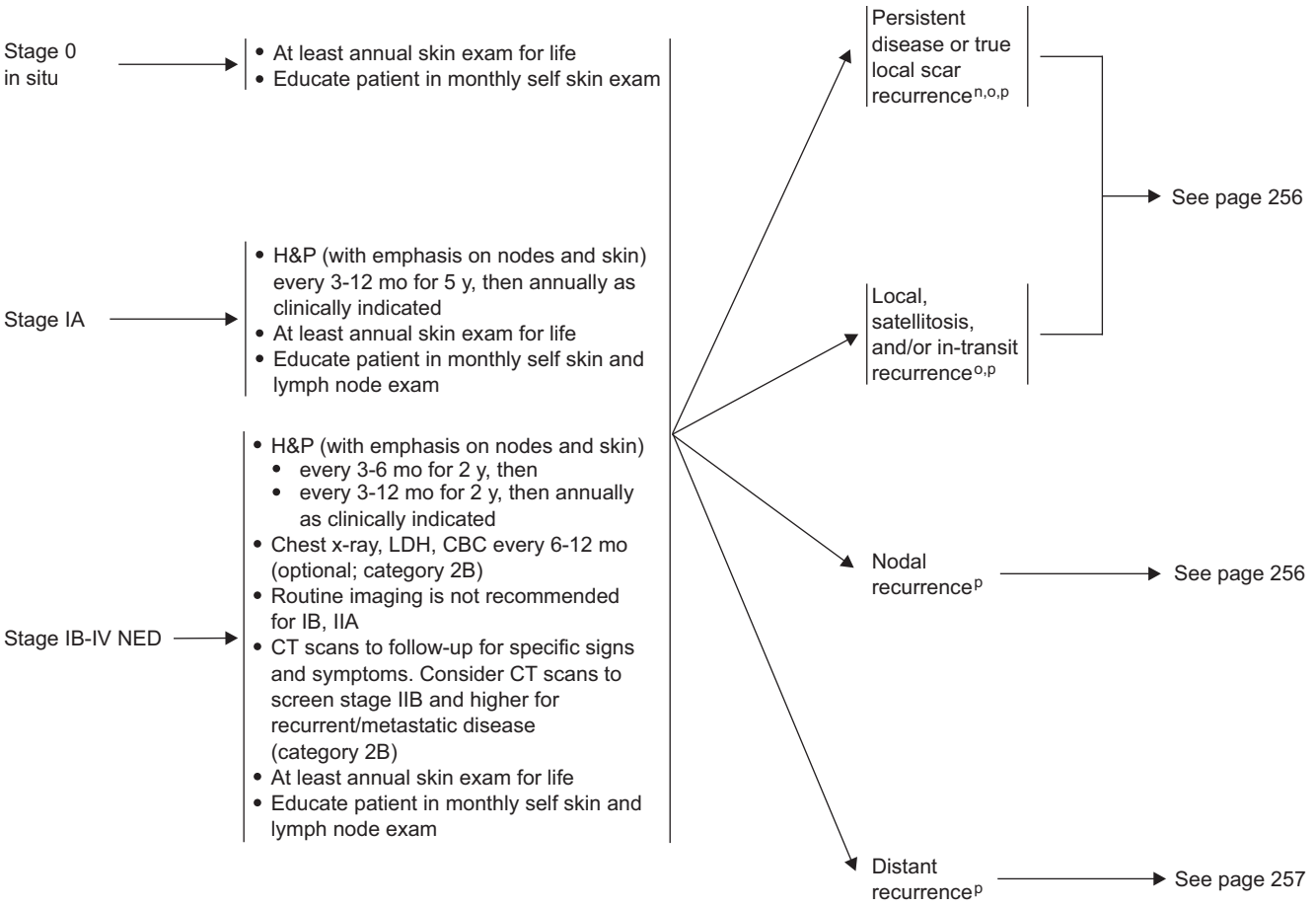
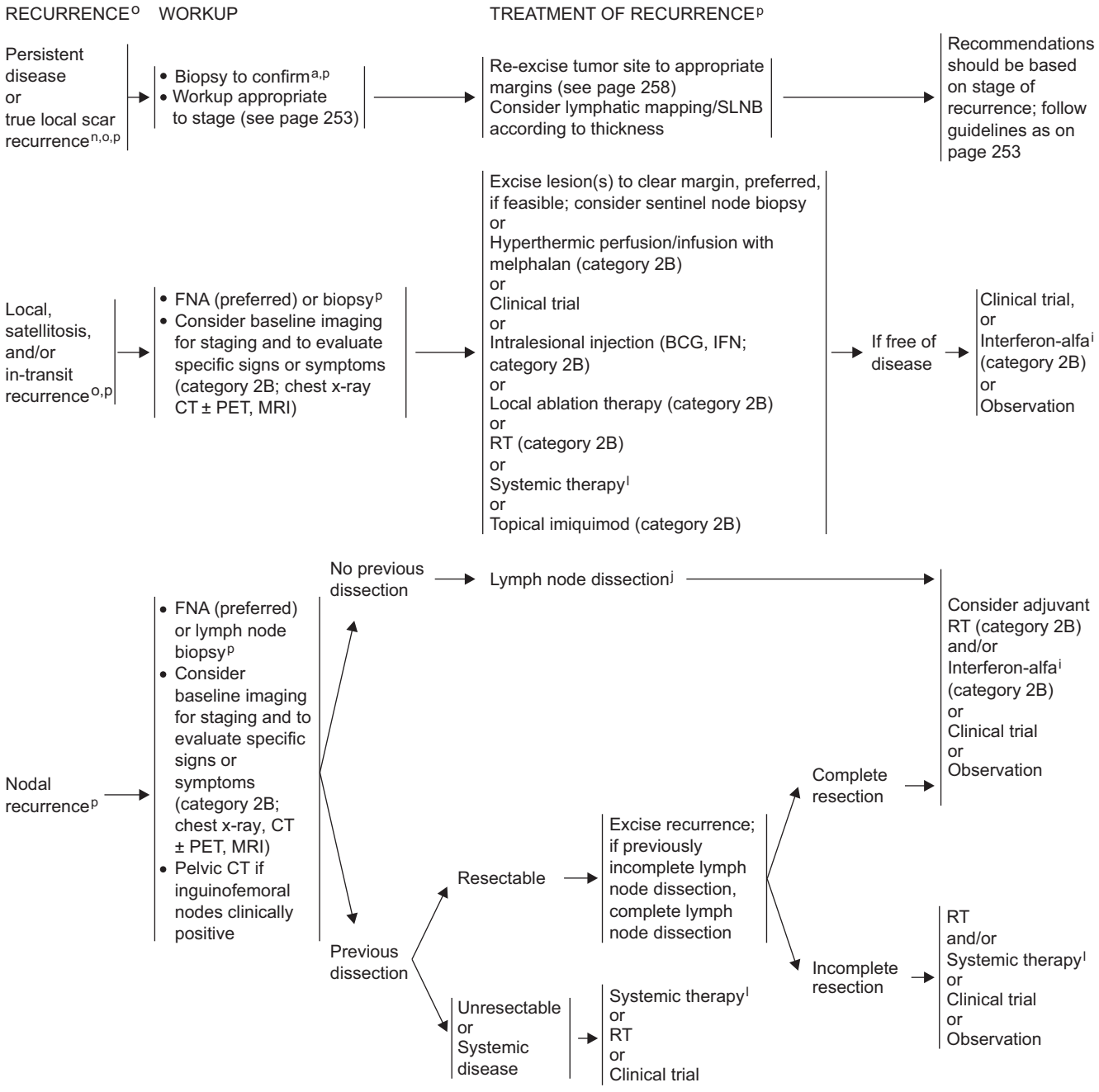


[m] Follow-up schedule influenced by risk for recurrence, prior primary melanoma, and family history of melanoma, and includes other factors, such as atypical moles, dysplastic nevi, and patient anxiety.
[n] Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.
[o] "Local recurrence" without in situ or radial growth phase, with deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar.
[p] Initial clinical recurrence should be confirmed pathologically whenever possible.



