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Melanoma

Clinical Practice Guidelines in Oncology

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Overview

In 2010, an estimated 68,130 new cases of melanoma were diagnosed and approximately 8700 patients died of the disease in the United States.[1] However, these figures for new cases may represent a substantial underestimation, because many superficial and in situ melanomas treated in the outpatient setting are not reported. The incidence of melanoma continues to increase dramatically. Melanoma is increasing in men more rapidly than any other malignancy, and in women more rapidly than any other malignancy except lung cancer. For someone born in the United States in the year 2005, the lifetime risk for developing melanoma may be as high as 1 in 55.[2] The median age at diagnosis is 59 years. Therefore, melanoma ranks second to adult leukemia in terms of loss of years of potential life, per death.

NCCN Clinical Practice Guidelines in Oncology for Melanoma

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, melanoma, skin cancer, biopsy, surgical excision, adjuvant therapy, metastases, radiation therapy, chemotherapy, interferon, sentinel lymph node, margin, lymph node dissection, pathology

(JNCCN 2012;10:366–400)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN 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 the NCCN 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® (NCCN®) 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 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 online. 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 Panel members can be found on page 400. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

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

Risk factors for melanoma include a positive family history of melanoma, prior melanoma, multiple clinically atypical moles or dysplastic nevi,[3,4] and, rarely, inherited genetic mutations. Genetic counseling could be considered for individuals with a strong family history. In addition to genetic factors, sun exposure may also contribute to the development of melanoma.[5] Individuals with an inability to tan and fair skin that sunburns easily have a greater risk of developing melanoma.[6] However, melanoma can occur in any ethnic group and also in areas of the body without substantial sun exposure.

As with nearly all malignancies, the outcome of melanoma initially depends on the stage at presentation.[7] 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, within stage III, 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

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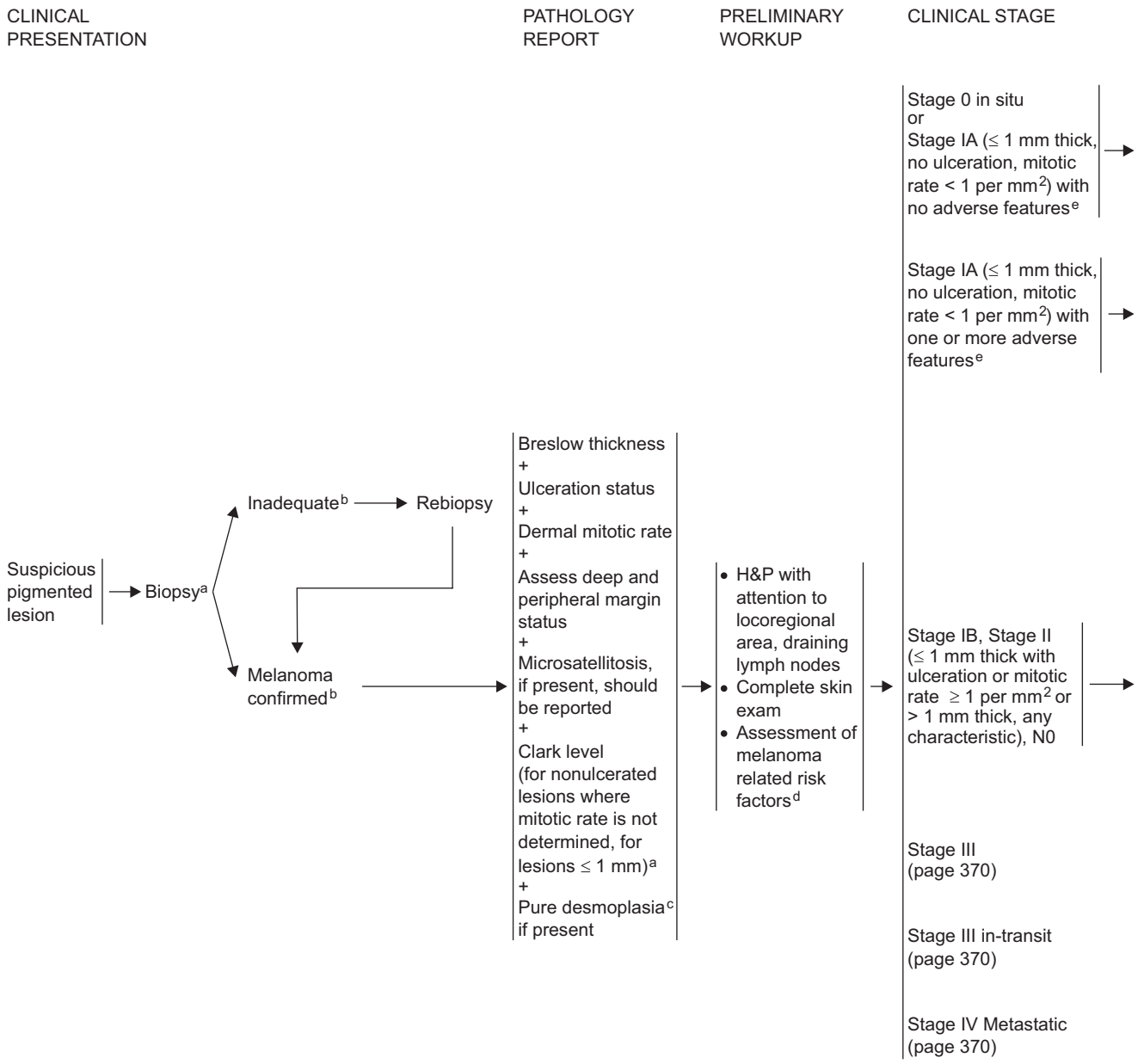

[a] See Principles of Biopsy and Principles of Pathology (page 374).
[b] If diagnostic biopsy is inadequate for treatment decisions, rebiopsy may be appropriate.
[c] Given the very low rates of sentinel lymph node positivity with pure desmoplastic melanoma, when a pure desmoplastic lesion is suspected, it is important that an experienced dermatopathologist examine the entire lesion before making the decision to perform a sentinel lymph node biopsy (SLNB). (Busam KJ. Desmoplastic Melanoma. Clin Lab Med 2011;31:321-330.)
[d] Risk factors for melanoma include family history of melanoma, prior primary melanoma, and other factors such as atypical moles/dysplastic nevi.
[e] Adverse features include ≥ 0.75 mm thick, positive deep margins, lymphovascular invasion (LVI), or Clark level IV.

