NCCN National Comprehensive Cancer Network®

The NCCN

Merkel Cell Carcinoma

Clinical Practice Guidelines in Oncology™

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Overview

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous tumor that combines the local recurrence rates of infiltrative non-melanoma skin cancer along with the regional and distant metastatic rates of thick melanoma.[1–16] Several large reviews document the development of local recurrence in 25% to 30% of all cases of MCC, regional disease in 52% to 59%, and distant metastatic disease in 34% to 36%.[1,16,17] MCC has a mortality rate that exceeds that of melanoma;[18] overall 5-year survival rates range from 30% to 64%.[3,19] A history of extensive sun exposure is a

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Key Words

NCCN Clinical Practice Guidelines, Merkel cell carcinoma, non-melanoma skin cancer, sentinel lymph node biopsy, neuroendocrine carcinoma (*JNCCN* 2009;7:322–332)

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 Merkel Cell Carcinoma 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 Merkel Cell Carcinoma Guidelines Panel members can be found on page 332. (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 factor for MCC. Older white men (≥ 65 years) are at higher risk for MCC, which tends to occur on the areas of the skin that are exposed to sun.[20]

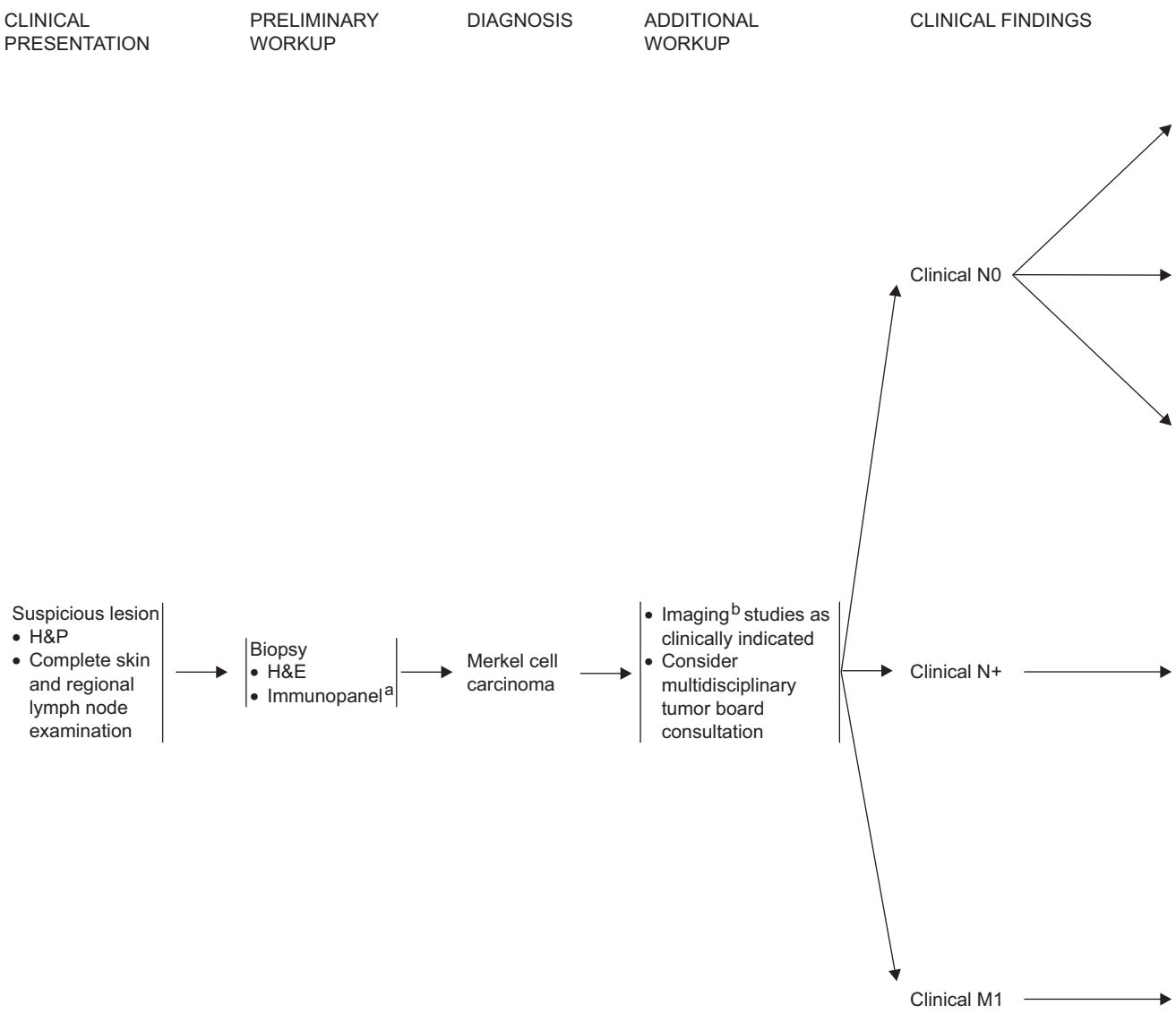
The NCCN Non-Melanoma Skin Cancer Panel has developed guidelines outlining treatment of MCC to supplement the squamous cell and basal cell skin cancer guidelines (see NCCN Basal Cell and Squamous Cell Skin Cancers Guidelines [to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org]).[21] MCC is a rare tumor; therefore, no prospective, statistically significant data are available to verify the validity of any prognostic features or treatment outcomes. The panel relied on trends that are documented in smaller, individual studies and in meta-analyses and their own collective experiences.