[a] See Principles of Biopsy (page 258).
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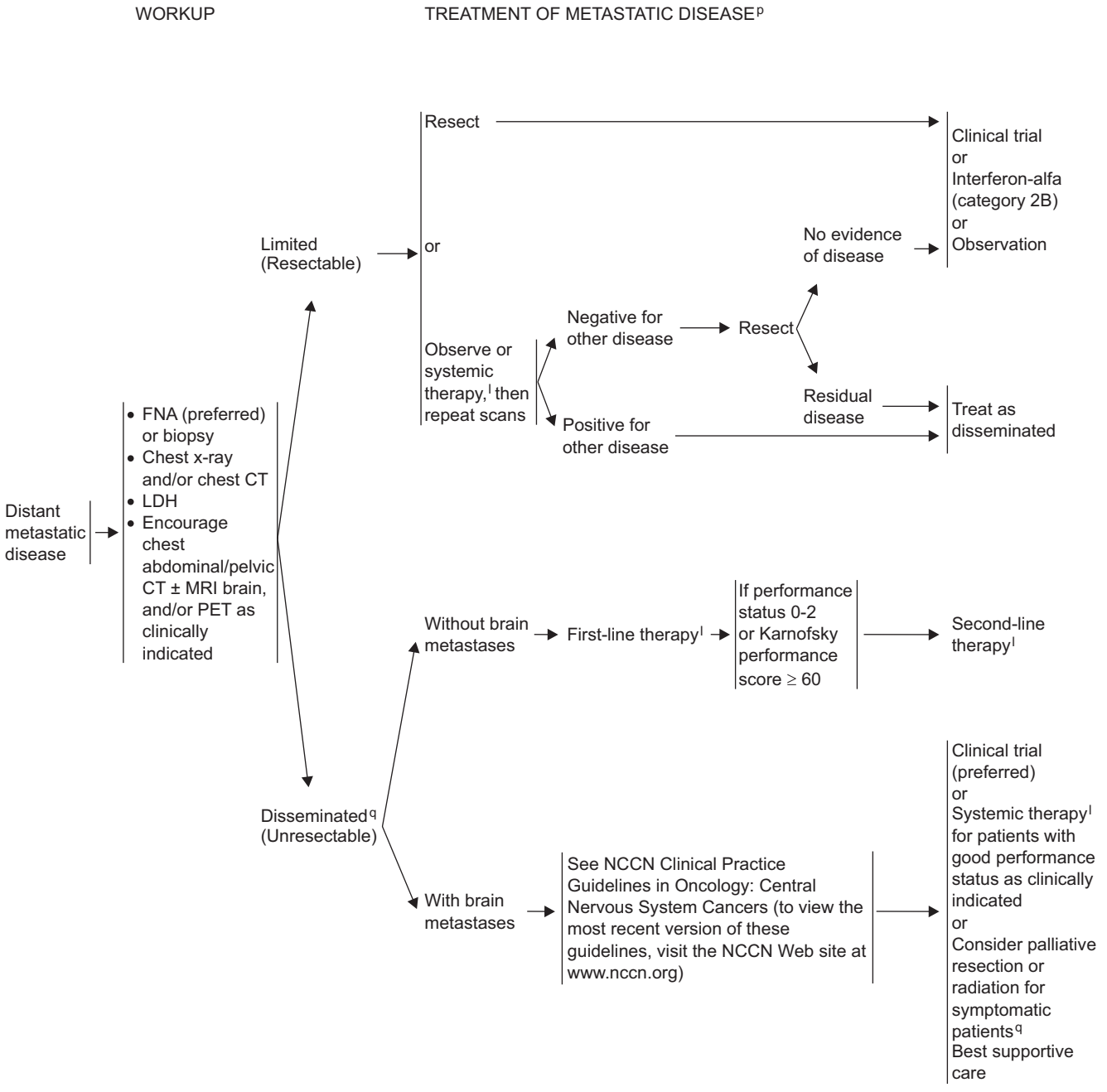

[l] See Principles of Systemic Therapy for Advanced or Metastatic Melanoma (pages 259 and 260).
[p] Initial clinical recurrence should be confirmed pathologically by biopsy whenever possible.
[q] In patients with disseminated metastases, resection or radiation may be indicated to palliate symptoms such as gastrointestinal bleeding or obstruction, ulcerated soft tissue cutaneous metastases, or bulky adenopathy.

PRINCIPLES OF BIOPSY

- Excisional biopsy (elliptical, punch, or saucerization) with 1-3 mm margins preferred. Avoid wider margins to permit accurate subsequent lymphatic mapping.
- Full thickness incisional or punch biopsy[1] of clinically thickest portion of lesion acceptable, in certain anatomic areas (e.g., palm/sole, digit, face, ear) or for very large lesions.
- Shave biopsy[1,2] may compromise pathologic diagnosis and complete assessment of Breslow thickness, but is acceptable when the index of suspicion is low.
- 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 (optional for Breslow > 1 mm), mitotic rate per mm^2, 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
  - Tumor-infiltrating lymphocytes
  - Vertical growth phase
  - Angiolymphatic invasion
  - Neurotropism
  - Histologic subtype

PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Clinical Margins[3]
In situ[4]	0.5 cm
≤ 1.0 mm	1.0 cm (category 1)
1.01 - 2 mm	1 - 2 cm (category 1)
2.01 - 4 mm	2.0 cm (category 1)
> 4 mm	2.0 cm

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

[1] If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excision.
[2] For lentigo maligna, melanoma in situ, a broad shave biopsy may help to optimize diagnostic sampling.
[3] Clinical margins may not correlate with histologic margins.
[4] For large melanoma in situ, lentigo maligna type, surgical margins > 0.5 cm may be necessary to achieve histologically negative margins; techniques for more exhaustive histologic assessment of margins should be considered.

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. All recommendations are category 2A unless otherwise noted.

PRINCIPLES OF COMPLETE LYMPH NODE DISSECTION

Adequacy of regional lymph node dissection:

- An anatomically complete dissection[1] of involved nodal basin is required.
- In the groin, consider elective iliac and obturator lymph node dissection if clinically positive superficial nodes or ≥ 3 superficial nodes positive (category 2B).
- Iliac and obturator lymph node dissection indicated if pelvic CT is positive (category 2A) or if Cloquet's node is positive (category 2B).

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[2] (category 2B)
- Dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without interleukin-2, interferon-alfa; category 2B)
- Paclitaxel (category 2B)
- Paclitaxel/cisplatin (category 2B)
- Paclitaxel/carboplatin (category 2B)

[1] Anatomic boundaries of lymph node dissection should be described in operative report.
[2] High-dose interleukin-2 should not be used for patients with untreated/active brain metastases.

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

Dacarbazine
- 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.

Temozolomide
- Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000;18:158-166.

High-Dose Interleukin-2
- Smith FO, Downey SG, Klapper JA, et al. Treatment of metastatic melanoma using interleukin-2 alone or in conjunction with vaccines. Clin Cancer Res 2008;14:5610-5618.

Dacarbazine or Temozolomide-Based Combination Chemotherapy or Biochemotherapy Including Cisplatin, Vinblastine, With or Without Interleukin-2 or Interferon-alfa
- Atkins MB, Hsu J, Lee S, et al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2008;26:5748-5754.
- 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.
- 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;20:2045-2052.

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

Paclitaxel and Carboplatin
- Rao RD, Holtan SG, Ingle JN, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer 2006;106:375-382.
- Agarwala SS, Keilholz U, Hogg D, et al. Randomized phase III study of paclitaxel plus carboplatin with or without sorafenib as second-line treatment in patients with advanced melanoma [abstract]. J Clin Oncol 2007;25(Suppl 1):Abstract 8510.

Text continued from p. 251

to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among panel members during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise < 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The NCCN Melanoma Panel strongly supports early diagnosis and appropriate treatment of melanoma.

Clinical Presentation and Workup

Biopsy

Patients presenting with a suspicious pigmented lesion optimally should undergo an excisional biopsy, preferably with 1- to 3-mm margins (see page 258). The orientation of the excisional biopsy should always be planned with definitive treatment in mind (e.g., a longitudinal orientation in the extremities). Because use of lymphatic mapping and sentinel node biopsy is increasing, biopsies should also be planned so they will not interfere with these procedures, and wider margins for the initial diagnostic procedure should be avoided.

Excisional biopsy may be inappropriate for certain sites (including the face, palmar surface of the hand, sole of the foot, ear, distal digit, or subungual lesions) or for very large lesions. In these instances, a full-thickness incisional or punch biopsy of the clinically thickest portion of the lesion is an acceptable option, rather than a shave biopsy. These procedures should provide accurate primary tumor microstaging, without interfering with definitive local therapy. If the incisional biopsy is inadequate to make a diagnosis or to accurately microstage the tumor (based on evaluation by a dermatopathologist) for treatment planning, re-biopsy with narrow margin excision should be considered.