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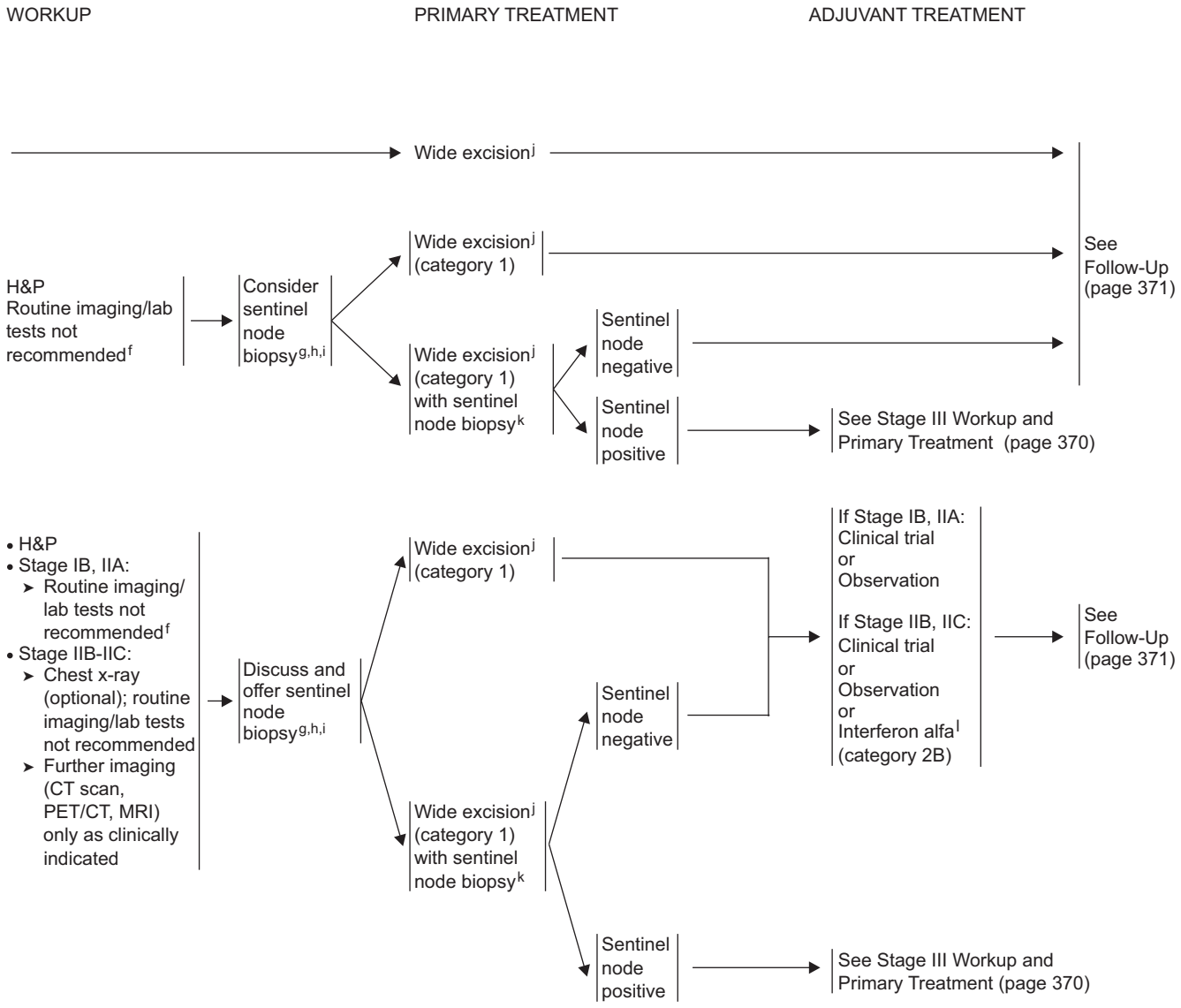
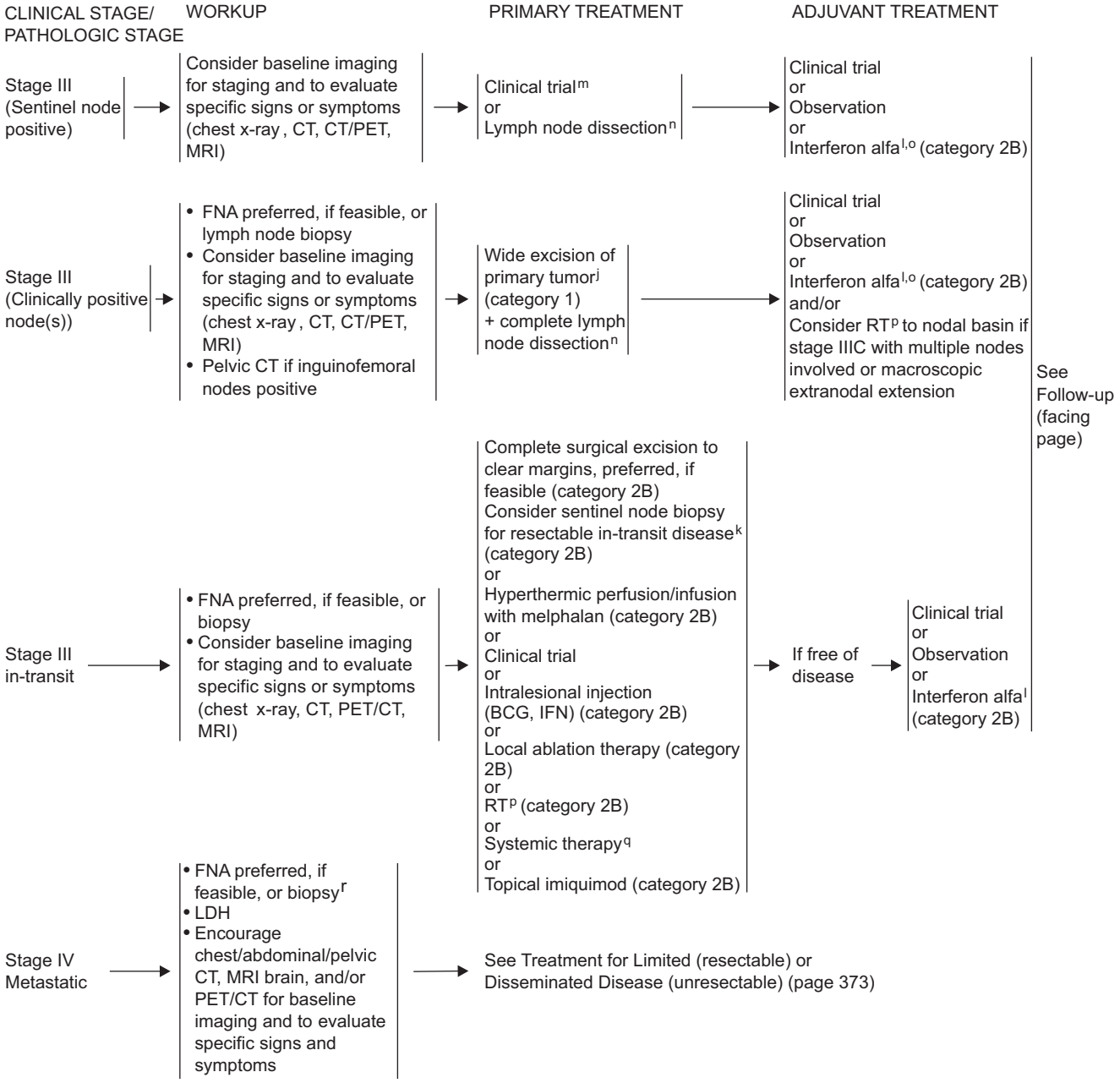


[e] Adverse features include ≥ 0.75 mm thick, positive deep margins, lymphovascular invasion (LVI), or Clark level IV.
[f] Imaging only to evaluate specific signs or symptoms (CT scan, PET/CT, MRI).
[g] Decision not to perform SLNB may be based on significant patient comorbidities, patient preference or other factors.
[h] Sentinel node biopsy is an important staging tool, but the impact of SLNB on overall survival is unclear.
[i] For lower risk patients, such as those with IA and IB lesions ≤ 0.5 mm thick and mitotic rate < 2 per mm^2, SLNB should generally not be recommended, unless there are specific adverse features (category 2B).
[j] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (page 375).
[k] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[l] Adjuvant interferon has been associated with improved disease-free survival, but its impact on overall survival is unclear.



[j] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (page 375).
[k] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[l] Adjuvant interferon has been associated with improved disease-free survival, but its impact on overall survival is unclear.
[m] Clinical trials assessing alternatives to complete lymph node dissection, such as careful observation with nodal basin ultrasound.
[n] See Principles of Complete Lymph Node Dissection (page 375).
[o] Interferon alfa can be given as high-dose interferon for 1 year or as peginterferon alfa-2b for up to 5 years.
[p] See Principles of Radiation Therapy (pages 376-377).
[q] See Systemic Therapy Options for Advanced or Metastatic Melanoma (pages 378-380).
[r] Obtain tissue for genetic analysis if the patient is being considered for targeted therapy or if it is relevant to eligibility for participation in a clinical trial.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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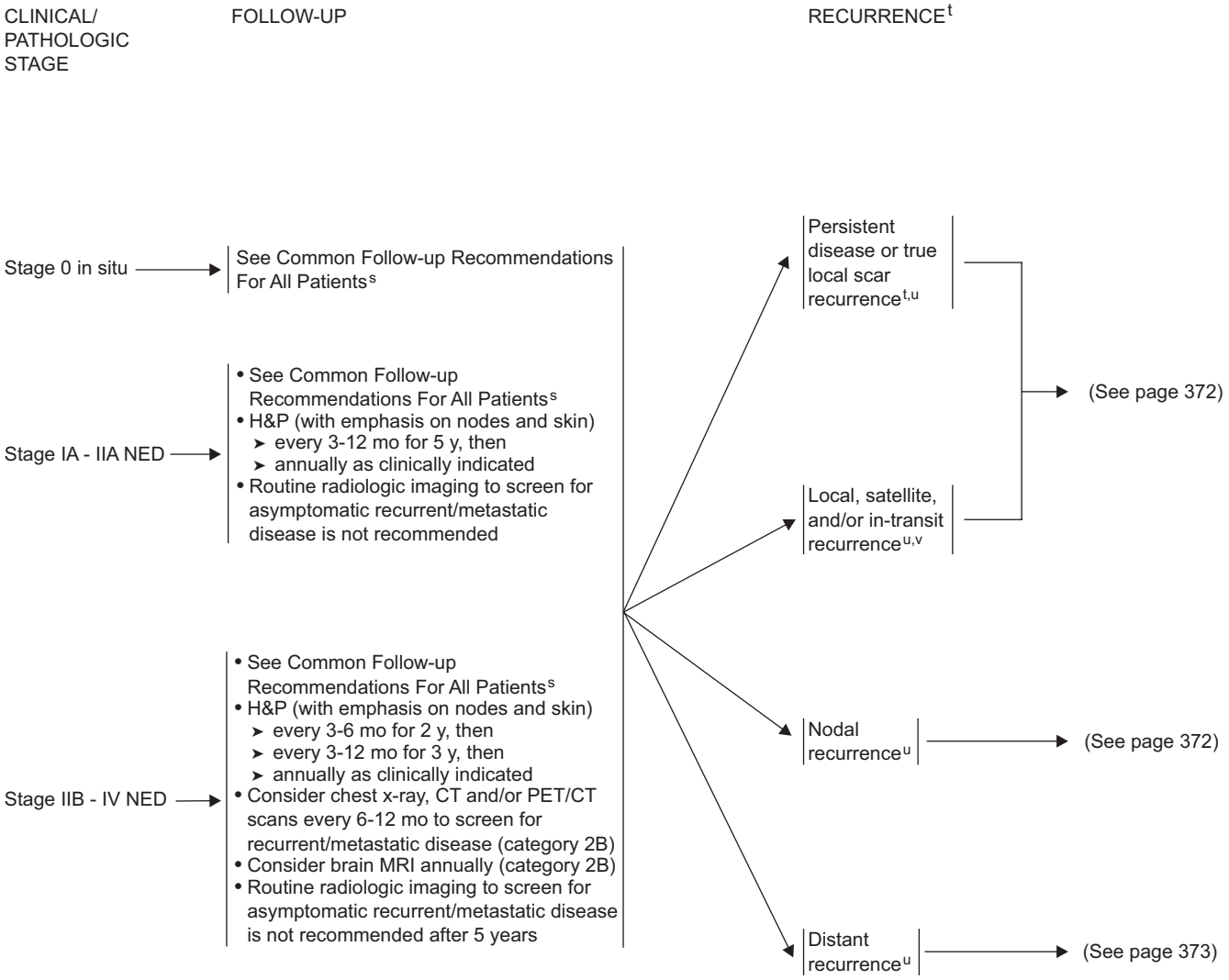