Diagnosis and Workup

Initial workup of a suspicious lesion starts with a complete examination of skin and regional lymph nodes followed by biopsy (see page 324). The primary goal in biopsy of an MCC is to confirm the diagnosis. The tumor rarely presents clinically as a classic lesion when MCC is expected to be the main diagnosis. The histologic diagnosis may be challenging, because MCC is similar to various other widely recognized small, round, blue cell tumors. The most difficult differentiation is often between primary MCC and metastatic small cell carcinoma of the lung.

Initial diagnosis of MCC in the primary lesion by hematoxylin and eosin staining (H&E) should be further confirmed by performing immunohistochemical (IHC) staining.

Text continues on p. 329



[a]An appropriate immunopanel should preferably include CK-20 and thyroid transcription factor-1 (TTF-1).
[b]Imaging (CT, MR, or PET) may be indicated to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma (e.g., small cell lung cancer), especially in cases where CK-20 is negative.

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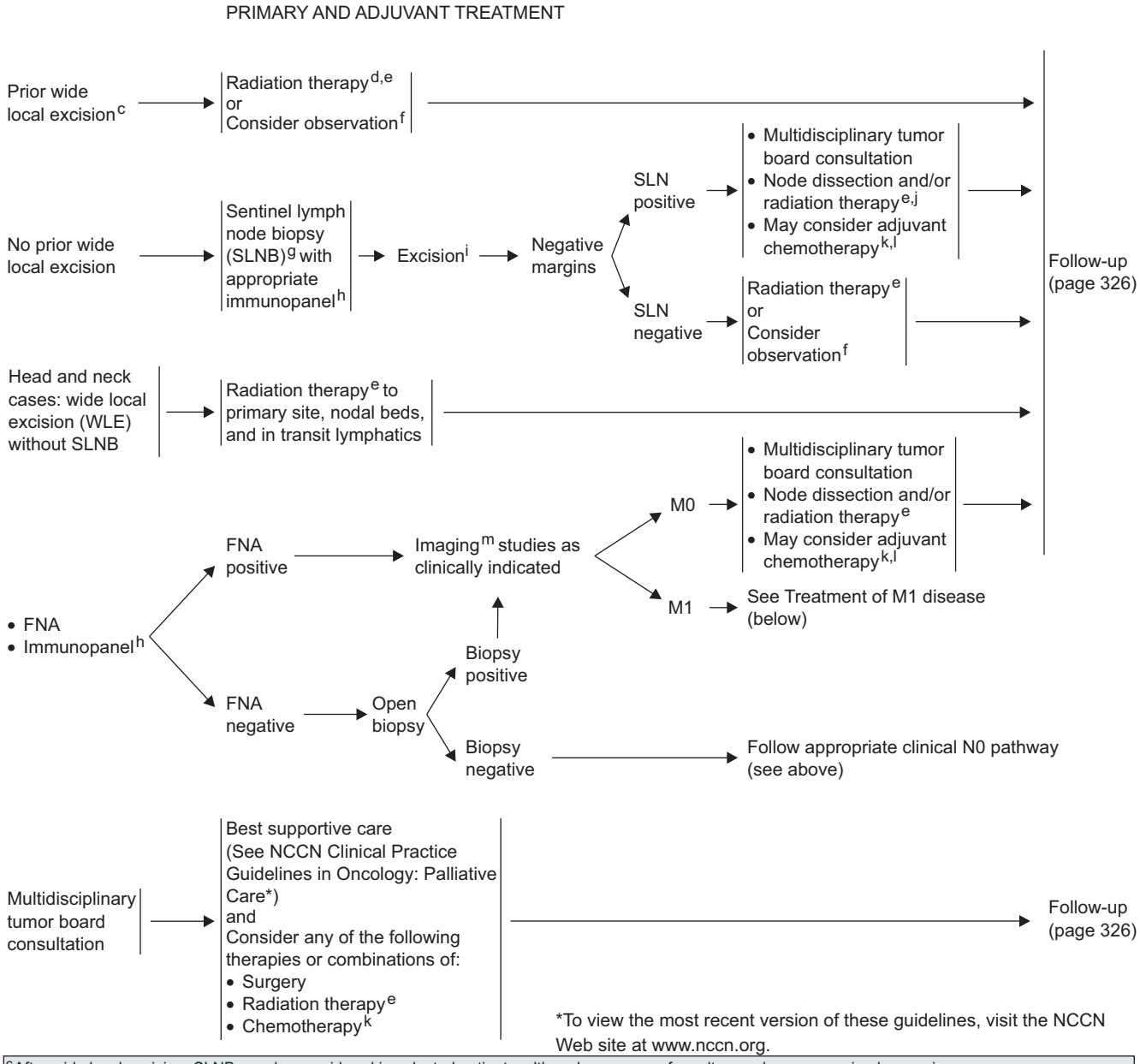
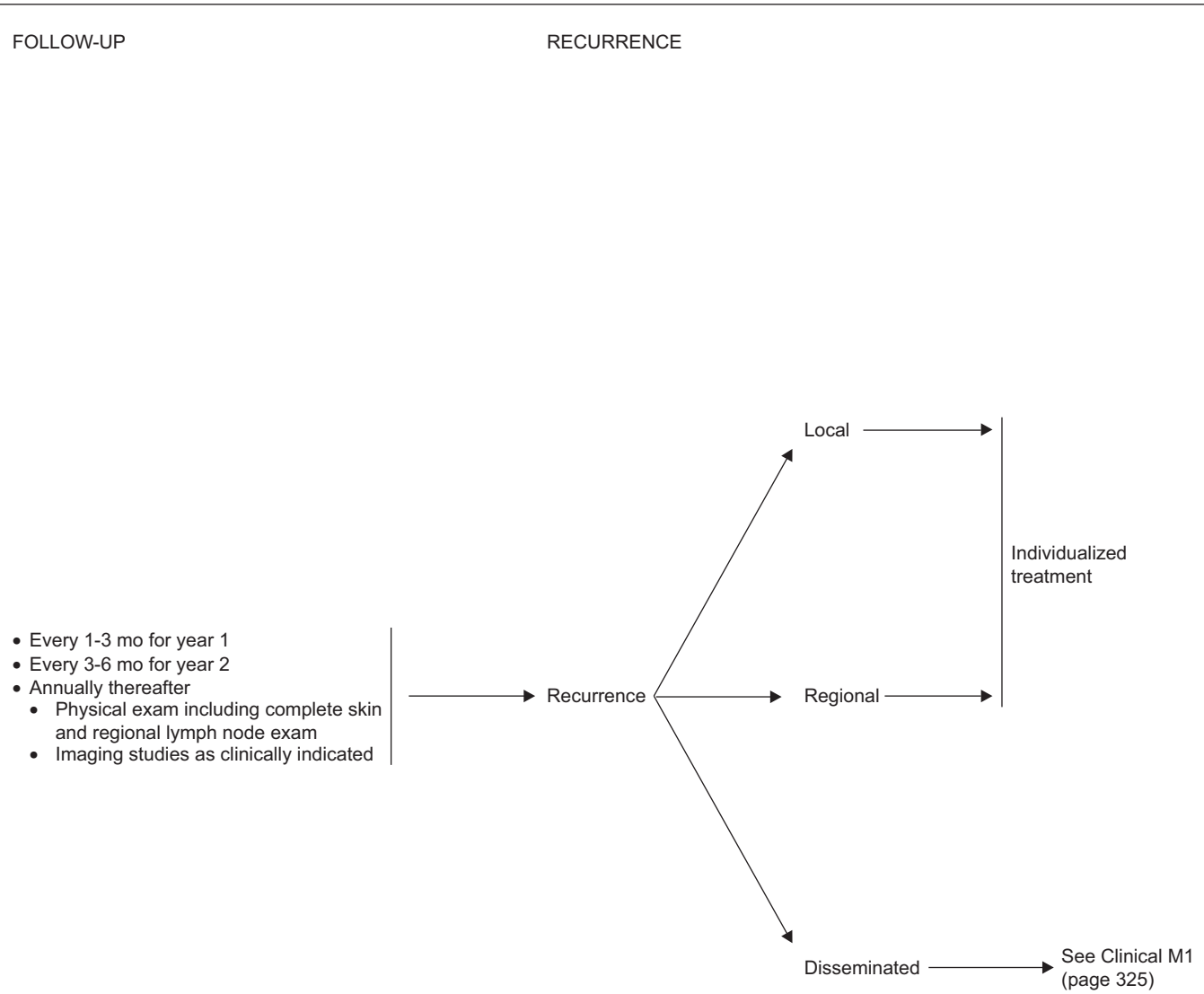