Pathology Report

In the revised American Joint Committee of Cancer (AJCC) staging system, melanoma patients are categorized into 3 groups: localized disease with no evidence of metastases (stage I–II), regional disease (stage III), and distant metastatic disease (stage IV).[8,9] Breslow tumor thickness and ulceration are the 2 most important characteristics of the primary tumor predicting outcome in patients with localized melanoma (stage I or II).[10] In the most recent version of the AJCC staging system, Clark level was also a strong independent predictor of outcome for primary melanomas less than 1 mm thick.[8]

Mitotic rate (MR) is an indicator of tumor proliferation and is measured as the number of mitoses per mm^2. Barnhill et al.[11] compared the relative importance of MR to ulceration as major prognostic factors in localized melanoma. In a multivariate analysis including MR and ulceration, tumor thickness, moderate MR (1–6), and MR greater than 6 emerged as the most important independent prognostic factors. Several other studies have also confirmed the prognostic importance of MR in patients with primary cutaneous melanoma.[12–14] In multivariate analyses, MR and younger age were identified as independent predictors of a positive sentinel lymph node (SLN) in addition to Breslow thickness.[15,16]

The American Academy of Dermatology (AAD) Task Force recommends including MR in the biopsy report as optional along with other additional factors, such as vertical growth phase, tumor-infiltrating lymphocytes (TIL), and regression.[17] Microscopic satellitosis, if present, should also be recorded, because this defines a patient subgroup at high risk for regional and systemic failure, prognostically similar to stage III.

For patients with stage I and II disease, the panel recommends including Breslow thickness, ulceration status, MR, deep and peripheral margin status, satellitosis if present, and Clark level (especially for lesions ≤ 1.0 mm) in the pathology report. MR should be reported for all lesions because it is emerging as an independent predictor of outcome (category 2B). The panel agreed that recording the parameters identified by the AAD Task Force would be helpful, but not mandatory.

Among patients with localized melanoma undergoing SLN biopsy (SLNB), the status of the sentinel node is the most important prognostic factor.[10] Among those with nodal metastases (stage III), the number of metastatic nodes and clinical nodal status (nonpalpable vs. palpable) are the most important predictors of survival, followed by the presence or absence of primary tumor ulceration. Other prognostically relevant factors include the presence of extranodal tumor extension and, in patients with positive sentinel nodes, size and location of the metastatic melanoma in the sentinel nodes.

For patients with stage III disease, the panel recommends reporting the number of positive nodes, total number of nodes examined, and presence or absence of extranodal tumor extension. In addition, the panel recommends recording the size and location of tumor present in a positive sentinel node.

The site of metastases is the most significant predictor of outcome among patients with distant metastases (stage IV). Elevated lactate dehydrogenase (LDH) is also an independent predictor of poor outcome in patients with stage IV disease and has been incorporated into the AJCC staging system.[10,18]

For stage IV patients, the panel recommends reporting all sites of metastatic disease and the serum LDH at diagnosis of stage IV.

Preliminary Workup

Once the diagnosis of melanoma has been confirmed, a history, physical examination, and complete dermatologic examination are recommended. Preliminary workup of patients presenting with dysplastic nevi should include detailed personal and family history, including any history of dysplastic nevi removal.[3] During 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.

Clinical Staging

Patients can be clinically staged after histopathologic microstaging, history and physical including examination of locoregional area and draining lymph nodes, and a complete skin examination (see page 253). In accordance with the AJCC staging system, these guidelines have categorized patients into the following clinical groups: 1) stage 0 (melanoma in situ); 2) stage IA, (≤ 1.0 mm, Clark level II–III) with or without potentially adverse features such as positive deep margins, lymphovascular invasion, and MR ≥ 1 per mm^2; 3) stage IB to II (≤ 1.0 mm with ulceration or Clark level IV–V; or > 1.0 mm, with any characteristic and clinically negative nodes); 4) stage III, clinically positive nodes; 5) stage III, in-transit disease; and 6) stage IV, distant metastatic disease.

Pathologic Staging

Patients with clinically localized stage I to II melanoma may be further pathologically staged by lymphatic mapping with SLNB. Depending on the primary tumor thickness, ulceration, and other factors described earlier, 5% to 30% of patients undergoing SLNB will be upstaged from clinical stage I or II to pathologic stage III, based on subclinical micrometastatic disease in the SLN. These patients have a distinctly better prognosis than those with clinically positive nodes containing macrometastatic disease.[10,19] The AJCC staging system clearly recognizes this difference in prognosis among patients with pathologic stage III melanoma.[8]

Workup

An extent-of-disease workup in patients with melanoma can be considered for several reasons: 1) to establish a set of baseline images against which to compare future studies in patients at risk for relapse; 2) to detect clinically occult disease that would affect immediate treatment decisions, and 3) to define homogeneously staged patients for inclusion into clinical trials. Although patients greatly value the negative result of a cross-sectional imaging study, physicians must be cautious about overinterpreting the significance of the findings, recognizing that all tests have relatively insensitive lower limits of resolution. Finally, all tests have a real possibility of detecting findings unrelated to the melanoma, which can lead to morbid invasive biopsy procedures or, at the very least, substantial patient anxiety incurred while awaiting results of interval follow-up studies.

The yield of routine blood work and imaging studies in screening patients with clinical stage I to II melanoma for asymptomatic distant metastatic disease is very low. Screening blood tests are very insensitive and the findings of cross-sectional imaging are often nonspecific, with frequent false-positive findings unrelated to melanoma.[20–22]

The yield of imaging studies has been more extensively evaluated in the context of patients with stage III melanoma. In patients with a positive SLN, the yield of cross-sectional imaging in detecting clinically occult distant metastatic disease ranges from 0.5% to 3.7%.[23–25] All series report a high rate of indeterminate and false-positive findings. True-positive findings are most often found in patients with ulcerated thick primary tumors with large tumor burden in their sentinel nodes. In asymptomatic patients with clinically positive nodes, the yield of routine cross sectional imaging is a bit higher than in patients with positive sentinel nodes, reported at 4% to 16%.[26–28] These series also report a high incidence of radiologic findings that are unrelated to melanoma.

These retrospective studies are reporting minimum estimates, because defining a study population of patients who have truly imaging-naïve stage III disease is very difficult. Among the entire denominator of patients with stage III disease, some probably would have been defined as stage IV based on imaging before the study cohort was assembled. Furthermore, because most patients with clinical stage III disease will ultimately develop distant metastases, the inability of CT scans to detect this at stage III diagnosis is a relatively poor predictor of future events.

Although PET scanning has attracted interest as a means of enhancing detection of subclinical metastatic disease, most investigators have described very low yield and poor sensitivity in detecting metastatic disease in patients with clinically localized melanoma.[29–31] In patients with more advanced stage III disease, PET may be more useful. In particular, it can help to characterize lesions found to be indeterminate on CT scan, and often image areas of the body not studied with routine body CT scans (i.e., arms and legs).[32]

NCCN Recommendations: Workup of patients with melanoma varies greatly among the NCCN member institutions. In the absence of compelling data beyond the retrospective series cited earlier, the extent of workup is mostly at the discretion of the treating physician.

Routine imaging studies such as CT, PET, or MRI are not recommended for patients with localized thin melanomas (stage I). The NCCN recommendation is consistent with National Institutes of Health (NIH) consensus guidelines.[33] However, these tests may be performed as clinically indicated to evaluate specific signs or symptoms in patients with stage II melanoma. A baseline chest radiograph is optional for patients with stage IB to II melanoma, because this test is insensitive for detecting clinically occult distant metastases in the lungs (see page 253).

Most panel members acknowledged the low yield of screening CT or PET scans in patients with stage III melanoma. Based on the study results reported in the literature and the absence of conclusive data, the panel left the extent of scanning to the discretion of the treating physician. For patients presenting with clinical stage III disease who have clinically positive nodes, all panel members believe it is appropriate to confirm the suspicion of regional metastatic disease, preferably with fine-needle aspiration (FNA) or open biopsy of the clinically enlarged lymph node. Clearly, in patients without an antecedent history of melanoma, this would have been the initial diagnostic test. A pelvic CT scan is recommended in the setting of inguinofemoral lymphadenopathy to rule out associated pelvic or retroperitoneal lymphadenopathy.

For the small group of patients presenting with stage III in-transit disease, the workup just outlined for stage III nodal disease, including histologic confirmation of the in-transit metastasis, is appropriate (see page 254).

