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NCCN Clinical Practice Guidelines in Oncology™

Merkel Cell Carcinoma

V.1.2010

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Merkel Cell Carcinoma guidelines from the 1.2009 version include:

(MCC-1)

- **Clinical Presentation; Suspicious lesion; Second bullet: "Complete skin and regional lymph node examination" changed to "Complete skin and lymph node examination".**
- **Footnote "b":**
  - **PET changed to PET-CT. (Also for MCC-3)**
  - **The sentence "It may be useful in identifying distant metastases." was added.**

(MCC-2)

- **After "Clinical N0": Formerly the page was separated into 3 pathways "Prior wide excision", No prior wide excision, and "Head and Neck cases". The pathways have been revised into two separate pathways "Prior wide excision" and No prior wide excision" for clarity.**
- **Footnote "i" that states, "Because of the high rate of false negativity, SLNB may not always be considered reliable in the head and neck region. However, it may have prognostic value" is new to the page.**
- **Footnote "f" regarding when to consider observation was revised.**
- **Footnote "j" that states, " In selected cases in which surgical excision is not possible, surgery is refused by the patient, or would result in significant morbidity, radiation mono-therapy may be considered" is new to the page.**

(MCC-A): Principles of Radiation Therapy

- **Nodal bed; No SLNB or LN Dissection: The second and third arrows regarding dosing for clinical adenopathy for head and neck/axilla groin were combined and are now listed as "Clinically evident lymphadenopathy".**
- **Footnote "2" is new to the page.**
- **Footnotes "4" and "5" were revised.**

(MCC-B): Principles of Excision.

- **Footnote "2" that states, "If Mohs is used for MCC, a debulked specimen of the central portion of the tumor should be sent for permanent section microstaging," is new to the page.**

(MCC-C): Chemotherapy Agents

- **Disseminated disease:**
  - **The phrase "As clinical judgment indicates" was added.**
  - **"Cisplatin plus etoposide" changed to "Cisplatin ± etoposide".**
  - **"Carboplatin plus etoposide" changed to "Carboplatin ± etoposide".**
  - **"Topetecan has been used" changed to "Topetecan".**