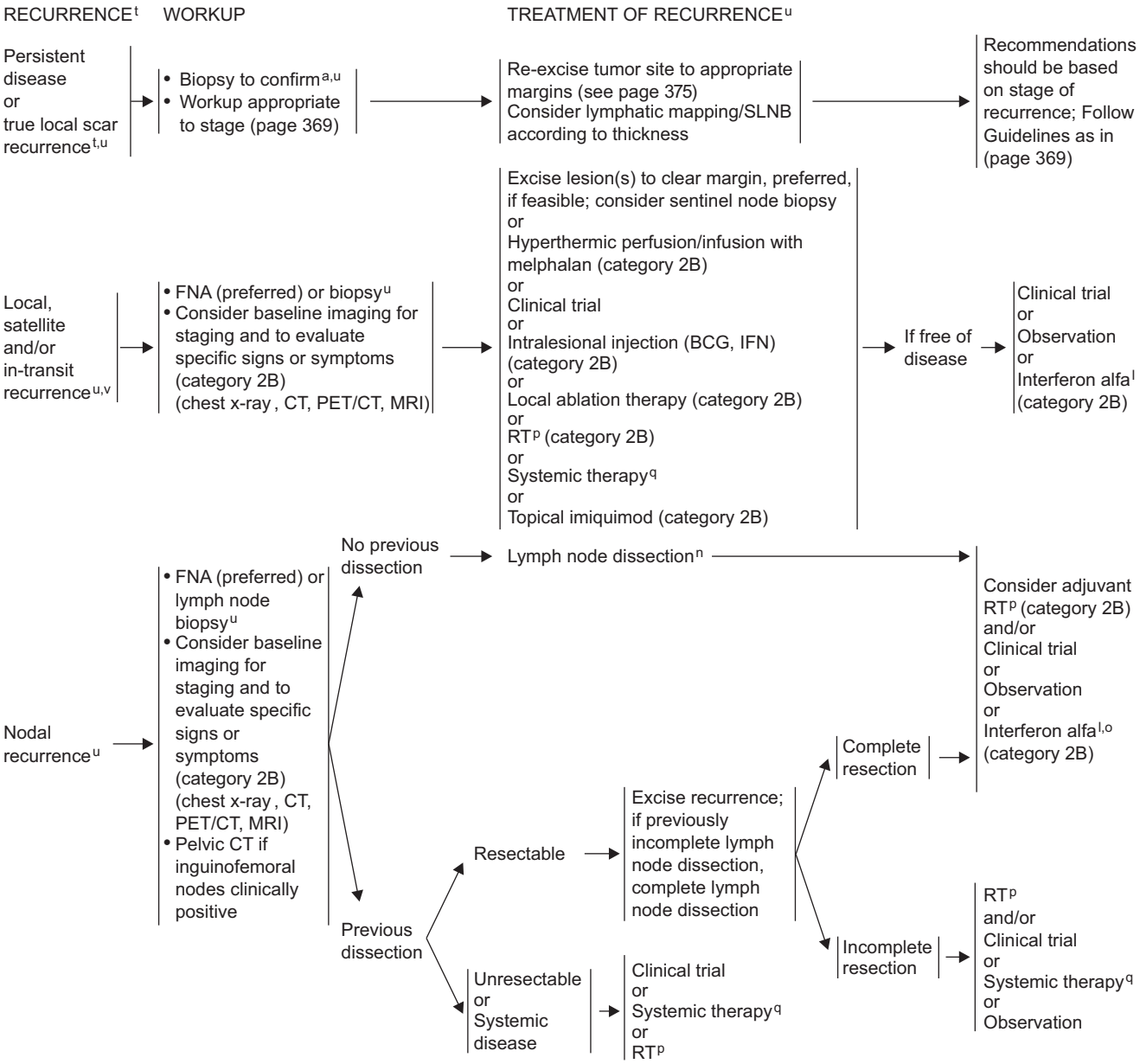
[s]Common Follow-up Recommendations For All Patients:
- At least annual skin exam for life
- Educate patient in monthly self skin exam (and monthly self lymph node exam for stage IA - IV NED)
- Routine blood tests are not recommended
- Radiologic imaging is indicated to investigate specific signs or symptoms

Follow-up schedule influenced by risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors, such as atypical moles/dysplastic nevi, and patient anxiety.

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

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

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



[a] See Principles of Biopsy and Pathology (page 374).
[l] Adjuvant interferon has been associated with improved disease-free survival, but its impact on overall survival is unclear.
[n] See Principles of Complete Lymph Node Dissection (page 375).
[o] Interferon alfa can be given as high-dose interferon for 1 year or as peginterferon alfa-2b for up to 5 years.
[p] See Principles of Radiation Therapy (pages 376-377).
[q] See Systemic Therapy Options for Advanced or Metastatic Melanoma (pages 378-380).
[t] Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.
[u] Initial clinical recurrence should be confirmed pathologically by biopsy whenever possible. Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.
[v] Local, satellite recurrence without in situ or radial growth phase, with deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar.

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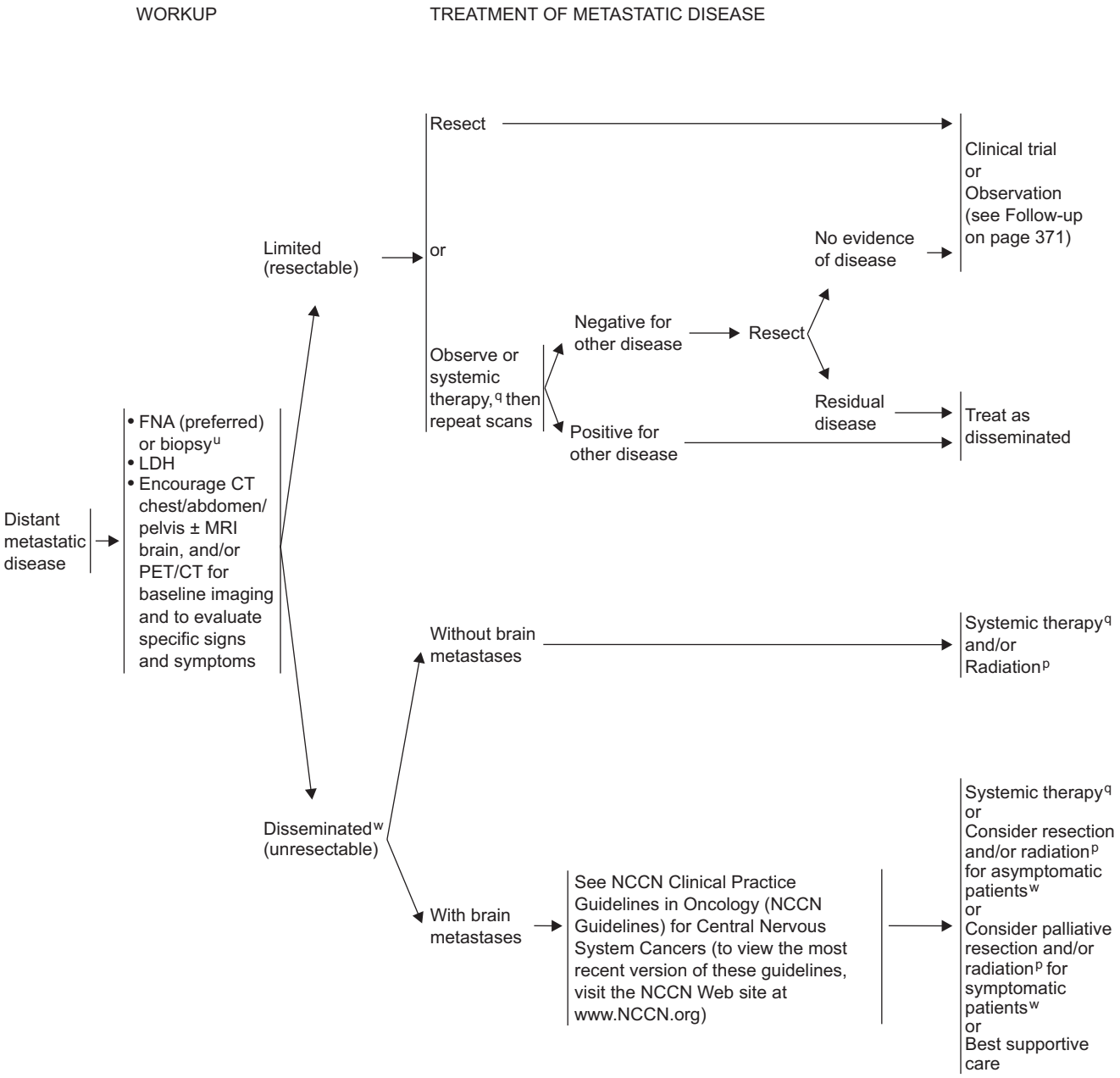

[p] See Principles of Radiation Therapy (pages 376-377).
[q] See Systemic Therapy Options for Advanced or Metastatic Melanoma (pages 378-380).
[u] Initial clinical recurrence should be confirmed pathologically by biopsy whenever possible. Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.
[w] 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.
- The orientation of the biopsy should be planned with definitive wide excision in mind.
- 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.