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 open biopsy of the lesion (see page 254). LDH level plus chest radiograph and/or chest CT are recommended. Abdominal/pelvic CT, with or without PET, and/or head MRI should be considered (category 2B).

Because patients with metastatic melanoma have a high incidence of brain metastases, brain MRI or CT scan with contrast should be performed if patients have even minimal suggestions of symptoms or physical findings of central nervous system (CNS) involvement or if results of imaging would affect decisions about treatment.

Although LDH is not a sensitive marker for detecting metastatic disease, the panel recognizes its prognostic role and recommends obtaining serum LDH at diagnosis of stage IV disease. Other blood work may be performed at the physician's discretion.

Treatment of Primary Melanoma

Wide Excision

Surgical excision is the primary treatment for melanoma. Several prospective randomized trials have been conducted in an effort to define optimal surgical margins for primary melanoma. An international prospective study conducted by WHO randomized 612 patients with primary melanomas not thicker than 2.0 mm to wide excision with 1.0- or 3.0-cm margins.[34,35] At median follow-up of 90 months, both groups had similar rates of local recurrence and disease-free and overall survival.

The National Intergroup Trial randomized 468 patients with melanomas that were 1.0 to 4.0 mm in thickness to wide excision with either 2.0- or 4.0-cm margins. At median follow-up of 10 years, no differ-

ences were seen in local recurrence, disease-free survival, or overall survival.[36,37] Prospective randomized trials from Sweden have confirmed that satisfactory local control and melanoma-specific survival are not compromised by narrower margins.[38,39]

In a more recent prospective randomized trial comparing 1- versus 3-cm margins for melanomas thicker than 2 mm, wider margins were associated with a slightly lower rate of combined local/regional/nodal recurrence, but without improvement in local recurrence alone or in melanoma-specific survival.[40] A systemic review and meta-analysis also reported that surgical excision margins no more than 2 cm are adequate, and surgical margins should not be less than 1 cm around primary melanoma.[41]

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, all aimed at complete surgical excision with meticulous margin control, have shown high local control rates and are used at some NCCN centers, although they are not universally accepted.[42,43]

NCCN Recommendations: The NCCN recommendations for surgical margins for wide excision are based on the results of clinical trials discussed earlier. In cases for which no prospective data were available (in situ and thick melanoma), recommendations were made based on consensus (see page 258). The clinical/surgical margins discussed do not necessarily correlate with gross pathologic/histologic margins.

For in situ melanoma, a measured margin of 0.5 cm around the visible lesion should be obtained. For large in situ lentigo maligna melanoma, surgical margins greater than 0.5 cm may be necessary to achieve histologically negative margins. For patients with stage IA melanoma (≤ 1.0 mm), wide excision with a 1.0 cm margin is recommended (category 1).

For patients with melanomas measuring 1.01 to 2.0 mm in thickness, wide excision with a 1.0- to 2.0-cm margin is recommended (category 1). For melanomas measuring more than 2.0 mm in thickness, wide excision with 2.0-cm margins is recommended (category 1 for tumors ≤ 4 mm in thickness; category 2A for tumors > 4 mm in thickness). Surgical margins may be modified to accommodate individual anatomic or cosmetic considerations. The panel recognized that 1.0- to 2.0-cm margins might be acceptable in anatomically difficult areas in which a full 2.0-cm margin would be difficult to achieve.

Although surgical excision remains standard care for in situ melanoma, it is sometimes not feasible because of comorbidity or cosmetically sensitive tumor location. Topical imiquimod has emerged as a treatment option, especially for lentigo maligna.[44–47] However, long-term comparative studies are still needed and the panel did not include specific recommendations for this treatment option for in situ melanoma.

SLNB

SLNB is a minimally invasive procedure developed to identify patients with nodal metastases and who could be candidates for complete lymph node dissection.[48] The Multicenter Selective Lymphadenectomy Trial 1 (MLST-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.[49] In a preliminary publication, Morton et al.[49] reported an initial sentinel node identification rate of 95%. SLNB was also associated with low false-negative and complication rates.

Recently, Morton et al.[50] published data from the third interim analysis of results from the MSLT-I trial. Among patients with intermediate-thickness primary melanoma (1.2–3.5 mm), those undergoing wide excision with SLNB (and completion lymph node dissection if their sentinel nodes were positive) showed no significant improvement in melanoma-specific survival rates compared with those undergoing initial wide excision and nodal observation, and delayed therapeutic lymphadenectomy if necessary. However, an improvement was seen in the estimated 5-year disease-free survival in the SLNB group (78% after SLNB vs. 73% after observation; $P = .009$), at least partly because of the higher nodal relapse rate in the observation group. Among patients undergoing SLNB, sentinel node status was the most important prognostic factor for disease-specific survival. Furthermore, among all patients with nodal metastases, those who had immediate lymph node dissection after lymphatic mapping and positive SLNB had higher survival rates than those who underwent delayed lymphadenectomy for clinical disease (72% vs. 52%). This difference was largely attributed to a lower nodal tumor burden in patients with positive SLNs than in those with clinically positive nodes. These results confirm that SLNB has

prognostic value and that the procedure can identify patients with low-volume nodal metastases whose survival is superior to that of patients whose nodal metastases are detected on clinical examination.

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

The value of SLNB for patients with thin (≤ 1.0 mm) and thick melanomas (≥ 4.0 mm) was not addressed specifically in the MSLT-I trial. Because patients with thin melanoma have a generally favorable prognosis, the role of SLNB in this cohort is unclear. Three recent retrospective reviews have shown that the incidence of positive SLNs is 2% to 5% for patients with melanomas less than or equal to 1 mm thick.[51] Factors predicting an increased probability of a positive SLN in patients with thin melanomas include increasing Breslow thickness and Clark level, higher MR, and younger age. However, with relatively short follow-up, only 1 center has shown any convincing evidence that the SLN status was predictive of outcome in this low-risk group of patients.[52] Larger series and longer-term follow-up are required to assess the prognostic value of SLN in patients with thin melanoma.[53–55]

The probability of a positive sentinel node in patients with thick melanoma (≥ 4 mm) is 30% to 40%. Almost every retrospective series has shown that SLN status is a strong independent predictor of outcome in patients with thick melanoma.[56–58] Thus, in these high-risk patients, offering SLNB would seem reasonable to help define prognostically homogeneous groups for participation in clinical trials of adjuvant therapy.

NCCN Recommendations: Sentinel node biopsy may be offered to patients with melanoma either as standard care or in the context of a clinical trial. The panel does not recommend SLNB for patients with in situ melanoma (stage 0) or stage IA melanoma that is 1.0 mm or less with no adverse features. Discussion of SLNB should be considered for patients with stage IA thin melanomas (≤ 1.0 mm) with adverse prognostic features such as thickness greater than 0.75 mm, high MR, and young patient age. Other factors, such as positive deep margins and lymphovascular invasion, could be considered indications for SLNB on an individual basis (category 2B; see page 253).[59–62] The significance of tumor regression is debatable, with more recent studies reporting no association of regression incidence to increased SLN positivity.[63,64]

Because the yield of a positive sentinel node biopsy in patients with stage IA melanoma is low and the clinical significance of a positive SLN in these patients remains unclear, these factors should be discussed with patients considering the procedure. For patients with stage IB or II melanoma (≤ 1.0 mm thick with ulceration or Clark level IV to V, or > 1.0 mm thick), the panel encourages the use of SLNB. However, although SLNB is a useful staging tool, its impact on the overall survival of these patients is unclear. In patients who would be candidates for SLNB, the decision to not perform SLNB may be based on significant patient comorbidities or patient preference.

Sentinel nodes should be evaluated with serial sectioning and immunohistochemistry. The validity of sentinel node biopsy in accurately staging patients after prior wide excision is unknown. Therefore, wide excision before planned sentinel node biopsy is discouraged, although patients may be considered for sentinel node biopsy on an individual basis if they present after initial wide excision. The panel had a substantial discussion about the appropriate management of clinically negative lymph nodes in patients at risk for regional metastases, if SLNB is unavailable. Based on the results of 3 prospective randomized trials, the panel does not recommend routine elective lymph node dissection for this group. Wide excision alone or referral to a center where lymphatic mapping is available are both acceptable options in this situation.