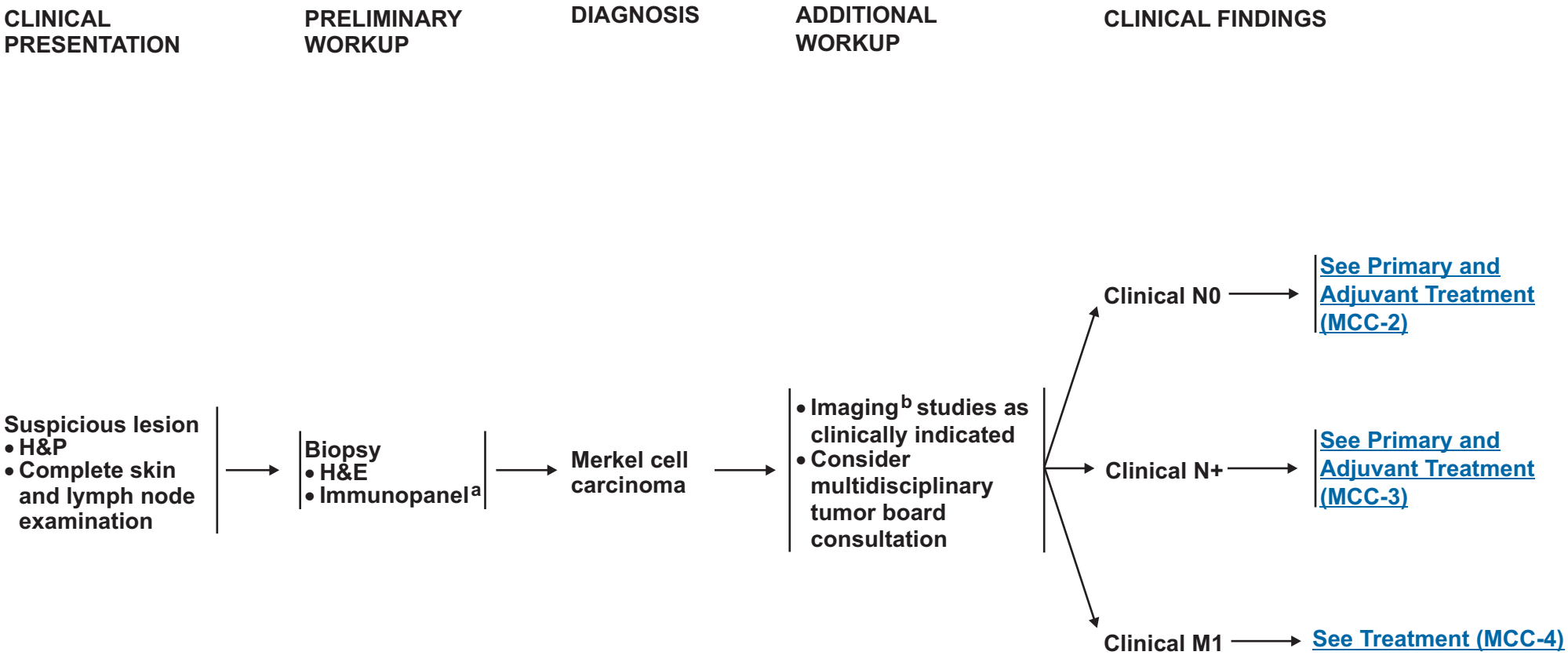
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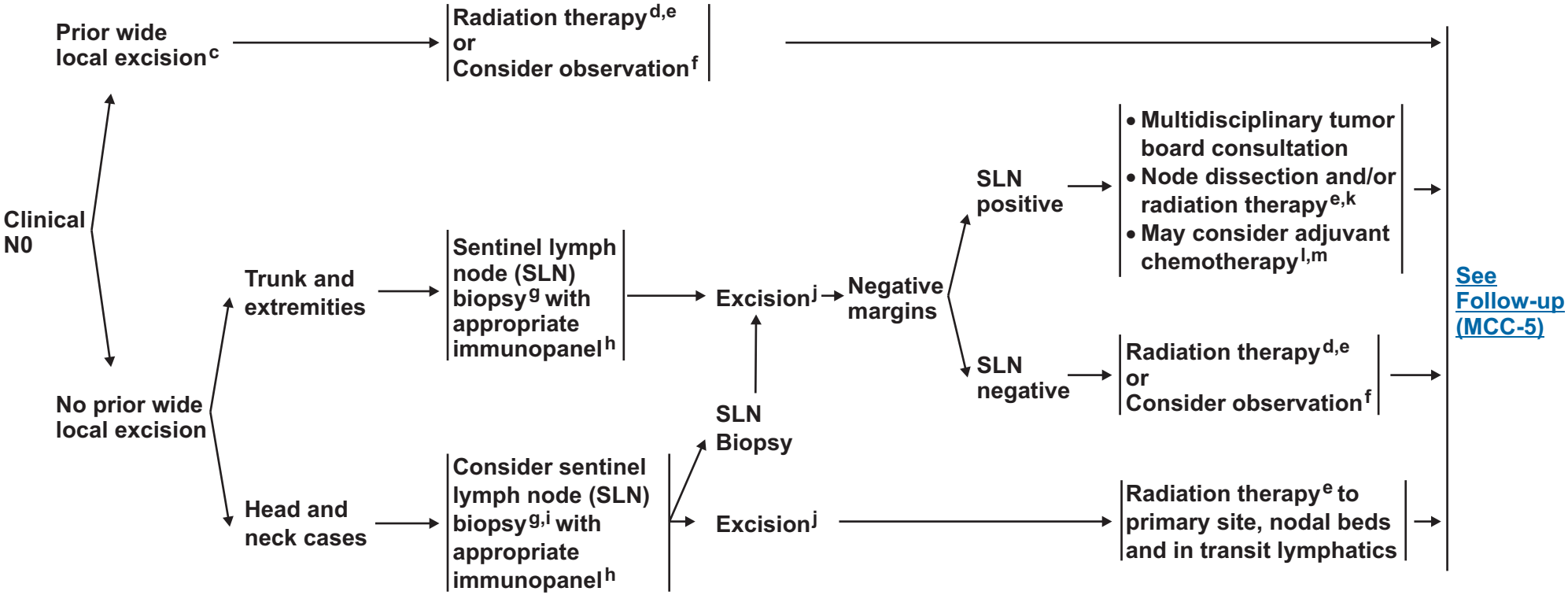
[a] An appropriate immunopanel should preferably include CK-20 and thyroid transcription factor-1 (TTF-1).
[b] Imaging (CT, MR, or PET-CT) may be indicated to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma (eg, small cell lung cancer), especially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