PRINCIPLES OF PATHOLOGY

- Biopsy to be read by a pathologist experienced in pigmented lesions.
- Minimal elements to be reported should include Breslow thickness (mm), histologic ulceration, dermal mitotic rate (per mm^2)[3] Clark level (encouraged for lesions $\leq$ 1 mm, optional for lesions > 1 mm), and peripheral and deep margin status of biopsy (positive or negative).
- Microsatellitosis, if present, should be reported.
- Encourage consistent reporting of these additional factors (compatible with American Academy of Dermatology recommendations):
  - Location
  - Regression
  - Tumor infiltrating lymphocytes (TIL)
  - Vertical growth phase (VGP)
  - Angiolymphatic invasion
  - Neurotropism
  - Histologic subtype
  - Pure desmoplasia, if present
    (specify pure vs. mixed desmoplastic with spindle cell and/or epithelioid cells)
- Consider use of comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH) for histologically equivocal lesions.[4]

[1] If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
[2] For lentigo maligna, melanoma in situ, a broad shave biopsy may help to optimize diagnostic sampling.
[3] Dermal mitotic rate should be determined using the "hot spot" technique and expressed as number of mitoses per square millimeter. (Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity; lessons learned from the generation of a probabilistic model. Ann Surg Oncol 2004;11:247-258, and Clark WH, Elder DE, Guerry D. Model predicting survival in stage I melanoma based on tumor progression. J Natl Cancer Inst 1989;81:1893-1904.)
[4] CGH may be more accurate than FISH in identifying relevant genetic mutations (Raskin L, Ludgate M, Iyer RK, et al. Copy number variations and clinical outcome in atypical spitz tumors. Am J Surg Pathol 2011;35:243-252).

PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

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

PRINCIPLES OF COMPLETE LYMPH NODE DISSECTION

Adequacy of regional lymph node dissection:

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

[1]For large melanoma in situ (MIS), lentigo maligna type, surgical margins > 0.5 cm may be necessary to achieve histologically negative margins; techniques for more exhaustive histologic assessment of margins should be considered. For selected patients with positive margins after optimal surgery, consider topical imiquimod (for patients with MIS) or RT (category 2B).
[2]Excision recommendations are based on clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist (category 1).
[3]Anatomic boundaries of lymph node dissection should be described in operative report.

PRINCIPLES OF RADIATION THERAPY

Consider radiation therapy in the following situations:[1]

PRIMARY DISEASE
- Adjuvant treatment for selected patients with desmoplastic melanoma with extensive neurotrophism

REGIONAL DISEASE
- Extracapsular extension
- ≥ 4 involved nodes
- Size ≥ 3 cm
- Cervical[2] > axillary > inguinal location
- Recurrent disease after prior complete nodal dissection[3]

METASTATIC DISEASE
- Brain metastases (see NCCN Guidelines for Central Nervous System Cancers; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org)
  - ➤ Definitive or palliative stereotactic radiosurgery and/or whole-brain radiation therapy
  - ➤ Adjuvant radiation following resection of brain metastases
- Other symptomatic or potentially symptomatic soft tissue and/or bone metastases

[1] Most systemic treatments should be held during radiation.
[2] In the cervical location, consider adjuvant radiation if ≥ 2 lymph nodes are involved and for lymph nodes ≥ 2 cm.
[3] A wide range of radiation dose/fractionation schedules is effective. Hypofractionated regimens may increase the risk for long-term complications, such as lymphedema and small bowel obstruction.

PRINCIPLES OF RADIATION THERAPY
(References)

Primary Disease

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- Farshad A, Burg G, Panizzon R, et al. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. Br J Dermatol 2002;146:1042-1046.
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Regional Disease

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Metastatic Disease

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- Konefal JB, Emami B, Pilepich MV. Analysis of dose fractionation in the palliation of metastases from malignant melanoma. Cancer 1988;61:243-246.
- Olivier KR, Schild SE, Morris CG, et al. A higher radiotherapy dose is associated with more durable palliation and longer survival in patients with metastatic melanoma. Cancer 2007;110:1791-1795.
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SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA[1]

- Clinical trial (preferred)
- Ipilimumab (category 1)[2,3]
- Vemurafenib (category 1)[4,5]
- Dacarbazine
- Temozolomide
- High-dose interleukin-2[6,7]
- Dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without interkeukin-2, interferon alfa) (category 2B)[7]
- Paclitaxel (category 2B)
- Paclitaxel/cisplatin (category 2B)
- Paclitaxel/carboplatin (category 2B)

[1] Patients who progress after initial therapy may be offered subsequent therapy if they maintain a performance status of ECOG 0-2 or Karnofsky score ≥ 60.
[2] Ipilimumab has the potential for significant immune-mediated complications. Participation in the risk evaluation and mitigation strategy (REMS) program and/or experience in use of the drug as well as resources to follow the patient closely are essential. Ipilimumab should be used with extreme caution, if at all, in patients with serious underlying autoimmune disorders.
[3] Reinduction with ipilimumab may be considered for select patients who experienced no significant systemic toxicity during prior ipilimumab therapy and who experience relapse after initial clinical response or progress after stable disease > 3 months.
[4] Vemurafenib is recommended for patients with V600 mutation of the BRAF gene documented by an FDA-approved or Clinical Laboratory Improvement Amendments (CLIA)-approved facility.
[5] Vemurafenib has the potential for significant dermatologic complications including cutaneous squamous cell carcinoma and extreme photosensitivity. Regular dermatologic evaluation with referral to a dermatologist as clinically indicated. Patients should also be carefully monitored for the development of other adverse reactions such as joint pain and swelling.
[6] High-dose interleukin-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, interleukin-2 therapy may be considered (category 2B).
[7] Administration of multiagent regimens and high-dose interleukin-2 is complex and associated with significant toxicities. Therapy should be restricted to an institution with medical staff experienced in the administration and management of regimens.

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SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA
(References)

Ipilimumab
- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Eng J Med 2010;363:711-723.
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517-2526.

Vemurafenib
- Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Eng J Med 2011;2507-2516.

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
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SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA
(References)

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

- 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.
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- 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;26:5746-5754.

Paclitaxel

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Paclitaxel and cisplatin

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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):Abstract 8510.
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have a more indolent clinical course that is biologically distinct from that of most patients with advanced disease.

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

Clinical Presentation and Workup

Biopsy

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

Excisional biopsy may be inappropriate for certain sites (including the face, palmar surface of the hand, sole of the foot, ear, distal digit, or subungual lesions) or for very large lesions. In these instances, a full-thickness incisional or punch biopsy of the clinically thickest portion of the lesion 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 accurately microstage the tumor (based on evaluation by a dermatopathologist) for treatment planning, rebiopsy with narrow margin excision should be considered.

Pathology Report

In the revised American Joint Committee of Cancer (AJCC) staging system, patients with melanoma 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).[7,8] Breslow tumor thickness, ulceration, and mitotic rate are the 3 most important characteristics of the primary tumor predicting outcome in patients with localized melanoma (stage I or II).

Mitotic rate is an indicator of tumor proliferation and is measured as the number of mitoses per mm^2. The latest AJCC staging manual recommended the "hot spot" technique for calculating the mitotic rate.[8] Barnhill et al.[9] compared the relative importance of mitotic rate with ulceration as major prognostic factors in localized melanoma. In a multivariate analysis including mitotic rate and ulceration, tumor thickness and mitotic rate (< 1, 1–6, > 6) emerged as the most important independent prognostic factors. Several other studies have also confirmed the prognostic importance of mitotic rate in patients with primary cutaneous melanoma.[10–12] In the evidence-based derivation of the 2010 AJCC staging system, mitotic rate greater than or equal to 1 per mm^2 was independently associated with worse disease-specific survival, especially in patients with melanoma less than or equal to 1.0-mm thick. Therefore, mitotic rate has replaced Clark level as a criterion for upstaging patients with melanomas less than or equal to 1.0 mm in thickness from IA to IB. In multivariate analyses, mitotic rate and younger age were identified as independent predictors of a positive sentinel lymph node (SLN), in addition to Breslow thickness.[13,14] In contrast to mitotic index, no threshold of age has been determined to be an independent predictor of a positive SLN. Young age alone is not a sufficient cause for performing sentinel lymph node biopsy (SLNB).

The American Academy of Dermatology (AAD) task force recommends including mitotic rate in the biopsy report, along with other additional optional factors, such as vertical growth phase, tumor-infiltrating lymphocytes, and regression.[15] 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. Clinicians should also note cases of pure desmoplastic melanoma (as opposed to mixed desmoplasia with spindle cell and/or epithelioid cells), because these have a very low incidence of nodal involvement that does not support the routine use of SLNB.[16–18] Mixed desmoplasia has a similar rate of lymph node spread to that of conventional

melanoma. When pure desmoplastic melanoma is suspected, the entire lesion should be examined by an experienced dermatopathologist; SLNB should not be performed on confirmed pure desmoplasia.

Some melanocytic proliferations can be diagnostically challenging. Examples are atypical melanocytic proliferation, melanocytic tumor of uncertain malignant potential, superficial melanocytic tumor of uncertain significance, atypical Spitz tumor, and atypical cellular blue nevus. These lesions are more frequently seen in younger patients, and when suspected, referral to a pathologist with expertise in atypical melanocytic lesions is recommended. When melanoma is in the differential diagnosis, the report should include prognostic elements as for melanoma. Comparative genomic hybridization (CGH) or fluorescence in situ hybridization (FISH), if available, should be considered to detect the presence of selected gene mutations for histologically equivocal lesions. CGH is a more comprehensive technique than FISH, which may offer higher sensitivity and specificity in identifying relevant copy number changes, as suggested by a recent small study on atypical Spitz tumors.[19]

Among patients with localized melanoma undergoing SLNB, the status of the sentinel node is the most important prognostic factor.[20] Among patients with nodal metastases (stage III), the number of metastatic nodes and clinical nodal status (nonpalpable vs. palpable) are the most important predictors of survival, followed by the presence or absence of primary tumor ulceration. Other prognostically relevant factors include the presence of extranodal tumor extension and, in patients with positive sentinel nodes, the size and location of the metastatic melanoma in the sentinel nodes.