Lymph Node Dissection

Complete lymph node dissection consists of an anatomically complete dissection of the involved nodal basin (see page 259). The extent of complete lymph node dissection is often modified according to the anatomic area of lymphadenopathy. In the absence of clinical or radiologic evidence of deep node involvement, patients with melanoma metastatic to inguinal nodes are at risk for pelvic node involvement when more than 3 superficial nodes are involved, the nodes are clinically positive, or Cloquet's node is positive.[65–67]

NCCN Recommendations: If the sentinel node is negative, regional lymph node dissection is not in-

dicated. Patients with stage III disease based on a positive SLN should be offered a complete lymph node dissection of the involved nodal basin, either as standard care or in the context of a clinical trial. Published studies have shown additional positive non–sentinel nodes in approximately 20% of these complete lymph node dissection specimens.[68,69] However, the impact of completion lymph node dissection on regional control and survival in this setting has not been clearly shown. Participation in MSLT-II, assessing the option of nodal observation in patients with positive sentinel nodes, is encouraged when available.

Patients presenting with clinical stage III and clinically positive nodes, without radiologic evidence of distant metastases, should undergo wide excision of the primary site (if present) and complete lymph node dissection of the involved nodal basin (see page 254). In the setting of inguinal lymphadenopathy, a deep groin dissection is recommended if PET or pelvic CT scan shows iliac and/or obturator lymphadenopathy or if a positive Cloquet's lymph node is found intraoperatively.[66,67] Deep groin dissection also should be considered for clinically positive nodes or if more than 3 superficial nodes are involved.[65]

One measure of the completeness of a regional lymph node dissection is the number of lymph nodes examined. However, the panel believed that the available retrospective evidence was insufficient to mandate that a specific number of nodes be required to deem a lymph node dissection adequate. As a measure of quality control to ensure adequacy of lymphadenectomy, the panel recommended that the operative note should fully describe the anatomic boundaries of the lymph node dissection (see page 259).

Adjuvant Treatment for Melanoma

Low- and Intermediate-Dose Interferon

The first major randomized trial of adjuvant interferon therapy conducted by WHO[70] showed no significant improvement in overall survival (35% for the interferon group vs. 37% for observation alone). In the French Cooperative Group trial, after a median follow-up of 5 years, adjuvant interferon therapy showed a significant relapse-free survival benefit and also a trend toward increased overall survival.[71] In another prospective randomized study, adjuvant interferon prolonged disease-free survival for all patients at median follow-up of 41 months.[72]

Two other randomized clinical trials (EORTC 18952 and the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglyceride and Impact on Global Health Outcomes [AIM HIGH]) compared adjuvant interferon with observation in patients with resected stage IIB and III melanoma. In the AIM HIGH study, low-dose interferon alfa-2a did not improve either overall survival or recurrence-free survival.[73] EORTC 18952 reported no significant improvement in progression-free survival for intermediate-dose interferon alfa-2b.[74]

High-Dose Interferon

High-dose interferon has been evaluated in 3 randomized clinical trials. ECOG 1684 compared high-dose interferon alfa-2b with observation in patients with stage IIB (≥ 4.0 mm with no evidence of lymph node involvement) and stage III melanomas with either regional lymph node disease or in-transit metastases. Median follow-up of 6.9 years showed a statistically significant improvement in survival for patients in the interferon group. However, at 12.6 years of follow-up, overall survival was not significantly different between the groups, although a significant benefit was seen in relapse-free survival.[75]

The results of a larger follow-up trial of high-dose interferon alfa-2b (ECOG 1690) also showed a relapse-free survival advantage but none for overall survival.[76] E1694 compared high-dose interferon alfa-2b with an experimental vaccine. At approximately 2 years median follow-up, the interferon alfa-2b group showed a statistically significant improvement in relapse-free and overall survival.[77]

A recent retrospective review of 200 patients with melanoma (stage IIB, IIC, or III) reported that those who had autoantibodies or clinical manifestations of autoimmunity after treatment with high-dose interferon alfa-2b showed improved survival (both relapse-free and overall).[78]

Review of data combined from the randomized controlled trials found that adjuvant interferon-alfa was not associated with improved overall survival in patients with melanoma who were at increased risk for recurrence.[79] A pooled analysis of E1684, E1690, and E1694 confirmed an improvement in relapse-free survival in patients with high-risk resected melanoma (two-sided log-rank P value = .006) but found no significant improvement in overall survival.[80]

The ECOG studies included patients with stage

IIB (≥ 4.0 mm with no evidence of lymph node involvement) and stage III melanomas with either regional lymph node disease or in-transit metastases. In a recent systematic review, Verma et al.[81] concluded that, although high-dose interferon-alfa is associated with improved disease-free survival in patients with high-risk primary melanomas, the role of adjuvant interferon for those with intermediate- to high-risk melanoma remains undefined.

NCCN Recommendations

Most patients with in situ or early-stage melanoma will be cured through primary excision alone. For patients with in situ or node-negative primary melanoma (stage IA, ≤ 1 mm thick or without adverse features), no standard adjuvant therapy is recommended. For patients with node-negative early-stage melanoma who are at risk for recurrence (stage IB or II, ≤ 1.0 mm thick with ulceration or Clark level IV to V, or ≥ 1.0 mm thick), adjuvant treatment options include a clinical trial or observation (see page 253). For patients with node-negative stage IIB or IIC disease, adjuvant treatment options include clinical trial, interferon-alfa, or observation. For patients with stage III melanoma, adjuvant treatment options include clinical trial, interferon-alfa, or observation (see page 254).

Treatment with adjuvant interferon-alfa is a category 2B recommendation. Decisions about the appropriateness of adjuvant interferon alfa-2b treatment for patients should be made on an individual basis, after a discussion with the patient that includes an explanation of the potential benefits and side effects of interferon therapy.[82–84]

Adjuvant hypofractionated radiotherapy to the nodal bed should be considered (category 2B) for patients with stage IIIC disease 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.[85,86]

For all patients who have been rendered free of disease through surgery, after initial treatment for recurrent or metastatic disease (stage III in-transit metastases or stage IV), consideration of adjuvant treatment is appropriate. The guidelines recommend clinical trial, interferon-alfa (category 2B), or observation as adjuvant treatment options (see pages 254 and 257).

Treatment of Metastatic Melanoma

Metastatic melanoma is associated with a poor prognosis. Several chemotherapeutic agents, including dacarbazine and temozolomide, have shown activity in patients with metastatic melanoma when used as single agents or in combination chemotherapy regimens.[87] However, little consensus currently exists regarding standard therapy for patients with metastatic melanoma, which most likely reflects the low level of activity of all available agents.[88,89]

Dacarbazine still remains standard care in community practice, and has been used as a standard for comparing the efficacy of new regimens.[90] A small randomized trial has shown similar response rates and survival for dacarbazine and temozolomide treatment of metastatic melanoma.[91] Both dacarbazine and temozolomide result in response rates of approximately 10% to 20%, with median response duration of 3 to 4 months.[87,91]

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.[92,93] However, subsequent clinical trials have not replicated these rates. A phase III randomized trial showed that survival after treatment with Dartmouth regimen was not superior to dacarbazine alone.[94]

Paclitaxel alone or in combination with carboplatin may provide clinical benefit to some patients with metastatic melanoma; however, the duration of clinical benefit is short (2–7 months).[95,96]

Interleukin-2 (IL-2) was approved by the FDA for treating metastatic melanoma in 1998. High-dose intravenous bolus IL-2 treatment resulted in overall objective response rates of approximately 12% to 21%. In a highly selected patient population, IL-2 induced durable complete responses in approximately 6% and partial responses in 10% of patients with metastatic melanoma, albeit with high levels of toxicity.[97] A recent study showed increased response rates in metastatic melanoma for IL-2 given with the 210M peptide vaccine (22%) compared with IL-2 (13%) alone.[98]

Biochemotherapy is the combination of chemotherapy and biologic agents. In initial single-institutional phase II trials, biochemotherapy (cisplatin, vinblastine, dacarbazine, interferon-alfa, and IL-2) produced an overall response rate of 64% and a complete response rate of 21% in patients with metastatic

melanoma.[99,100] A report of a small phase III randomized trial comparing sequential biochemotherapy (CVD with IL-2 and interferon-alfa administered on a distinct schedule) with CVD showed response rates of 48%, compared with 25% for CVD alone; median survival for patients treated with biochemotherapy was 11.9 versus 9.2 months for CVD.[101]

In a phase III randomized intergroup trial (E3695), biochemotherapy (cisplatin, vinblastine, dacarbazine, IL-2 and interferon, alpha-2b) produced a slightly higher response rate and progression-free survival than CVD alone, but was not associated with improved quality of response or overall survival in patients with metastatic melanoma.[102] Biochemotherapy was substantially more toxic than CVD. Additional attempts to decrease toxicity of biochemotherapy by administering subcutaneous outpatient IL-2 did not show a substantial benefit of biochemotherapy versus chemotherapy alone.[103–105] A recent report from a meta-analysis also showed that, although biochemotherapy improves overall response rates, patients with metastatic melanoma experienced no survival benefit.[106]

NCCN Recommendations

Stage III (In-transit Metastases): Many different treatment options are available for patients presenting with stage III in-transit metastases (see page 254). For those with 1 or a small number of in-transit metastases, complete surgical excision with histologically negative margins is preferred (category 2B), if feasible. In patients undergoing curative resection of a solitary in-transit metastasis, sentinel node biopsy (category 2B) can be considered because of the high probability of occult nodal involvement.[107] Although a positive sentinel node in the presence of in-transit metastasis portends a more ominous prognosis, the impact of sentinel node biopsy on outcome is unproven.