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PRIMARY AND ADJUVANT TREATMENT: CLINICAL N0 DISEASE



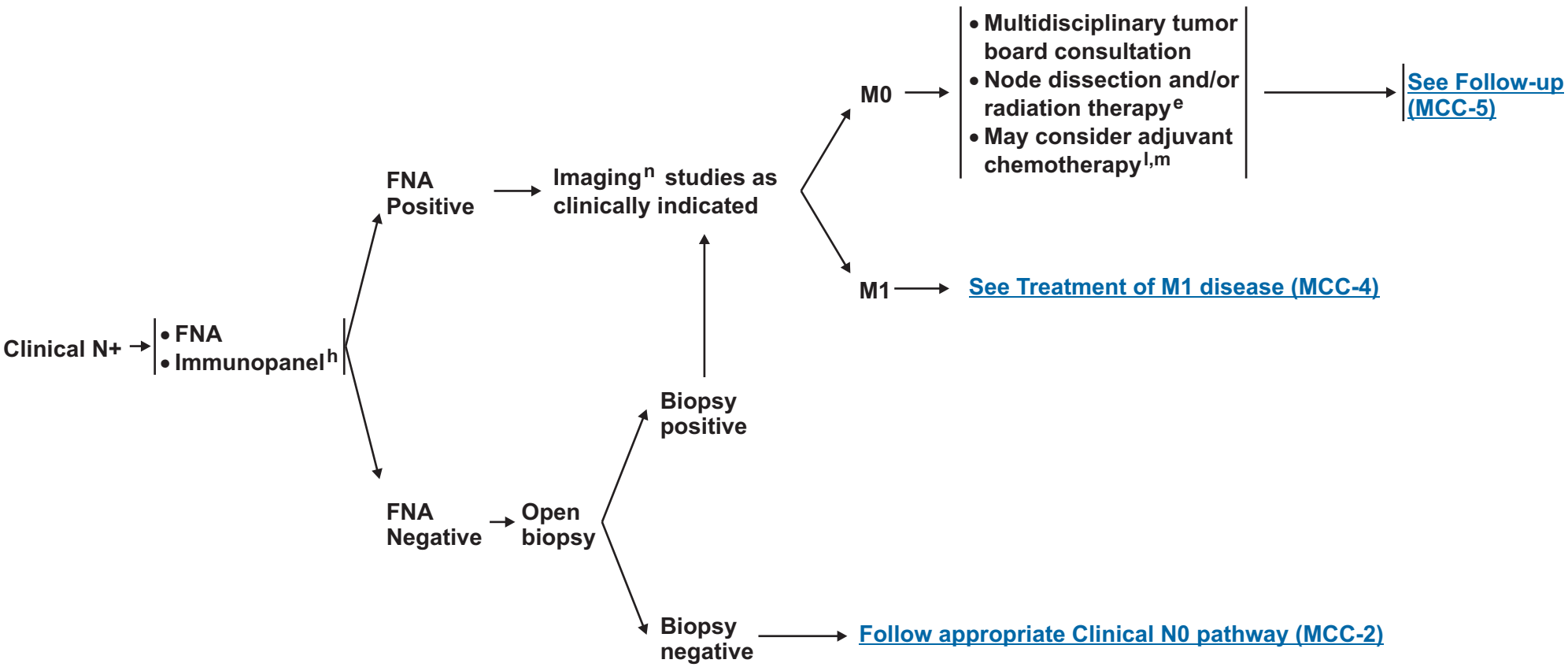
[c] After wide local excision, sentinel lymph node biopsy may be considered in selected patients, although accuracy of results may be compromised, especially in non-extremity regions.
[d] Radiation therapy to primary site, in transit lymphatics (when feasible), and/or draining nodal basins.
[e] See Principles of Radiation Therapy (MCC-A).
[f] Consider observation of the tumor bed, in cases where the primary tumor is small, widely excised with no other adverse risk factors.
[g] The preferred treatment sequence is for the sentinel lymph node biopsy to precede the excision.
[h] An appropriate immunopanel for SLN examination should preferably include CK-20, and pancytokeratins (AE1/AE3).
[i] Because of the high rate of false negativity, SLNB may not always be considered reliable in the head and neck region. However, it may have prognostic value.
[j] See Principles of Excision (MCC-B). In selected cases in which complete surgical excision is not possible, surgery is refused by the patient, or would result in significant morbidity, radiation mono-therapy may be considered (See Principles of Radiation Therapy [MCC-A]).
[k] 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).
[l] See Chemotherapy Agents (MCC-C).
[m] Available retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.