The site of metastasis is the most significant predictor of outcome among patients with distant metastases (stage IV). Elevated lactose 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.[20,21]

NCCN Recommendations: The NCCN Melanoma Panel recommends including Breslow thickness, ulceration status, mitotic rate, deep and peripheral margin status (positive or negative), satellitosis (if present), and Clark level for nonulcerated lesions 1.0 mm or less when mitotic rate is not determined in the pathology report. Ideally, mitotic rate should be reported for all lesions, because it is emerging as an independent predictor of outcome. The panel agreed that recording of the parameters identified by the AAD task force would be helpful but not mandatory.

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

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

Preliminary Workup

After the diagnosis of melanoma has been confirmed, a history and physical examination (H&P) and complete dermatologic examination are recommended. Preliminary workup of patient presenting with melanoma or dysplastic nevi should include a detailed personal and family history, including any history of melanoma or dysplastic nevi removal.[3] In the physical examination of patients with invasive melanoma, physicians should pay special attention to the locoregional area and lymph node drainage basins of the established melanoma.

Clinical Staging

Patients can be clinically staged after histopathologic microstaging, an H&P including examination of locoregional area and draining lymph nodes, and a complete skin examination. In accordance with the AJCC staging system, these guidelines have categorized patients into the following clinical groups:

- Stage 0: melanoma in situ
- Stage IA: 1.0 mm thick or less; mitotic rate less than 1 per mm^2; no ulceration; with or without adverse prognostic features, such as thickness greater than 0.75 mm; positive deep margins; lymphovascular invasion; or Clark level IV
- Stage IB–II: 1.0 mm thick or less with ulceration or mitotic rate greater than or equal to 1 per mm^2; or greater than 1.0 mm thick and clinically negative nodes
- Stage III: clinically positive nodes and/or in-transit disease
- Stage IV: distant metastatic disease

Pathologic Staging

Patients with clinically localized stage I–II melanoma may be further pathologically staged by lymphatic mapping with sentinel lymph node biopsy. Depending on the primary tumor thickness, ulceration, and other factors described earlier, 5% to 40% of patients undergoing SLNB will be upstaged from clinical stage I–II to pathologic stage III based on subclinical micrometastatic disease in the SLN. These patients have a distinctly better prognosis than those with clinically positive nodes containing macrometastatic disease.[20,22] The AJCC staging system clearly recognizes this difference in prognosis among patients with pathologic stage III melanoma.[7]

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 a patient 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 in 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, findings that can lead to morbid invasive biopsy procedures or, at the very least, substantial patient anxiety while awaiting results of interval follow-up studies.

The yield of routine blood work and imaging studies in screening patients with clinical stage I–II melanoma for asymptomatic distant metastatic disease is very low. Screening blood tests are very insensitive, and the findings of cross-sectional imaging are often nonspecific, with frequent false-positive findings unrelated to melanoma.[23–25]

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%.[26–29] 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%.[30–32] These series also report a significant incidence of indeterminate or false-positive radiologic findings that are unrelated to the melanoma.

These retrospective studies are reporting minimum estimates, because defining a study population of patients with truly imaging-naïve stage III 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 cross-sectional imaging studies to detect metastatic disease at stage III diagnosis is a 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.[33–35] In patients with more advanced stage III disease, PET/CT scan may be more useful. In particular, PET/CT scans can help further characterize lesions found to be indeterminate on CT scan, and can image areas of the body not studied on routine body CT scans (e.g., arms, legs).[36]

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, recommendations for the appropriate extent of workup is mostly based on nonuniform consensus within the panel.

Routine cross-sectional imaging (CT, PET/CT, MRI) is not recommended for patients with stage I to II melanoma. These tests should only be used to investigate specific signs or symptoms. For patients with stage IIB–IIC, chest radiograph is optional. Routine blood tests are not recommended for stage I and II disease.

Most panel members acknowledged the low yield of screening CT or PET/CT scans in patients with stage III melanoma. Based on the results of the studies reported in the literature and the absence of conclusive data, the panel left the extent of cross-sectional imaging 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. At a minimum, a pelvic CT scan is recommended in the setting of inguinofemoral lymphadenopathy to rule out associated pelvic or retroperitoneal lymphadenopathy. Most of the panel also endorsed chest/abdominal CT, PET/CT, and/or MRI of the brain.

For the small group of patients presenting with stage III in-transit disease, the workup outlined for clinical 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 open biopsy of the lesion. Sample tissue may be obtained during biopsy for genetic analysis (e.g., *BRAF* or *c-KIT* mutational status) if considering targeted therapy or if it potentially impacts enrollment in clinical trials of targeted therapy (see Treatment of Metastatic Melanoma on page 389). Chest abdominal/pelvic CT, with or without PET/CT, should be considered to define the extent of stage IV disease.

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 that serum LDH be obtained at diagnosis of stage IV disease. Other blood work may be performed at the discretion of the treating physician.

Treatment of Primary Melanoma

Wide Excision

Surgical excision is the primary treatment for melanoma. Several prospective randomized trials have been conducted in an effort to define optimal surgical margins for primary melanoma.

An international prospective study conducted by the WHO randomized 612 patients with primary melanomas not thicker than 2.0 mm to wide excision with either 1.0- or 3.0-cm margins.[37,38] At a median follow-up of 90 months, local recurrence and disease-free and overall survival rates were similar in both groups.

The National Intergroup Trial randomized 468 patients with melanomas 1.0 to 4.0 mm in thickness to wide excision with either 2.0- or 4.0-cm margins. At a median follow-up of 10 years, no differences were seen in local recurrence and disease-free and overall survivals.[39,40] Prospective randomized trials from Sweden have confirmed that satisfactory local control and melanoma-specific survival are not compromised by narrower margins.[41,42]

In a more recent prospective randomized trial comparing 1.0- versus 3.0-cm margins for melanomas thicker than 2.0 mm, wider margins were associated with a slightly lower rate of combined local/regional/nodal recurrence, but not improvement in local recurrence alone or melanoma-specific survival.[43] A systematic review and meta-analysis also reported that surgical excision margins no more than 2.0 cm are adequate, and that surgical margins should not be less than 1.0 cm around primary melanoma.[44]

Management of lentigo maligna and in situ 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 to achieve complete surgical excision with meticulous margin control have shown high local control rates and are used at some NCCN Member Institutions, although they are not universally accepted.[45,46]

NCCN Recommendations: The clinical/surgical margins discussed in this section refer to those taken at surgery and do not necessarily correlate with gross pathologic/histologic margins measured by pathologists.

For in situ melanoma, a measured margin of 0.5 cm around the visible lesion should be obtained. For large in situ lentigo maligna melanoma, surgical margins greater than 0.5 cm may be necessary to achieve histologically negative margins. In the absence of prospective clinical trials, this margin is recommended based on panel consensus.

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 measur-

ing 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 ≤ 4.0 mm in thickness; category 2A for tumors > 4.0 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 the standard of 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.[47–51] However, long-term comparative studies are still needed. Radiotherapy (RT) has also been used selectively for lentigo maligna. In a retrospective review by Farshad et al.,[52] a 5% crude local failure rate occurred with definitive radiation, with a mean time to recurrence of 45.6 months. Of the 5 recurrences, 4 were at the edge of the radiation field, and the authors suggested targeting a margin of at least 10 mm around the visible lesion.

Sentinel Lymph Node Biopsy

SLNB is a minimally invasive staging procedure developed to identify patients with subclinical nodal metastases at higher risk of recurrence who could be candidates for complete lymph node dissection or adjuvant systemic therapy.[53] MSLT-I, an international multicenter phase III trial conducted by the Multicenter Selective Lymphadenectomy Trial Group, was initiated to evaluate the accuracy, morbidity, and use of lymphatic mapping and SLNB for staging patients with early-stage melanoma.[54] In a preliminary publication, Morton et al.[54] reported an initial sentinel node identification rate of 95%. SLNB was also associated with low false-negative and complication rates.

Recently, Morton et al.[55] 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 rate 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 following 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 compared with in those with clinically positive nodes. 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.

The value of SLNB for patients with thin melanomas (≤ 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.[56] A review by Andtbacka and Gershenwald[57] reported an overall SLN metastasis rate of 2.7% in patients with melanoma thinner than 0.75 mm from 7 studies. In patients with melanoma 0.75 to 1.0 mm thick, 6.2% of patients undergoing SLNB were found to have a positive SLN. Factors predicting an increased probability of a positive SLN in patients with thin melanomas include increasing Breslow thickness and, less consistently, Clark level, higher mitotic rate, and younger age. However, with relatively short follow-up, only one center showed any convincing evidence that the SLN status was predictive of outcome in this low-risk group of patients.[58] Larger series and longer-term follow-up are required to assess the prognostic value of the SLN in patients with thin melanoma.[59–61]

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.[62–64] 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.

The significance of tumor regression is debatable, with more recent studies reporting no association between the presence of regression and the incidence of SLN positivity.[65,66]

Meticulous pathologic examination of all sentinel nodes is mandatory. Serial sectioning and immunohistochemical staining should be performed. Because the presence of even scattered clusters of melanoma cells in a sentinel node is clinically relevant, the AJCC was unable to determine a sentinel node tumor burden too low to report as metastatic disease. However, the presence of bland or benign-appearing melanocytes should be interpreted with caution; these nodal nevi can masquerade as metastatic disease. In the presence of any doubt, review by an experienced dermatopathologist is recommended.