*To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

[c] After wide local excision, SLNB may be considered in selected patients, although accuracy of results may be compromised, especially in non-extremity regions.
[d] Radiation therapy to primary site, in transit lymphatics (when feasible), and/or draining nodal basins.
[e] See Principles of Radiation Therapy (page 327).
[f] Consider observation with small tumors, widely excised with no other adverse risk factors.
[g] The preferred treatment sequence is for the SLNB to precede the excision.
[h] An appropriate immunopanel for sentinel lymph node examination should preferably include CK-20 and pancytokeratins (AE1/AE3).
[i] See Principles of Excision (page 328).
[j] For lymph nodes that are positive only by immunohistochemical methods but not H&E, consider RT as the sole therapy to the draining nodal basin(s).
[k] See Chemotherapy Agents (page 328).
[l] Available retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.
[m] Imaging (CT, MR, or PET) may be indicated to evaluate extent of lymph node and/or visceral organ involvement.



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Principles of Radiation Therapy

Dose Recommendations for Radiation Therapy:

Primary site:	
• Negative resection margins	50-56 Gy
• Microscopic (+) resection margins	56-60 Gy
• Gross (+) resection margins or unresectable	60-66 Gy
Nodal bed:	
• No SLNB or LN dissection	
• Clinically (-) but at risk for subclinical disease	46-50 Gy
• Clinically evident adenopathy: head and neck	60-66 Gy
• Clinically evident adenopathy: axilla or groin [1]	– – [1]
• After SLNB without LN dissection	
• Negative SLNB: axilla or groin	Radiation not indicated [2]
• Negative SLNB: head and neck, if at risk for false-negative biopsy	46-50 Gy [2]
• Microscopic N+ on SLNB: axilla or groin	50 Gy [3]
• Microscopic N+ on SLNB: head and neck	50-56 Gy
• After LN dissection	
• Lymph node dissection: axilla or groin	50-54 Gy [4]
• Lymph node dissection: head and neck	50-60 Gy

- All doses at 2 Gy/d standard fractionation. Bolus is used to achieve adequate skin dose. Wide margins (5 cm) should be used, if possible, around the primary site. If electron beam is used, an energy and isodose line (e.g., 90%) should be used to deliver adequate lateral and deep margins.
- Extremity and torso MCC: after negative SLNB and WLE, in most instances, radiation therapy is given to the primary site only. SLNB dictates the need for regional irradiation. If SLNB is negative, then regional nodal basins can be observed. If SLNB is not performed, consider irradiating nodal beds for subclinical disease. Irradiation of in-transit lymphatics is usually not feasible unless the primary site is close to the nodal bed.
- Head and neck MCC: risk for false-negative sentinel node biopsy is higher, because of aberrant lymph node drainage and frequent presence of multiple sentinel node basins. The radiation field to treat the primary site is often overlying the draining lymph node beds. Treatment options for clinically node negative MCC of the head and neck include:
  - Perform SLNB and WLE. If SLNB is negative, options are to irradiate the primary site ± nodal beds and in-transit lymphatics or observe.
    OR
  - Perform WLE without performing SLNB and irradiate the primary tumor site, in-transit lymphatics, and regional nodal sites.