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PRIMARY AND ADJUVANT TREATMENT: CLINICAL N+ DISEASE



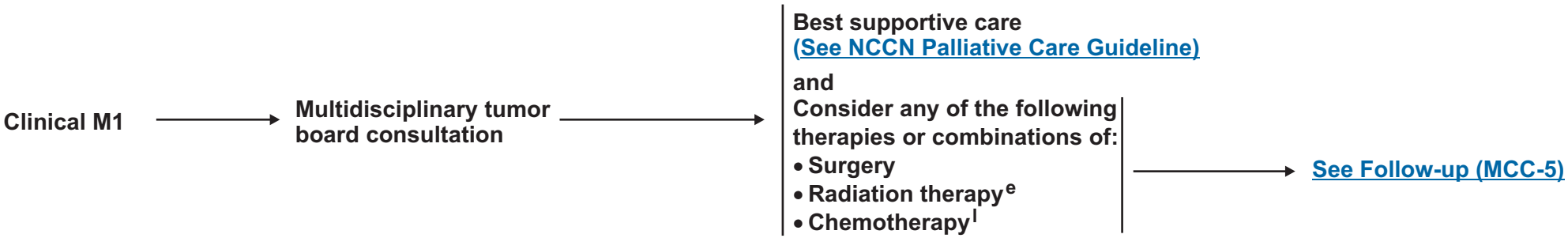
[e] See Principles of Radiation Therapy (MCC-A).
[h] An appropriate immunopanel for LN examination should preferably include CK-20 and pancytokeratins (AE1/AE3).
[l] See Chemotherapy Agents (MCC-C).
[m] Available retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.
[n] Imaging (CT, MR, or PET-CT) may be indicated to evaluate extent of lymph node and/or visceral organ involvement.

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TREATMENT: CLINICAL M1 DISEASE



[e] See Principles of Radiation Therapy (MCC-A).
[l] See Chemotherapy Agents (MCC-C).

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FOLLOW-UP

- Every 1-3 mo for year 1
- Every 3-6 mo for year 2
- Annually thereafter
  - Physical exam including complete skin and regional lymph node exam
  - Imaging studies as clinically indicated

→ **Recurrence**

RECURRENCE

- **Local** → **Individualized treatment**
- **Regional** → **Individualized treatment**
- **Disseminated** → **See Clinical M1 (MCC-4)**

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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 lymphadenopathy	60-66 Gy[1,2]
• After SLNB without LN Dissection	
▸ Negative SLN biopsy: axilla or groin	Radiation not indicated[3]
▸ Negative SLN biopsy: head and neck, if at risk for false negative biopsy	46-50 Gy[3]
▸ Microscopic N+ on SLNB: axilla or groin	50 Gy[4]
▸ Microscopic N+ on SLNB: head and neck	50-56 Gy[4]
• After LN Dissection	
▸ Lymph node dissection: axilla or groin	50-54 Gy[5]
▸ Lymph node dissection: head and neck	50-60 Gy

- **All doses at 2 Gy/day 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 (eg, 90%) should be used that will deliver adequate lateral and deep margins.**
- **Extremity and torso MCC: After negative SLNB and wide local excision (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 often not feasible unless the primary site is in close proximity to the nodal bed.**
- **Head and neck MCC: Risk of false negative sentinel node biopsy is higher, due to 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] Shrinking field technique.