If the patient has a limited number of in-transit metastases, particularly dermal lesions that are not amenable to complete surgical excision, intralesional local injections with bacillus Calmette-Guérin (BCG)[108] or interferon-alfa, or topical imiquimod[109] can be considered (category 2B for all of the options). Laser ablation may be used in selected patients (category 2B).

Thompson and Kam[110] reported that isolation limb infusion was a simpler technique, with response rates comparable to limb perfusion. The panel included hyperthermic isolated limb perfusion or infusion as a treatment option for patients with unresectable in-transit metastases (category 2B).[111–113]

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 treatment in the context of a clinical trial.

Stage IV (Distant Metastatic Disease): Treatment of stage IV metastatic melanoma depends on whether disease is limited (resectable) or disseminated (unresectable; see page 257). A clinical trial is the preferred treatment option for patients with distant metastatic disease.

Resection, if feasible, followed by adjuvant treatment with interferon-alfa is recommended for limited metastatic disease.[114] In selected patients with a solitary site of visceral metastatic melanoma, a short period of observation or systemic treatment followed by repeat scans may be appropriate to rule out the possibility that the visceral metastasis is the first of many metastatic sites and to better select patients for surgical intervention.

After observation, patients with resectable solitary sites of disease should be assessed for surgery. Patients who undergo resection can be offered adjuvant treatment with interferon-alfa or clinical trial (category 2B). Alternatively, limited metastatic disease can be treated with systemic therapy either as standard care or in the context of a clinical trial (preferred).

Residual disease after incomplete resection for limited metastases is treated as described later for disseminated disease. Systemic therapy options are listed in the following paragraph.

Disseminated disease is treated based on the presence or absence of brain metastases. For patients without brain metastases, options for systemic therapy include 1) single-agent chemotherapy (dacarbazine, temozolomide, or paclitaxel) or high-dose IL-2; 2) combination chemotherapy (paclitaxel with cisplatin or carboplatin); or 3) combination chemotherapy or biochemotherapy (dacarbazine or temozolomide-based including cisplatin and vinblastine, with or without IL-2, interferon-alfa). These options are all category 2B recommendations (see pages 259 and 260).

For patients with disseminated melanoma that is unresponsive to or relapses after first-line systemic therapy and have a performance status of 0 to 2, additional systemic therapy may be indicated (see page 257). Options for second-line therapy include clinical trial (preferred) or treatment with a differ-

ent first-line option (indicated earlier). In addition to systemic therapy, surgical resection or radiation may be considered for palliation and management of symptoms, such as gastrointestinal bleeding or obstruction, ulcerated soft tissue cutaneous metastases, or bulky adenopathy.

For patients with brain metastases, treatment of the CNS disease usually takes priority to delay or prevent intratumoral hemorrhage, seizures, or neurologic dysfunction. Treatment for patients with brain metastases is based on symptoms and the number and location of the lesions, as described in the NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers (to view the most recent version, visit the NCCN Web site at www.nccn.org). In patients with both brain and extracranial metastases, therapy as outlined in the preceding paragraph may be administered during or after treatment of the CNS disease (see page 257).

Follow-up

In the absence of any clear data, opinions vary widely on the appropriate follow-up of patients with melanoma. The follow-up schedule is influenced by risk for recurrence, previous primary melanoma, and family history of melanoma; it includes other factors, such as dysplastic nevi and patient anxiety.[115] The optimal duration of follow-up remains controversial. Although most patients who have recurrent disease will present in the first 5 years after treatment, late recurrence (≥ 10 years) is well documented for melanoma.[116] Following up all patients intensively for metastatic disease beyond 5 to 10 years is probably not cost-effective (depending on relative risk for metastasis). However, because the lifetime risk for developing a second primary melanoma is 4% to 8%, the panel decided that a recommendation for lifetime dermatologic surveillance for patients with melanoma was justified.

Documenting the effect of intensive surveillance on the outcome of patients with melanoma is difficult. A structured follow-up program could allow recurrent disease to be detected earlier when it might be more amenable to potentially curative surgical resection. This follow-up would be particularly appropriate for patients at risk for regional nodal recurrence who have not undergone sentinel node biopsy, or in those with a positive sentinel node who elected not to undergo completion lymphadenectomy. Several other reasons for a structured follow-up program include detection of a subsequent second primary melanoma, provision of ongoing psychosocial support, identification of familial kindreds, screening for second non-melanoma primary malignancies, patient education, and documentation of treatment results.[117–119]

Skin cancer prevention, including sun protection measures, should be promoted for patients with melanoma and their families.[120] Patients can be made aware of the various resources that discuss skin cancer prevention. Some useful resources are can be found on the Web sites of the American Academy of Family Physicians (www.aafp.org/afp/20000715/375ph.html), American College of Preventive Medicine (www.acpm.org/skinprot.htm), and Centers for Disease Control and Prevention (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 patients with melanoma, including those with stage 0, in situ melanoma (page 255). Frequency of dermatologic surveillance should be determined individually, based on risk factors, including skin type, family history, presence of dysplastic nevi, and history of non-melanoma skin cancers. Clinicians should also consider educating patients about performing monthly self-examination of their skin and lymph nodes.

For patients with stage IA melanoma, a comprehensive history and physical (with specific emphasis on the regional nodes and skin) should be performed every 3 to 12 months for 5 years and annually thereafter as clinically indicated.[121] For patients with stage IB to IV melanomas that have no evidence of disease, a comprehensive history and physical (with emphasis on the regional nodes and skin) should be performed every 3 to 6 months for 2 years, then every 3 to 12 months for 3 years, and annually thereafter, as clinically indicated. A chest radiograph, serum LDH, and hematocrit may be performed every 6 to 12 months at the discretion of the physician. These recommendations recognize the extremely low yield of routine screening chest radiographs and blood tests in this population.[122]

The consensus of the panel was that routine cross-sectional imaging is not recommended for patients with stage IB or IIA disease. In the absence of evaluable data, CT, MRI, and/or PET scans can be considered to follow-up specific signs and symptoms or

detect recurrent or metastatic disease in patients with stage IIB or more advanced stage disease, at the discretion of the treating physician (category 2B). However, the clinical benefit of routine CT screening has not been shown, and the risks for cumulative radiation exposure from medical imaging should be considered.[123]

Treatment of Recurrence

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

Local Scar Recurrence

The panel recognized the distinction between true local scar recurrence after inadequate initial excision (which most likely represents locally persistent disease) and local recurrence after adequate initial excision (which likely represents dermal lymphatic disease appearing near the wide excision scar). In the former situation, the prognosis after re-excision should be better, whereas the latter scenario is prognostically similar to recurrent regional disease.

For true local scar recurrence after inadequate primary therapy, the workup should be similar to that of the primary tumor based on lesion thickness (see page 253). Re-excision to appropriate margins is recommended, with or without lymphatic mapping and sentinel node biopsy, appropriate to the microstaging of the recurrence. For a local recurrence after adequate prior wide excision, baseline imaging (chest radiograph, CT, and/or PET or MRI) should be considered for staging and to evaluate specific signs or symptoms (see page 256). In the absence of extra regional disease, surgical excision with negative margins is recommended for local recurrence after initial adequate wide excision (see page 256). Lymphatic mapping with sentinel node biopsy may be considered in these patients on an individual basis. After complete resection of a local recurrence after adequate primary therapy, adjuvant treatment options include clinical trial, interferon-alfa (category 2B), or observation.

In-transit Recurrence

For patients with in-transit recurrence (see page 256), 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 may be considered in these patients on an individual basis.