[1] Lymph node dissection is the recommended initial therapy for clinically evident adenopathy in the axilla or groin, followed by postoperative radiation if indicated.
[2] Consider RT when there is a potential for anatomic (e.g., previous history of surgery including WLE), operator, or histologic failure (e.g., failure to perform appropriate immunohistochemistry on SLNs) that may lead to a false-negative SLNB.
[3] Microscopic N+ is defined as single-node involvement that is neither palpable clinically nor abnormal by imaging criteria, which microscopically consists of small metastatic foci without extracapsular extension.
[4] RT may be omitted after axillary/groin LN dissection for microscopic disease. Postoperative radiation is indicated for multiple involved nodes and/or presence of more than focal extracapsular extension.

PRINCIPLES OF EXCISION

Goal:
- Clear surgical margins when clinically feasible

Varied Approaches:
- 1- to 2-cm margins to investing fascia of muscle or pericranium with clear pathologic margins, when clinically feasible.
- Mohs technique [1]
- Modified Mohs = Mohs technique with additional final margin for permanent section assessment
- CCPDMA = Complete circumferential and peripheral deep-margin assessment

Reconstruction:
- Immediate reconstruction in most cases
- It is preferable to delay reconstruction involving extensive undermining or flaps until negative surgical margins are assessed and certified pathologically clear
- When primary closure is not possible, consider split-thickness skin grafting to monitor for recurrence

CHEMOTHERAPY AGENTS [2]

Local disease:
- Adjuvant chemotherapy not recommended unless clinical judgment dictates otherwise

Regional disease:
- Adjuvant chemotherapy not routinely recommended because adequate trials to evaluate usefulness have not been performed, but could be used on a case-by-case basis if clinical judgment dictates
- Cisplatin alone or combined with etoposide
- Carboplatin alone or combined with etoposide

Disseminated disease:
- Cisplatin plus etoposide
- Carboplatin plus etoposide
- Cyclophosphamide, doxorubicin (or epirubicin), and vincristine
- Topotecan has been used

[1] Mohs technique is used primarily in MCC to insure complete removal and clear margins, and secondarily for its tissue-sparing capabilities.
[2] When available and clinically appropriate, enrollment in a clinical trial is recommended. The literature is not directive regarding the specific chemotherapeutic agent(s) offering superior outcomes, but the literature does provide evidence that Merkel cell carcinoma is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.

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.

Text continued from p. 323

An appropriate immunopanel should preferably include cytokeratin 20 (CK-20) and thyroid transcription factor 1 (TTF-1), which often provide the greatest sensitivity and specificity to exclude small cell lung cancer (SCLC).[22–24] CK-20 is a very sensitive marker for MCC, because it is positive in 89% to 100% of tumors. TTF-1 is expressed in 83% to 100% of SCLC but is consistently absent in MCC. Other immunohistochemical markers, including chromogranin A, synaptophysin, neurofilament protein, neuron-specific enolase, leukocyte common antigen (CD45), S-100 protein, and pancytokeratin (panCK), may be used in addition to CK-20 and TTF-1 to exclude other diagnostic considerations.[5] Most primary and metastatic MCCs also express KIT receptor tyrosine kinase (CD117).[25]

Additional workup of patients with MCC includes imaging studies as clinically indicated, which parallels most suggested approaches to these patients in the biomedical literature.[5,6,13] Imaging (radiograph, CT, MRI, or PET scan) may be indicated to evaluate for the possibility of a skin metastasis from a non–cutaneous carcinoma (e.g., small cell carcinoma of the lung), especially in cases where CK-20 is negative. One diagnostic test to consider is a radiolabeled scan using a somatostatin analogue.[5,6]

Treatment primarily depends on accurate histopathologic interpretation and microstaging of the primary lesion. Thus, excisional biopsy of the entire lesion with narrow clear surgical margins is preferred, whenever possible, to obtain the most accurate diagnostic and microstaging information. Then, definitive excision with or without sentinel lymph node biopsy (SLNB) can best be performed. IHC analysis has been shown to be effective in detecting more lymph node metastases in patients with MCC.[3,26] CK-20 immunostaining in the pathologic assessment of sentinel lymph nodes removed from patients is a valuable diagnostic adjunct, because it allows accurate identification of micrometastases.[27,28] An appropriate immunopanel for SLNB should include CK-20 and pancytokeratins. Performing a wide local excision initially, especially in the head, neck, and trunk regions, may potentially interfere with the accuracy of subsequent SLNB.

Staging

In biomedical literature, the most consistently reported adverse prognostic feature is tumor stage followed by tumor size.[1,2,6,8,10,11,13,14,16] NCCN staging of MCC parallels the American Joint Committee on Cancer (AJCC) guidelines and divides presentation into local, regional, and disseminated disease.[29] An MCC Web site from Seattle Cancer Care Alliance also has a useful staging table (www.merkelcell.org).