NCCN Recommendations: SLNB may be offered to appropriate patients with localized melanoma for pathologic staging. 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, positive deep margins, lymphovascular invasion, or young age (although no threshold of young age alone is sufficient to recommend SLNB). Because the yield of a positive SLNB 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 mitotic rate ≥ 1 per mm^2; or > 1.0 mm thick), SLNB should be discussed and offered. SLNB may also be considered for patients with resectable solitary in-transit stage III disease. However, although SLNB is a useful staging tool, its impact on the overall survival of these patients remains 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.

The validity of SLNB in accurately staging patients after prior wide excision is unknown. Therefore, wide excision before planned SLNB is discouraged, although patients may be considered for the procedure on an individual basis if they present after initial wide excision.

The panel discussed the appropriate management of clinically negative lymph nodes in patients at risk for regional metastases in the event that SLNB is unavailable. Based on the results of 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.

The panel discussed at length the absolute lower limit of probability of sentinel node positivity that should prompt a discussion of SLNB. They agreed that the procedure should be considered for patients with high-risk stage IA melanoma, and should be discussed and offered to patients with stage IB–IIC melanomas. For patients with stage IA or IB melanoma at very low risk for either positive sentinel lymph node or melanoma recurrence (≤ 0.5 mm thick and mitotic rate < 2 per mm^2), there is nonuniform panel consensus that it would be appropriate to omit SLNB unless other specific adverse features are present (category 2B). In the absence of firm data, the decision about SLNB in this setting should be left to the patient and the treating physician.

Lymph Node Dissection

Among patients with a positive sentinel node, published studies have reported additional positive nonsentinel nodes in approximately 15% to 20% of these complete lymph node dissection specimens.[67,68] However the impact of completion lymph node dissection on regional control and survival in this setting has not been clearly shown. 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 (Clinical-Trials.gov identifier: NCT00297895).

Complete lymph node dissection consists of an anatomically complete dissection of the involved nodal basin. The extent of complete lymph node dissection is often modified according to the anatomic area of lymphadenopathy. In the absence of clinical or radiologic evidence, patients with melanoma metastatic to inguinal nodes are at risk for pelvic node involvement and are candidates for elective pelvic lymph node dissection when more than 3 superficial nodes are involved, when the nodes are clinically positive, or when Cloquet's node is positive.[69–71]

NCCN Recommendations: If the sentinel node is negative, regional lymph node dissection is not indicated. Patients with stage III disease based on a positive SLN should be offered a complete lymph node dissection of the involved nodal basin, either as standard care or in the context of a clinical trial evaluating alternative strategies (such as close monitoring with nodal basin ultrasound). Participation in MSLT-II, assessing the option of nodal observation in patients with positive sentinel nodes, is encouraged if available. Nodal basin observation for these patients has not been studied sufficiently to be recommended as a standard option.

Patients presenting with clinically positive nodes without radiologic evidence of distant metastases should undergo wide excision of the primary site (if present) and complete lymph node dissection of the involved nodal basin. In the setting of inguinal lymphadenopathy, a pelvic dissection is recommended if the PET/CT or pelvic CT scan reveals iliac and/or obturator lymphadenopathy, or if a positive Cloquet's lymph node is found intraoperatively (category 2B). Pelvic dissection also should be considered for clinically positive nodes or if more than 3 superficial nodes are involved (category 2B).

One measure of the completeness of a regional lymph node dissection is the number of lymph nodes examined. However, the panel believed that available retrospective evidence was insufficient to mandate that a specific number of nodes be required to deem a lymph node dissection adequate for any designated lymph node basin. 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.

Adjuvant Treatment for Melanoma

Low- and Intermediate-Dose Interferon

The first major randomized trial of adjuvant interferon for completely resected stage III melanoma conducted by the WHO[72] showed no improvement in overall survival (35% for the interferon group vs. 37% for those assigned to observation alone). In the French Cooperative Group trial evaluating adjuvant interferon in patients with melanoma larger than 1.5 mm thick and clinically negative nodes, after a median follow-up of 5 years, adjuvant interferon therapy showed a significant relapse-free survival benefit and a nonsignificant trend toward increased overall survival.[73] In another prospective randomized study, adjuvant interferon prolonged disease-free survival for patients with resected stage II melanoma at a median follow-up of 41 months.[74]

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] study) compared adjuvant interferon with observation in patients with resected stage IIB and stage III melanoma. In the AIM HIGH study, low-dose interferon alfa-2a did not improve either overall or recurrence-free survivals.[75] EORTC 18952 reported no significant improvement in progression-free survival for intermediate-dose interferon alfa-2b.[76]

High-Dose and Pegylated 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 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 relapse-free and overall 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.[77]

The results of a larger follow-up trial, ECOG 1690, also showed a relapse-free survival advantage but none for overall survival.[78] ECOG 1694 compared high-dose interferon alfa-2b with an experimental vaccine, GM2-KLH21. At approximately 2 years' median follow-up, the interferon alfa-2b group showed better relapse-free and overall survivals than the vaccine group. More recently, concerns have been raised concerning the vaccine control group used in ECOG 1694. The randomized phase III trial of adjuvant GM2-KLH21 in 1314 patients with stage II melanoma (EORTC 18961) was closed early by the data monitoring committee because of inferior survival in the vaccine arm.[79]

A recent retrospective review of 200 patients with melanoma (stage IIB, IIC, or III) reported that those who had autoantibodies or clinical manifestations of autoimmunity after treatment with high-

dose interferon alfa-2b had improved relapse-free and overall survivals compared with patients who did not show manifestation of autoimmunity.[80]

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.[81] A pooled analysis of E1684, E1690, and E1694 confirmed an improvement in relapse-free survival in patients with high-risk resected melanoma (2-sided log-rank *P* value = .006) but found no significant improvement in overall survival.[82]

The ECOG studies included patients with stage IIB (≥ 4.0 mm with no evidence of lymph node involvement) and III melanomas with either regional lymph node disease or in-transit metastases. In a recent systematic review, Verma et al.[83] 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. Adjuvant high-dose interferon is a toxic therapy that is decreasingly being used in most institutions, but panelists agree that it still may have a role in community practice.

The EORTC protocol (18991) randomized 1256 patients with completely resected stage III melanoma to either observation or pegylated interferon alfa treatment for an intended duration of 5 years. Four-year relapse-free survival was significantly better in the interferon group compared with the observation group (45.6% vs. 38.9%); however, no significant effect of pegylated interferon was seen on overall survival.[84] Based on these data, pegylated interferon alfa received approval by the FDA in 2011 as an option for adjuvant therapy in patients with melanoma with nodal involvement. The panel included pegylated interferon as an adjuvant option for completely resected nodal disease.

A recent post hoc analysis of 2 large randomized phase III trials (EORTC1892 and EORTC18991) indicated that a reduction in risk for recurrence and death in patients treated with adjuvant interferon was observed primarily in patients with ulcerated primary melanomas.[85] The clinical and biologic significance of this observation remains unclear.

Adjuvant Radiation Therapy

Adjuvant RT is rarely necessary for excised local melanoma. One exception may be desmoplastic neurotropic melanoma (DNM), which tends to be locally aggressive. In a retrospective series of 128 patients with DNM (84% stage II), patients who did and did not receive adjuvant radiation had a similar incidence of local failure (7% with RT vs. 6% without) despite worse prognostic features in the radiated group (thicker tumors, deeper Clark level invasion, and narrower excision margins).[86] The authors concluded that radiation should be considered for patients with inadequate margins, which in this series occurred predominately in the head and neck region.

Radiation has a role in controlling nodal relapse in patients at risk. The largest retrospective review investigating the role of RT was performed by Agrawal et al.,[87] who evaluated 615 patients who met the specific criteria portending a high risk of regional nodal relapse based on lymph node number, size, location, and extracapsular extension. At a median follow-up of 5 years, regional recurrence occurred in only 10.2% of the radiated patients versus 40.6% of the nonradiated patients. Adjuvant radiation was associated with improved locoregional control on multivariate analysis ($P < .0001$). Notably, treatment-related morbidity was significantly increased with RT (5-year rate of 20% vs. 13%; $P = .004$), particularly lymphedema. A prospective randomized trial of adjuvant nodal basin RT versus observation in patients at risk for nodal relapses has been completed in Australia,[88] and preliminary results have been reported in abstract form. In this phase III trial, 250 patients with an isolated lymph node field melanoma relapse that was completely resected received either adjuvant radiation to the nodal basin or observation. Eligible patients included those with 1 or more parotid, 2 or more cervical or axillary, or 3 or more groin nodes; maximum node diameter of 3 cm or larger in neck or axilla or 4 cm or larger in the groin; or nodal extracapsular extension. Lymph node field recurrence was significantly less frequent in the adjuvant radiation group (hazard ratio [HR], 1.77; 95% CI, 1.02–3.08; $P < .041$), but no improvement was seen in overall survival. Postoperative radiation with various fractionation schemes has been used in other clinical studies.[89–91]

Publication of trial results is anticipated soon. Hypofractionated RT seems as equally effective as standard fractionation. Although particular concern for toxicity should be exercised when using higher doses per fraction, all studied regimens seem well tolerated.

NCCN Recommendations: Most patients with in situ or early-stage melanoma will be cured with primary excision alone. However, patients who have desmoplastic lesions with extensive neurotrophism are at high risk for local recurrence, especially if margins are suboptimal. Adjuvant radiation after surgery may be considered to improve local control. If positive margins remain after optimal surgery, topical imiquimod (for melanoma in situ) or RT may be considered in selected patients (category 2B). 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 mitotic rate ≥ 1 per mm^2; or > 1.0 mm thick), adjuvant treatment options include a clinical trial or observation. For patients with node-negative stage IIB or IIC disease, adjuvant treatment options include clinical trial, observation, or high-dose interferon alfa. For patients with stage III melanoma, adjuvant treatment options include clinical trial (preferred), observation, or interferon alfa. Pegylated interferon alfa is an alternative to high-dose interferon in completely resected stage III disease with either positive sentinel nodes or clinically positive nodes, but not for stage III in-transit disease. Adjuvant RT to the nodal bed should be considered for high-risk nodal disease: multiple positive nodes, large nodes, or macroscopic extranodal soft tissue extension, with a lower threshold for using RT in the cervical lymph node location.