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

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

Regional Nodal Recurrence

For patients presenting with regional nodal recurrence, the clinical diagnosis should be confirmed preferably with FNA biopsy. Workup of these patients includes FNA (preferred) or lymph node biopsy, chest radiograph 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 (see page 256).

For patients who have not undergone prior lymph node dissection, a complete lymph node dissection is appropriate. For patients who have had an incomplete prior lymph node dissection, complete lymph node dissection is recommended. For patients who underwent a previous complete lymph node dissection, excision of the recurrence to negative margins is recommended. Postoperative adjuvant radiotherapy may decrease the likelihood of further regional nodal recurrences and can be considered in selected patients with completely resected nodal recurrence who have risk factors such as multiple involved nodes or extranodal disease, especially in the head and neck region (category 2B). Options for patients with incompletely resected nodal recurrence or unresectable recurrence are shown on page 256.

Distant Recurrence

For patients presenting with distant recurrence (see page 257), the workup and treatment options are similar for patients presenting initially with stage IV metastatic disease.

Summary

These 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 melanoma patients, 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, and the individual patient's needs, wishes, and expectations. Furthermore, these guidelines are revised annually and continually as new data become available.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.
2. Surveillance Epidemiology and End Results. SEER stats fact sheet. Available at: http://seer.cancer.gov/statfacts/html/melan.html#ref11. Accessed 8 December 2008.
3. Naeyaert JM, Brochez L. Clinical practice. Dysplastic nevi. N Engl J Med 2003;349:2233–2240.
4. Rigel DS, Rivers JK, Kopf AW, et al. Dysplastic nevi. Markers for increased risk for melanoma. Cancer 1989;63:386–389.
5. Ivry GB, Ogle CA, Shim EK. Role of sun exposure in melanoma. Dermatol Surg 2006;32:481–492.
6. Jensen EH, Margolin KA, Sondak VK. Melanoma and other skin cancers. In: Pazdur R, Coia L, Hoskins WJ, Wagman LD, eds. Cancer Management: A Multidisciplinary Approach, 9th edition. New York: CMP Media; 2005:531–562.
7. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. N Engl J Med 2004;351:998–1012.
8. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 2001;19:3635–3648.
9. Greene FL, Page DL, Fleming ID. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag; 2002.
10. Balch CM, Soong SJ, 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.
11. Barnhill RL, Katzen J, Spatz A, et al. The importance of mitotic rate as a prognostic factor for localized cutaneous melanoma. J Cutan Pathol 2005;32:268–273.
12. Azzola MF, Shaw HM, Thompson JF, et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: an analysis of 3661 patients from a single center. Cancer 2003;97:1488–1498.
13. Francken AB, Shaw HM, Thompson JF, et al. The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up. Ann Surg Oncol 2004;11:426–433.
14. Gimotty PA, Elder DE, Fraker DL, et al. Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. J Clin Oncol 2007;25:1129–1134.
15. 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;109:100–108.
16. Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. Ann Surg Oncol 2004;11:247–258.
17. Sober AJ, Chuang TY, Duvic M, et al. Guidelines of care for primary cutaneous melanoma. J Am Acad Dermatol 2001;45:579–586.
18. Neuman HB, Patel A, Ishill N, et al. A single-institution validation of the AJCC staging system for stage IV melanoma. Ann Surg Oncol 2008;15:2034–2041.
19. Cascinelli N, Belli F, Santinami M, et al. Sentinel lymph node biopsy in cutaneous melanoma: the WHO Melanoma Program experience. Ann Surg Oncol 2000;7:469–474.
20. 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.
21. 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.
22. Yancovitz M, Finelt N, Warycha MA, et al. Role of radiologic imaging at the time of initial diagnosis of stage T1b-T3b melanoma. Cancer 2007;110:1107–1114.
23. 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;24:2858–2865.
24. Gold JS, Jaques DP, Busam KJ, et al. Yield and predictors of radiologic studies for identifying distant metastases in melanoma patients with a positive sentinel lymph node biopsy. Ann Surg Oncol 2007;14:2133–2140.
25. Miranda EP, Gertner M, Wall J, et al. Routine imaging of asymptomatic melanoma patients with metastasis to sentinel lymph nodes rarely identifies systemic disease. Arch Surg 2004;139:831–836; discussion 836–837.
26. Buzaid AC, Tinoco L, Ross MI, et al. Role of computed tomography in the staging of patients with local-regional metastases of melanoma. J Clin Oncol 1995;13:2104–2108.
27. Johnson TM, Fader DJ, Chang AE, et al. Computed tomography in staging of patients with melanoma metastatic to the regional nodes. Ann Surg Oncol 1997;4:396–402.
28. Kuvshinoff BW, Kurtz C, Coit DG. Computed tomography in evaluation of patients with stage III melanoma. Ann Surg Oncol 1997;4:252–258.
29. Clark PB, Soo V, Kraas J, et al. Futility of fluorodeoxyglucose F 18 positron emission tomography in initial evaluation of patients with T2 to T4 melanoma. Arch Surg 2006;141:284–288.
30. Maubec E, Lumbroso J, Masson F, et al. F-18 fluorodeoxy-D-glucose positron emission tomography scan in the initial evaluation of patients with a primary melanoma thicker than 4 mm. Melanoma Res 2007;17:147–154.
31. Wagner JD, Schauwecker D, Davidson D, et al. Inefficacy of F-18 fluorodeoxy-D-glucose-positron emission tomography scans for initial evaluation in early-stage cutaneous melanoma. Cancer 2005;104:570–579.
32. Brady MS, Akhurst T, Spanknebel K, et al. Utility of preoperative

[(18)]f fluorodeoxyglucose-positron emission tomography scanning in high-risk melanoma patients. Ann Surg Oncol 2006;13:525–532.

33. 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.

34. Veronesi U, Cascinelli N. Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. Arch Surg 1991;126:438–441.

35. 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.

36. Balch CM, Soong SJ, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1-4 mm melanomas. Ann Surg Oncol 2001;8:101–108.

37. 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; discussion 267–269.

38. Cohn-Cedermark G, Rutqvist LE, Andersson R, et al. Long term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0.8-2.0 mm. Cancer 2000;89:1495–1501.

39. Khayat D, Rixe O, Martin G, et al. Surgical margins in cutaneous melanoma (2 cm versus 5 cm for lesions measuring less than 2.1-mm thick). Cancer 2003;97:1941–1946.

40. Thomas JM, Newton-Bishop J, A'Hern R, et al. Excision margins in high-risk malignant melanoma. N Engl J Med 2004;350:757–766.

41. Haigh PI, DiFronzo LA, McCready DR. Optimal excision margins for primary cutaneous melanoma: a systematic review and meta-analysis. Can J Surg 2003;46:419–426.

42. Johnson TM, Headington JT, Baker SR, Lowe L. Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the "square" procedure. J Am Acad Dermatol 1997;37:758–764.

43. Zitelli JA, Brown C, Hanusa BH. Mohs micrographic surgery for the treatment of primary cutaneous melanoma. J Am Acad Dermatol 1997;37:236–245.

44. Cotter MA, McKenna JK, Bowen GM. Treatment of lentigo maligna with imiquimod before staged excision. Dermatol Surg 2008;34:147–151.

45. Naylor MF, Crowson N, Kuwahara R, et al. Treatment of lentigo maligna with topical imiquimod. Br J Dermatol 2003;149(Suppl 66):66–70.

46. Powell AM, Russell-Jones R, Barlow RJ. Topical imiquimod immunotherapy in the management of lentigo maligna. Clin Exp Dermatol 2004;29:15–21.

47. Spenny ML, Walford J, Werchniak AE, et al. Lentigo maligna (melanoma in situ) treated with imiquimod cream 5%: 12 case reports. Cutis 2007;79:149–152.

48. Johnson TM, Sondak VK, Bichakjian CK, Sabel MS. The role of sentinel lymph node biopsy for melanoma: evidence assessment. J Am Acad Dermatol 2006;54:19–27.

49. 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 311–303.

50. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006;355:1307–1317.

51. Thompson JF, Shaw HM. Sentinel node mapping for melanoma: results of trials and current applications. Surg Oncol Clin N Am 2007;16:35–54.

52. Wright BE, Scheri RP, Ye X, et al. Importance of sentinel lymph node biopsy in patients with thin melanoma. Arch Surg 2008;143:892–899; discussion 899–900.

53. Bleicher RJ, Essner R, Foshag LJ, et al. Role of sentinel lymphadenectomy in thin invasive cutaneous melanomas. J Clin Oncol 2003;21:1326–1331.