Treatment

Surgery is the primary treatment modality for MCC. The use of the following treatment options varies tremendously among individual clinicians and NCCN institutions:

1. SLNB or elective lymph node dissection for clinically normal regional lymph node basin(s)
2. Postoperative radiation therapy for the primary tumor, draining lymphatics, and/or regional lymph node basins
3. Adjuvant chemotherapy for local or regional disease

Therefore, the MCC guidelines are suitably broad to reflect all the approaches taken by participating NCCN institutions.

Excision

Local wide excision is the recommended primary treatment for clinically localized (N0) disease (see page 328). Because of the high historic risk for local recurrence in MCC, the panel's tenets for surgical excision emphasize complete extirpation of tumor at initial resection to achieve clear surgical margins when clinically feasible. Surgical techniques include excision with wide margins to the investing fascia layer with complete peripheral margin examination, and Mohs or modified Mohs surgery.[30] Mohs micrographic surgery is superior to conventional surgical excision in basal and squamous cell carcinoma. In MCC, it is primarily used to ensure complete tumor removal and clear margins, while secondarily sparing surrounding healthy tissue.[31]

SLNB

SLNB is important in the staging and treatment of MCC.[32] Studies suggest that elective lymph node dissection decreases regional recurrence rates and improves survival.[2,8] Most studies examining the use of SLNB in MCC suggest a positive benefit but have only short-term follow-up.[33–36] One review found that pathologic nodal staging was associated with improved survival and decreased nodal recurrence. Evidence suggests the incidence of a positive sen-

tinel lymph node is independent of primary tumor size.[19] Essentially all participating NCCN institutions use the SLNB technique routinely for MCC, as they do for melanoma. SLNB is offered for staging purposes to patients who are otherwise healthy; a positive sentinel lymph node is followed up with a completion lymph node dissection and/or radiation therapy if appropriate. The panel believes that identifying patients with positive microscopic nodal disease and then performing full lymph node dissections can maximize the care of regional disease in these patients. Finally, as with melanoma, SLNB is best performed before definitive local excision.

Radiation Therapy

Although reports on the benefits of radiation therapy have been mixed, recent studies provide increasing support for using postoperative radiation in MCC to minimize locoregional recurrence. According to a meta-analysis comparing surgery alone with surgery plus adjuvant radiation, local adjuvant radiation after complete excision lowered the risk for local and regional recurrences.[37] In a review of 82 cases diagnosed between 1992 and 2004, administering radiotherapy to the primary site or regional lymph nodes was associated with a prolonged time to recurrence and survival.[38] The panel included radiation as a treatment option for all stages of MCC. Specifications on radiation dosing for different MCC sites (head and neck vs. extremity and torso) are detailed on page 327.

Chemotherapy

Most NCCN institutions only use chemotherapy with or without surgery and/or radiation therapy for stage IV distant metastatic disease (M1). A few member institutions suggest considering adjuvant chemotherapy for selected cases of regional (N+) disease. Available data from retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.[39,40] Data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free or overall survival in patients with MCC who have distant metastatic disease.[41–44] If it is used, the panel recommends etoposide in combination with cisplatin or carboplatin, or cyclophosphamide in combination with doxorubicin and vincristine (see page 328). Topotecan has also been used in some instances (e.g., older patients).

Metastatic Disease

The panel recommends multidisciplinary tumor board consultation for patients with metastatic disease to consider any or a combination of radiation, surgery, and chemotherapy (see page 325). Full imaging workups are recommended for all patients with clinically proven regional or metastatic disease. In general, the care of patients with distant metastasis must be individualized.

Follow-up

Finally, the panel's recommendations for close clinical follow-up of patients immediately after diagnosis and treatment of MCC (see page 326) parallel the recommendations in the biomedical literature. The schedule is the same regardless of whether patients are N0, N+, or clinical M1. The physical examination should include a complete skin and regional lymph node examination every 1 to 3 months for the first year, every 3 to 6 months in the second year, and annually thereafter. The panel's recommendations also reflect the fact that the median time to recurrence in patients with MCC is approximately 8 months, with 90% of the recurrences occurring within 24 months.[3,10,19] Self-examination of the skin is useful for patients with MCC because they are likely at greater risk for other non-melanoma skin cancers.

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Individual Disclosures for the NCCN Merkel Cell Carcinoma Panel

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The NCCN guidelines staff have no conflicts to disclose.