Treatment with adjuvant high-dose or pegylated interferon alfa is currently a category 2B recommendation in all of the cases described because of low benefit-to-risk ratio. Decisions about the appropriateness of adjuvant interferon alfa-2b treatment for patients should be made on an individual basis after discussion with the patient, which should include an explanation of the potential benefits and side effects of interferon therapy.

In all patients who have been rendered free of disease by surgery, after initial treatment for recurrent regional or distant metastatic disease (stage III in-transit metastases or stage IV), consideration of adjuvant treatment is appropriate. No evidence supports the use of adjuvant interferon alpha for completely resected stage IV disease, and the panel does not recommend it as an option in that setting. Therefore, the main option for adjuvant therapy in this setting is participation in a clinical trial. See next section on Treatment of Metastatic Melanoma and Treatment of Recurrence section on page 394.

Treatment of Metastatic Melanoma

Local Treatment for In-Transit Disease

Many different treatment options, mostly local/regional, are available for patients presenting with stage III in-transit metastases. Treatment is based on the size, location, and number of tumor deposits, but evidence is limited and no consensus exists on the best approach. Excision to clear margins is the mainstay for resectable tumors in small numbers. Although in-transit disease has a high probability of occult nodal involvement, and a positive sentinel node in the presence of in-transit metastasis portends a more ominous prognosis, the impact of SLNB on outcome remains unproven.[92]

Several nonsurgical regional approaches are being used. Isolation limb perfusion or infusion is a method to administer high doses of chemotherapy to an affected extremity while avoiding systemic drug exposure.[93,94] Melphalan is the drug widely used for this technique. Isolation limb infusion has been reported by Thompson et al.[95] to be a simpler technique, with response rates comparable to those of limb perfusion. A recent study of isolated limb infusion in 128 patients showed a complete response rate of 31%.[96] However, a modified hyperthermic isolated limb perfusion procedure was associated with a higher complete response rate of 63%, with 5-year survival observed in 38% of patients.[97]

Other therapies include intralesional local injections with bacillus Calmette-Guérin (BCG)[98] or interferon alfa, laser ablation, and topical imiquimod.[99] Imiquimod may have some activity for small superficial dermal lesions but not for subcutaneous disease.[100] RT is sometimes used; however, patients with satellitosis are at risk for recurrence in the radiated field. In a series of high-risk patients who received adjuvant radiation, the only risk factor associated with in-field locoregional recurrence was satellitosis.[90]

Systemic Therapy

Traditional Chemotherapy: Metastatic melanoma is associated with a poor prognosis. Common agents currently being used in community practice include dacarbazine,[101,102] temozolomide,[102] high-dose interleukin-2,[103–106] and paclitaxel with or without cisplatin or carboplatin.[107–111] These have shown modest response rates of less than 20% in first- and second-line settings. Little consensus exists regard-

ing standard chemotherapy for patients with metastatic melanoma, which most likely reflects the low level of activity of older FDA-approved agents.[112,113] However, the therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents.

Novel Therapies: Ipilimumab, a monoclonal antibody directed to the immune checkpoint receptor termed *cytotoxic T lymphocyte antigen-4* (CTLA-4), received FDA approval for treatment of metastatic melanoma in March 2011. Approval was based on a randomized phase III trial of 676 patients with unresectable metastatic disease that progressed during systemic therapy.[114] Patients received ipilimumab plus a glycoprotein 100 peptide vaccine (gp100), ipilimumab alone, or gp100 alone in a 3:1:1 ratio. Overall survival was significantly longer in patients receiving the combination (10.0 months; HR, 0.68 compared with gp100 alone; $P < .001$) or ipilimumab alone (10.1 months; HR, 0.66 compared with gp100 alone; $P = .003$) compared with those receiving gp100 only (6.4 months). Notably, 15 of 23 patients experienced partial response or stable disease after reinduction.

Ipilimumab stimulates T cells and is associated with substantial risk of immune-related reactions. Patients with underlying autoimmune disorders may be especially susceptible to serious reactions. In this pivotal trial, immune-related events were recorded in 60% of patients treated with the agent. Of treated patients, 10% to 15% experienced grade 3 or 4 events. Diarrhea was the most common immune-related reaction; severe cases were treated with high-dose corticosteroids. In all, 7 deaths were attributed to immune-related toxicity in the trial.

In a second phase III study, 502 patients with previously untreated metastatic melanoma were randomly assigned to ipilimumab plus dacarbazine or dacarbazine plus placebo.[115] The primary end point was reached with the ipilimumab arm, showing longer overall survival than the control arm (11.2 vs 9.1 months). The 3-year survival rates were 20.8% and 12.2% for patients receiving ipilimumab and placebo, respectively (HR, 0.72; $P < .001$). A 56% incidence of grade 3 or 4 adverse events was recorded in the ipilimumab arm, but no drug-related deaths occurred.

Approximately 45% of patients with metastatic melanoma harbor an activating mutation of the intracellular signaling kinase, BRAF. Vemurafenib is a specific inhibitor of signaling by mutated BRAF.[116] A randomized phase III trial compared vemurafenib with dacarbazine in 675 patients with previously untreated metastatic melanoma containing a V600 mutation of *BRAF*.[117] Vemurafenib was associated with improved overall and progression-free survival (relative risk [RR] of death, 0.37; RR of death or progression, 0.26; $P < .001$). At 6 months, 84% and 64% of patients were alive in the vemurafenib and dacarbazine groups, respectively. Overall, 38% of patients receiving vemurafenib required dose modification because of adverse events. Skin complications were frequently associated with the agent: 18% of vemurafenib-treated patients developed cutaneous squamous cell carcinoma or keratoacanthoma that required simple excision, whereas 12% experienced grade 2 or 3 photosensitivity skin reactions. Arthralgia was the most common (21%) noncutaneous side effect.

Based on the results of this randomized study, vemurafenib was approved by the FDA in August 2011 for the treatment of metastatic or unresectable melanoma with the *BRAF* mutation. The Cobas 4800 BRAF V600 mutation test, a companion diagnostic test to determine the tumor mutational status, received approval along with the agent. The panel added vemurafenib to the list of available systemic treatments for patients with a documented V600 E or K mutation of the *BRAF* gene. Mutational status should be tested by an FDA-approved test or a facility approved by Clinical Laboratory Improvement Amendments (CLIA).

Although approval of ipilimumab and vemurafenib has significantly altered the initial management of patients with stage IV melanoma, each agent has unique limitations. Ipilimumab is associated with the potential for serious autoimmune toxicity, clinical responses may take months to become apparent, and the overall response rate is less than 20%. However, when responses are seen, they can be durable. Vemurafenib, on the other hand, is associated with a 40% to 50% response rate in patients with a V600-mutated *BRAF* gene, and responses may be seen days to weeks after starting the drug. Unfortunately, the median duration of response is only 5 to 6 months.

The success of these 2 agents has prompted a new wave of questions regarding their use in the adjuvant setting, augmenting response through

combining them with cytotoxic chemotherapy, and defining mechanisms of drug resistance.

The pace of change underscores the importance of participating in a clinical trial whenever possible; this remains the preferred choice of management for unresectable metastatic disease in these guidelines.

Biochemotherapy: Biochemotherapy is the combination of chemotherapy and biologic agents. In single-institutional phase II trials, biochemotherapy (cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2) produced overall response rates of 27% to 64% and complete response rates of 15% to 21% in patients with metastatic melanoma.[118–120] In a small phase III randomized trial comparing sequential biochemotherapy (dacarbazine, cisplatin, vinblastine with interleukin-2 and interferon alfa administered on a distinct schedule) versus dacarbazine plus cisplatin and vinblastine (CVD), response rates were 48% and 25%, respectively, and median survival was 11.9 versus 9.2 month, respectively.[121] In a phase III randomized intergroup trial (E3695), biochemotherapy (cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alpha-2b) produced a slightly higher response rate and progression-free survival than CVD alone, but it was not associated with improvement in either quality of response or overall survival.[122] Biochemotherapy was substantially more toxic than CVD. Additional attempts to decrease toxicity of biochemotherapy through administering subcutaneous outpatient interleukin-2 did not show a substantial benefit of biochemotherapy versus chemotherapy alone.[123–125] A recent meta-analysis also showed that although biochemotherapy improved overall response rates, it was not associated with a survival benefit in patients with metastatic melanoma.[126]

Palliative Radiation Therapy: Contrary to common perception that melanoma is radioresistant, RT often achieves good palliation of symptomatic metastatic disease. Studies have shown a 39% and 68% to 84% incidence of significant symptom relief for CNS and non-CNS metastasis, respectively.[127,128] The reported clinical complete response rate ranges from 17% to 69%, with 49% to 97% of patients experiencing either a partial or complete response.[91,129,130] In a single-institutional review of 121 patients receiving palliative RT, overall and complete response rates of 49% and 17% were observed in the stage IV group.[130] The brain metastases response rate was 54%. For nodal or in-transit metastases, a 77% overall response was reported, including 44% with a complete response.

NCCN Recommendations

Stage III: In-Transit Metastases: For patients with a single or a small number of in-transit metastases, complete surgical excision with histologically negative margins is preferred, if feasible (category 2B). In patients undergoing curative resection of a solitary in-transit metastasis, SLNB can be considered (category 2B).