54. Ranieri JM, Wagner JD, Wenck S, et al. The prognostic importance of sentinel lymph node biopsy in thin melanoma. Ann Surg Oncol 2006;13:927–932.

55. Wong SL, Brady MS, Busam KJ, Coit DG. Results of sentinel lymph node biopsy in patients with thin melanoma. Ann Surg Oncol 2006;13:302–309.

56. Ferrone CR, Panageas KS, Busam K, et al. Multivariate prognostic model for patients with thick cutaneous melanoma: importance of sentinel lymph node status. Ann Surg Oncol 2002;9:637–645.

57. Gershenwald JE, Mansfield PF, Lee JE, Ross MI. Role for lymphatic mapping and sentinel lymph node biopsy in patients with thick (> or = 4 mm) primary melanoma. Ann Surg Oncol 2000;7:160–165.

58. Gutzmer R, Satzger I, Thoms KM, et al. Sentinel lymph node status is the most important prognostic factor for thick (> or = 4 mm) melanomas. J Dtsch Dermatol Ges 2008;6:198–203.

59. Edwards MJ, Martin KD, McMasters KM. Lymphatic mapping and sentinel lymph node biopsy in the staging of melanoma. Surg Oncol 1998;7:51–57.

60. Glass FL, Cottam JA, Reintgen DS, Fenske NA. Lymphatic mapping and sentinel node biopsy in the management of high-risk melanoma. J Am Acad Dermatol 1998;39:603–610.

61. 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.

62. 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; discussion 463–465.

63. Fontaine D, Parkhill W, Greer W, Walsh N. Partial regression of primary cutaneous melanoma: is there an association with subclinical sentinel lymph node metastasis? Am J Dermatopathol 2003;25:371–376.

64. Morris KT, Busam KJ, Bero S, et al. Primary cutaneous melanoma with regression does not require a lower threshold for sentinel lymph node biopsy. Ann Surg Oncol 2008;15:316–322.

65. Coit DG. Extent of groin dissection for melanoma. Surg Clin North Am 1992;1:271–280.

66. Coit DG, Brennan MF. Extent of lymph node dissection in melanoma of the trunk or lower extremity. Arch Surg 1989;124:162–166.

67. 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.

68. 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;24:4464–4471.

69. Lee JH, Essner R, Torisu-Itakura H, et al. Factors predictive of

tumor-positive nonsentinel lymph nodes after tumor-positive sentinel lymph node dissection for melanoma. J Clin Oncol 2004;22:3677–3684.

70. Cascinelli N, Belli F, MacKie RM, et al. Effect of long-term adjuvant therapy with interferon alpha-2a in patients with regional node metastases from cutaneous melanoma: a randomised trial. Lancet 2001;358:866–869.

71. Grob JJ, Dreno B, de la Salmoniere P, et al. Randomised 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;351:1905–1910.

72. Pehamberger H, Soyer HP, 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;16:1425–1429.

73. 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.

74. Eggermont AM, Suciu 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): randomised controlled trial. Lancet 2005;366:1189–1196.

75. 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.

76. Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol 2000;18:2444–2458.

77. 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.

78. 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.

79. Lens MB, Dawes M. Interferon alfa therapy for malignant melanoma: a systematic review of randomized controlled trials. J Clin Oncol 2002;20:1818–1825.

80. 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.

81. Verma S, Quirt I, McCready D, et al. Systematic review of systemic adjuvant therapy for patients at high risk for recurrent melanoma. Cancer 2006;106:1431–1442.

82. Gray RJ, Pockaj BA, Kirkwood JM. An update on adjuvant interferon for melanoma. Cancer Control 2002;9:16–21.

83. Hauschild A, Gogas H, Tarhini A, et al. Practical guidelines for the management of interferon-alpha-2b side effects in patients receiving adjuvant treatment for melanoma: expert opinion. Cancer 2008;112:982–994.

84. Hurley KE, Chapman PB. Helping melanoma patients decide whether to choose adjuvant high-dose interferon-alpha2b. Oncologist 2005;10:739–742.

85. Bonnen MD, Ballo MT, Myers JN, et al. Elective radiotherapy provides regional control for patients with cutaneous melanoma of the head and neck. Cancer 2004;100:383–389.

86. Strom EA, Ross MI. Adjuvant radiation therapy after axillary lymphadenectomy for metastatic melanoma: toxicity and local control. Ann Surg Oncol 1995;2:445–449.

87. Atallah E, Flaherty L. Treatment of metastatic malignant melanoma. Curr Treat Options Oncol 2005;6:185–193.

88. Eigentler TK, Caroli UM, Radny P, Garbe C. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol 2003;4:748–759.

89. Houghton AN, Coit DG, Daud A, et al. NCCN Clinical Practice Guidelines in Oncology: Melanoma. J Natl Compr Canc Netw 2006;4:666–684.

90. Serrone L, Zeuli M, Sega FM, Cognetti F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J Exp Clin Cancer Res 2000;19:21–34.

91. 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.

92. Legha SS, Ring S, Papadopoulos N, et al. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. Cancer 1989;64:2024–2029.

93. McClay EF, Mastrangelo MJ, Bellet RE, Berd D. Combination chemotherapy and hormonal therapy in the treatment of malignant melanoma. Cancer Treat Rep 1987;71:465–469.

94. 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.

95. Agarwala SS, Keilholz U, Hogg D. Randomized phase III study of paclitaxel plus carboplatin with or without sorafenib as second-line treatment in patients with advanced melanoma [abstract]. J Clin Oncol 2007;25(Supp 1):Abstract 8510.

96. Rao RD, Holtan SG, Ingle JN, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer 2006;106:375–382.

97. 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;17:2105–2116.

98. Smith FO, Downey SG, Klapper JA, et al. Treatment of metastatic melanoma using interleukin-2 alone or in conjunction with vaccines. Clin Cancer Res 2008;14:5610–5618.

99. 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;7:827–835.

100. 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.

101. 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;20:2045–2052.

102. Atkins MB, Hsu J, Lee S, et al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic

,malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2008;26:5748–5754.

103. 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;17:571–577.

104. 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;23:6747–6755.

105. 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;20:1600–1607.

106. Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. J Clin Oncol 2007;25:5426–5434.

107. 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.

108. 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.

109. Wolf IH, Richtig E, Kopera D, Kerl H. Locoregional cutaneous metastases of malignant melanoma and their management. Dermatol Surg 2004;30:244–247.

110. Thompson JF, Kam PC. Isolated limb infusion for melanoma: a simple but effective alternative to isolated limb perfusion. J Surg Oncol 2004;88:1–3.

111. Fraker DL, Coit DG. Isolated perfusion of extremity tumors. Regional therapy of advanced cancer. 1997:333–350.

112. Lens MB, Dawes M. Isolated limb perfusion with melphalan in the treatment of malignant melanoma of the extremities: a systematic review of randomised controlled trials. Lancet Oncol 2003;4:359–364.

113. Lindner P, Doubrovsky A, Kam PC, Thompson JF. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. Ann Surg Oncol 2002;9:127–136.

114. Allen PJ, Coit DG. The surgical management of metastatic melanoma. Ann Surg Oncol 2002;9:762–770.

115. Ferrone CR, Ben Porat L, Panageas KS, et al. Clinicopathological features of and risk factors for multiple primary melanomas. JAMA 2005;294:1647–1654.

116. Crowley NJ, Seigler HF. Late recurrence of malignant melanoma. Analysis of 168 patients. Ann Surg 1990;212:173–177.

117. 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 Psychiatry 1993;50:681–689.

118. Gutman M, Cnaan A, Inbar M, et al. Are malignant melanoma patients at higher risk for a second cancer? Cancer 1991;68:660–665.

119. Kang S, Barnhill RL, Mihm MC Jr, Sober AJ. Multiple primary cutaneous melanomas. Cancer 1992;70:1911–1916.

120. Rhodes AR. Public education and cancer of the skin. What do people need to know about melanoma and nonmelanoma skin cancer? Cancer 1995;75:613–636.

121. Basseres N, Grob JJ, Richard MA, et al. Cost-effectiveness of surveillance of stage I melanoma. A retrospective appraisal based on a 10-year experience in a dermatology department in France. Dermatology 1995;191:199–203.

122. Weiss M, Loprinzi CL, Creagan ET, et al. Utility of follow-up tests for detecting recurrent disease in patients with malignant melanomas. JAMA 1995;274:1703–1705.

123. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007;357:2277–2284.

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