[3] Consider RT when there is a potential for anatomic (eg, previous history of surgery including WLE), operator, or histologic failure (eg, failure to perform appropriate immunohistochemistry on SLNs) that may lead to a false negative SLNB.

[4] 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. RT may be omitted after axillary/groin LN dissection for microscopic disease.

[5] Postoperative irradiation is indicated for multiple involved nodes or extracapsular extension.

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PRINCIPLES OF EXCISION

Goal:
- **Clear surgical margins when clinically feasible.**

Varied Approaches:
- **1-2 cm margins to investing fascia of muscle or pericranium with clear pathologic margins, when clinically feasible.**
- **Mohs technique[1,2]**
- **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 (STSG) to monitor for recurrence.**

[1]Mohs technique is used primarily in MCC to insure complete removal and clear margins, and secondarily for its tissue sparing capabilities.
[2]If Mohs is used for MCC, a debulked specimen of the central portion of the tumor should be sent for permanent section microstaging.

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CHEMOTHERAPY AGENTS[1]

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

Regional disease:
- **Adjuvant chemotherapy not routinely recommended as adequate trials to evaluate usefulness have not been done, but could be used on a case by case basis if clinical judgment dictates**
- **Cisplatin ± etoposide**
- **Carboplatin ± etoposide**

Disseminated disease:
As clinical judgment indicates:
- **Cisplatin ± etoposide**
- **Carboplatin ± etoposide**
- **Cyclophosphamide, doxorubicin (or epirubicin) and vincristine (CAV)**
- **Topotecan**

[1] 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.

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Discussion

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.

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 25-30% of all cases of MCC, regional disease in 52-59% of all cases, and distant metastatic disease in 34-36% of cases.[1,16,17] MCC has a mortality rate that exceeds that of melanoma.[18] The overall 5-year survival rates range from 30-64%.[3,19] A history of extensive sun exposure is a risk factor for MCC. Older white men (65 years or older) are at higher risk for MCC, which tends to occur on the areas of the skin that are exposed to sun.[20]

NCCN Non-Melanoma Skin Cancer Panel has developed guidelines outlining treatment of MCC to supplement the squamous cell and basal cell skin cancer guidelines (NCCN Basal Cell and Squamous Cell Skin Cancers Guidelines).[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 as well as their own collective experiences.

Diagnosis and Workup

Initial workup of a suspicious lesion starts with a complete examination of skin and lymph nodes followed by biopsy (MCC-1). The primary goal in biopsy of a MCC is to confirm the diagnosis. Rarely does MCC present clinically as a classic lesion where MCC is expected to be the main diagnosis. The histologic diagnosis may be challenging, because MCC is similar to a variety of 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. 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, since it is positive in 89-100% of tumors.TTF-1 is expressed in 83-100% of SCLC but it 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] In addition to the above mentioned markers, a majority of primary and metastatic MCCs also express KIT receptor tyrosine kinase (CD117).[25]

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Additional workup of a patient with MCC includes imaging studies as clinically indicated, which parallels most suggested approaches to such patients in the biomedical literature.[5,6,13] Imaging (x-ray, CT, MRI or PET/CT scan) may be indicated to evaluate for the possibility of a skin metastasis from a non-cutaneous carcinoma (eg. 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] Imaging may also be useful in identifying distant metastases. In a retrospective review, PET/CT resulted in a change of management for 9 out of 18 patients, all with late stage disease.[26]