In patients who have a limited number of in-transit metastases, particularly dermal lesions, which are not amenable to complete surgical excision, intralesional local injections with BCG or interferon alfa, or topical imiquimod, can be used. Laser ablation or RT may be given to selected patients. For patients with multiple, regional, in-transit metastases, regional chemotherapy by hyperthermic perfusion or infusion is an option. All of these treatments are category 2B recommendations. Other alternatives include systemic therapy (particularly after failure of local and/or regional therapy) or treatment in the context of a clinical trial.

Distant Metastatic Disease (Stage IV): Treatment of stage IV metastatic melanoma depends on whether disease is limited (resectable) or disseminated (unresectable).

Resection, if feasible, is recommended for limited metastatic disease. 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 in a clinical trial. There is panel consensus that adjuvant interferon alpha monotherapy outside of a clinical trial is inappropriate for resected stage IV disease. Alternatively, limited metastatic disease can be treated with systemic therapy either in the context of a clinical trial (preferred) or as standard care. Residual disease after incomplete resection for limited metastases is treated as described here for disseminated disease.

Disseminated disease is treated based on the presence or absence of brain metastases. For patients without brain metastases, options for systemic therapy include:

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

Close monitoring of potentially lethal immune-related events in patients receiving ipilimumab is essential, and panelists strongly recommend participation in the risk evaluation and mitigation strategy (REMS) program during the course of ipilimumab treatment. Patients treated with ipilimumab who experience stable disease of 3 months' duration after week 12 of induction or partial or complete response, who subsequently experience progression of melanoma, may be offered reinduction with up to 4 doses of ipilimumab at 3 mg/kg every 3 weeks. For patients on vemurafenib, the panel recommends regular dermatologic evaluation with referral to a dermatologist as indicated to monitor for skin complications.

Caution is warranted in the administration of high-dose interleukin-2 or biochemotherapy because of the high degree of toxicity reported. Some patients may attempt biochemotherapy for palliation or to achieve a response that may render them eligible for other therapies. In any case, if this therapy is considered, the panel recommends patients receive treatment at institutions with relevant expertise. Contraindications for interleukin-2 include inadequate organ reserve, poor performance score, and untreated or active brain involvement.

The recommendation for first-line systemic therapy of melanoma is based on several factors, including the *BRAF* mutation status, the tempo of disease, and the presence or absence of cancer-related symptoms. Patients with low-volume, asymptomatic metastatic melanoma may be good candidates for immunotherapy (ipilimumab or interleukin-2), because there will hopefully be time for an antitumor immune response to emerge. Patients with *BRAF*-mutant melanoma who have symptomatic disease or who have progressed despite immunotherapy should be considered for vemurafenib. Clinical trials are underway to address unanswered questions regarding the optimal sequencing and/or combination of these agents.

For patients who are intolerant to or experiencing relapse after first-line systemic therapy, additional systemic therapy may be indicated in those with an ECOG performance status of 0 to 2 or a Karnofsky status of 60 or greater. Options for second-line therapy include clinical trial (preferred) or treatment with a different agent from the list of first-line options indicated earlier.

For patients with brain metastases, the treatment of the CNS disease usually takes priority in an effort to delay or prevent intratumoral hemorrhage, seizures, or neurologic dysfunction. Treatment for patients with brain metastases is based on symptoms, number of lesions present, and location of the lesions, as described in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Central Nervous System Cancers (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Stereotactic radiosurgery and/or whole-brain radiotherapy may be administered either as the primary treatment or as an adjuvant following resection. In addition to systemic therapy, surgical resection and/or radiation may be considered for palliation or management of symptoms, such as gastrointestinal bleeding or obstruction, painful or ulcerated soft tissue cutaneous metastases, or bulky adenopathy. Best supportive care is an alternative for these patients.

In patients with both brain and extracranial metastases, therapy as outlined in the preceding paragraph may be administered during or after treatment of the CNS disease, with the exception of high-dose interleukin-2, which has low efficacy in patients with previously untreated brain metastases and may worsen edema surrounding the untreated metastases. Disagreement exists on the value of interleukin-2 therapy in patients with small brain metastases but no significant peritumoral edema; interleukin-2 may be considered in selected cases (category 2B).

Follow-Up

In the absence of 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; other factors, such as the presence and extent of dysplastic nevi and patient anxiety, will also impact the follow-up schedule.[131] 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 later) is well documented, especially for patients initially presenting with early-stage melanoma.[132] Following up all patients intensively for metastatic disease beyond 5 to 10 years (depending on relative risk for recurrence) is probably not cost-effective.[133] However, because the lifetime risk of 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.

In a recent large retrospective review on patients with relapsing stage III disease, Romano et al.[134] found that the risk of initial locoregional or nodal relapse decreases to less than 5% in 3 years for patients with stage IIIA disease, 2 years for those with stage IIIB disease, and 7 months for those with stage IIIC disease. This suggests that frequent physical examinations beyond these time points will unlikely detect many recurrences. However, increasing risk of systemic or brain relapse was associated with higher substage, with stage IIIC having a 48% risk of nonbrain recurrence and a 13% risk of brain involvement. The authors suggested that periodic surveillance CNS imaging for 3 years might avert some of the substantial morbidity incurred by patients with stage IIIC disease who present with symptomatic CNS recurrence.

Documenting the effect of intensive surveillance on the outcome of patients with melanoma is difficult. A structured follow-up program could detect recurrent disease 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 SLNB, 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 nonmelanoma primary malignancies, patient education, and documentation of treatment results.[135–137] Studies on medical imaging have reported low yield, significant false-positivity, and risks of cumulative radiation exposure.[138–141] Therefore, frequent imaging should not be part of the routine follow-up for all patients.

Education on skin cancer prevention, including sun protection measures, should be promoted for patients with melanoma and their families.[142] Increasing evidence shows that regular sunscreen use may diminish the incidence of subsequent melanoma.[143] Patients can be made aware of the various resources that discuss skin cancer prevention. Some useful resources can be found on the following Web sites:

- American Academy of Family Physicians. Information for your family doctor: "safe-sun" guidelines (www.aafp.org/afp/20000715/375ph.html).
- American College of Preventive Medicine Practice Policy Statement: skin protection from ultraviolet light exposure (http://www.acpm.org/resource/resmgr/policy-files/polstmt_ultraviolet.pdf).
- 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 patients with melanoma, including those with stage 0 in situ melanoma. All patients who had stage IA to IV melanoma should be educated about posttreatment monthly self-examination of their skin and lymph nodes. Specific signs or symptoms are indications for additional radiologic imaging.

For patients with stage IA to IIA melanoma and no evidence of disease, comprehensive H&P 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. The consensus of the panel is that routine blood testing or imaging is not useful for these patients.

For patients with stage IIB–IV melanomas and no evidence of disease, comprehensive H&P 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. The surveillance interval should be tailored to substage. Although not recommended at baseline, chest radiograph, CT, MRI, and/or PET/CT every 6 to 12 months can be considered to screen for recurrent or metastatic disease at the discretion of the physician (category 2B). Routine blood testing to detect recurrence is not recommended for these patients.

Because most recurrences manifest within the first 5 years, routine imaging is not recommended beyond this period.

Treatment of Recurrence

Initial clinical recurrence should be confirmed pathologically with FNA cytology or biopsy whenever possible. If the patient is potentially seeking enrollment in a clinical trial of targeted therapy, obtaining a sample for genetic testing during biopsy may be helpful.

NCCN Recommendations

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 close to the wide excision scar). In the former situation, the prognosis after re-excision is much better, whereas the latter scenario is prognostically similar to recurrent regional disease.

For true local scar recurrence after inadequate primary therapy, the workup should be similar to that of the primary tumor based on lesion thickness. Re-excision to appropriate margins is recommended, with or without lymphatic mapping and SLNB, appropriate to the microstaging of the recurrence.

Local, Satellite, and/or In-Transit Recurrence: For a local recurrence after adequate prior wide excision, baseline imaging (chest radiograph, CT and/or PET/CT or MRI) should be considered for staging and to evaluate specific signs or symptoms. In the absence of extraregional disease, surgical excision with negative margins is recommended for local recurrence after initial adequate wide excision. Lymphatic mapping with SLNB may be considered in these patients on an individual basis. Adjuvant treatment options following complete resection of a local recurrence after adequate primary therapy include clinical trial, observation, or interferon alfa (category 2B).

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

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

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

Regional Nodal Recurrence: For patients presenting with regional nodal recurrence, the clinical diagnosis should be confirmed preferably with biopsy (FNA or excision). The workup is similar to the one previously outlined for patients with clinically positive lymph nodes.

For patients who have not undergone prior lymph node dissection or had an incomplete lymph node dissection, a complete lymph node dissection is advised. If the patient underwent a previous complete lymph node dissection, excision of the recurrence to negative margins is recommended if possible. After complete resection of nodal recurrence, options for adjuvant treatment include a clinical trial, observation, or, in patients not previously treated, high-dose or pegylated interferon alfa (category 2B). Adjuvant radiation may also be considered (category 2B). Options for patients with incompletely resected nodal recurrence include radiation and/or clinical trial, systemic therapy, or observation. Those with unresectable disease may participate in a clinical trial or receive systemic therapy or RT.

Distant Recurrence: For patients presenting with distant recurrence, the workup and treatment options are similar to those outlined previously for patients presenting initially with stage IV metastatic disease.

Summary

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 those for treating recurrent disease. Few, if any, firm recommendations can be made about more controversial issues for patients with melanoma, 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 clinician judgment and other factors, such as local resources and expertise and the individual patient's needs, wishes, and expectations. Furthermore, these guidelines undergo annual revision and are continually updated as new data become available.

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