Treatment is primarily dependent on accurate histopathologic interpretation and on 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.[3,27] CK-20 immunostaining in the pathologic assessment of sentinel lymph nodes removed from MCC patients is a valuable diagnostic adjunct, as it allows accurate identification of micrometastases. [28,29] 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 a 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] The NCCN staging of MCC parallels the American Joint Committee on Cancer (AJCC) guidelines and divides presentation into local, regional, and disseminated disease.[30] 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. There was tremendous variability among individual clinicians and NCCN institutions regarding the use of following treatment options:

- SLNB or elective lymph node dissection for clinically normal regional lymph node basin(s);
- Postoperative radiation therapy for the primary tumor, draining lymphatics, and/or regional lymph node basins; and
- 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 (MCC-B). Because of the high historic risk of local recurrence in MCC, the panel's tenets for surgical excision emphasize complete extirpation of tumor at the time of 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.[31] Mohs micrographic surgery is superior to conventional surgical excision in basal cell carcinoma and squamous cell carcinoma. In MCC, it is primarily used to ensure complete tumor removal and clear margins, while secondarily sparing surrounding healthy tissue.[32] If Mohs was used, the panel emphasized that a specimen from the central portion of the tumor should be sent for permanent section microstaging.

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy is very important in the staging and treatment of MCC.[33] Studies suggest that elective lymph node

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dissection decreases regional recurrence rates and improves survival.[2,8] Most studies that examine the use of SLNB in MCC suggest a positive benefit but have only short-term follow-up.[34-37] One review found that pathologic nodal staging was associated with improved survival and decreased nodal recurrence. Evidence suggests the incidence of a positive sentinel 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 to patients who are otherwise healthy for staging purposes; a positive sentinel lymph node is followed up with a completion lymph node dissection and/or radiation therapy. Adjuvant chemotherapy may be considered if appropriate. The NCCN Panel believes that by identifying patients with positive microscopic nodal disease and then performing full lymph node dissections and/or radiation therapy, the care of regional disease in this patient population is maximized. However, it should be noted that SLNB is less reliable in the head and neck region compared to the trunk and extremities. The complex and variable drainage pattern of the area can lead to false negativity.[38] Finally, as with melanoma, it is always best to perform the SLNB before definitive local excision.

Radiation Therapy

Although the literature on the benefits of radiation therapy has been mixed, recent studies are providing increasing support of the use of postoperative radiation in MCC to minimize locoregional recurrence. According to a meta-analysis comparing surgery alone with surgery plus adjuvant radiation, the use of local adjuvant radiation after complete excision lowered the risk of local and regional recurrences.[39] In a review of 82 cases diagnosed between 1992 and 2004, administration of radiotherapy to the primary site or regional lymph nodes was associated with a prolonged time to recurrence and survival.[40] The panel included radiation as a treatment option for all stages of MCC. Radiation is acceptable as primary therapy in select cases when complete excision is not feasible or refused by the patient. An Australian retrospective review of 43 patients reported an in-field tumor control rate of 75% using radiation alone.[41] Specifications on radiation dosing, as well as for different MCC sites (head and neck versus extremity and torso), are detailed on MCC-A.

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. The most common regimen used for regional disease is cisplatin or carboplatin with or without etoposide. Available data from retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.[42,43] Data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free or overall survival in MCC patients with distant metastatic disease.[44-47] If it is used, the panel recommends cisplatin or carboplatin with or without etoposide,[48] or cyclophosphamide in combination with doxorubicin and vincristine (MCC-C). Topotecan has also been used in some instances (eg. older patients). Clinicians should exercise independent medical judgment in choosing the chemotherapeutic regimen. Although the NCCN panel recognized that MCC is a rare disease that precludes robust randomized studies, enrollment in clinical trials is encouraged whenever available and appropriate.

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 (MCC-4). Full imaging workups are recommended for all patients with clinically proven regional or metastatic disease. In general, the case of patients with distant metastasis must be individually tailored.

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Follow-up

Finally, the NCCN panel's recommendations for close clinical follow-up of MCC patients immediately after diagnosis and treatment (MCC-5) 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 1-3 months for the first year, every 3-6 months in the second year and annually thereafter. The panel's recommendations also reflect the facts that the median time to recurrence in patients with MCC is about 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 these patients are likely at greater risk for other non-melanoma skin cancers.

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