Focused Review

NCCN Guidelines Implementation in the Multidisciplinary Merkel Cell Carcinoma Program at the University of Michigan

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Abstract

Merkel cell carcinoma (MCC) is a rare malignancy of the skin, and prospective randomized clinical studies on management and treatment are very limited. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MCC provide up-to-date, best evidence–based, and consensus-driven management pathways with the purpose of providing best care and outcomes. Multidisciplinary management with consensus treatment recommendations to individualize patient care within the framework of these guidelines is optimal. The University of Michigan multidisciplinary MCC program uses NCCN Guidelines in the management and treatment of its patients. This article discusses 4 patient presentations to highlight the implementation of the NCCN Guidelines for MCC at the University of Michigan. *(J Natl Compr Canc Netw* 2014;12:434–441)

Merkel cell carcinoma (MCC), diagnosed primarily in the elderly white population, is an uncommon, clinically aggressive cutaneous malignancy with a high rate of local, regional, and distant recurrence. During the last 2 decades of the 20th century, the incidence of MCC more than tripled, a trend that is expected to continue with an increasingly aging population.[1]

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Despite its rarity, the increasing incidence and aggressive nature of MCC have brought attention on this disease and revealed a wide variability in the treatment and management of patients diagnosed with this malignancy. Patients with MCC may have very different work-up, treatment, and follow-up depending on the institution, physician, and specialty providing their care. These inconsistencies highlight the importance of having best evidence–based treatment guidelines. Unfortunately, prospective randomized clinical trials are extremely limited because of the rarity of the disease, necessitating that guidelines be based on best available evidence and expert consensus opinion. Multidisciplinary management to establish consensus recommendations for individualizing patient care within the framework of evidence-based guidelines constitutes the optimal treatment model within the existing limitations. This article discusses the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MCC, including the importance of multidisciplinary management, and highlights the implementation of these guidelines in the multidisciplinary MCC program at the University of Michigan (UM).

Background

MCC is rarely clinically suspected. The most common presentation is a nondistinctive, rapidly growing, asymptomatic, red-purple–colored nodule.[2] MCC occurs most frequently on sun-exposed skin of the head and neck (29.0%–45.3%) and extremities (21.0%–50.0%), followed by the trunk (4.7%–23.0%) and other sun-protected areas.[2–5] Immunosuppression from HIV, chronic lymphocytic leukemia, and certain immunosuppressant

drugs used after solid organ transplant and in patients with autoimmune disease increase the relative risk of MCC.[6–8]

MCC has an overall mortality rate of approximately 30% at 2 years and 50% at 5 years, with the extent of disease at diagnosis highly predictive of survival.[9] Most recurrences occur within 2 years after diagnosis, with recurrence rates ranging from 40% to as high as 77% on the head and neck.[3,4,10,11] Because the draining lymph node basin is the most common location of initial metastasis, sentinel lymph node biopsy (SLNB) has emerged as an important staging tool in patients without clinical evidence of metastases.[4,12–14] The 2010 AJCC staging system is the most recent consensus staging system for MCC, which incorporates sentinel lymph node (SLN) status.[9,15] Stage I is defined as local disease with a primary tumor of 2 cm or less; stage II as local disease with a primary tumor size greater than 2 cm; stage III as regional nodal disease; and stage IV as distant metastatic disease. Subcategories associated with survival of stages I and II are defined by the method of nodal evaluation (SLN/microscopically negative vs clinically negative); stage III is subcategorized by the extent of nodal metastasis. Other factors that may have prognostic significance include tumor thickness, angiolymphatic invasion, mitotic rate, histologic growth pattern, and immunosuppression status.[16–21]

In the past 5 years, the novel Merkel cell polyomavirus (MCPyV) has been characterized, with MCPyV DNA detected in 80% of MCC tumors and only 16% of normal skin tissue samples.[22] This finding has opened a new pathway to explore in the pathogenesis of MCC.

NCCN Guidelines

The NCCN Guidelines for MCC are best evidence–based, consensus-driven, and updated on an ongoing basis. These guidelines provide sequential management decisions and interventions with the intent to provide optimal care and outcomes for patients with cancer. Failure to follow established standardized treatment guidelines has been shown to result in suboptimal care.[23] The current NCCN Guidelines for MCC (in this issue; to view subsequent updates, visit NCCN.org) are a working algorithm that guides the management of patients from biopsy through treatment and follow-up.[24]

Multidisciplinary Management

The wide range of treatment options in the NCCN Guidelines for MCC and treatment inconsistencies throughout the literature reflect the lack of prospective randomized studies on treatment outcomes for this malignancy.[18,24] NCCN provides treatment guidelines based on best available evidence and expert consensus opinion, but optimal management with regard to surgery, radiation therapy, and systemic treatment remains controversial. However, the importance of a multimodality approach in this patient population is becoming more evident.[3,25,26] For many patients with MCC, no single treatment modality is sufficient, thus increasing the need for a coordinated multidisciplinary approach to patient care. Optimal management often requires involvement of multiple specialists, including pathologists, dermatologists, surgeons, and radiation and medical oncologists.

The impact of this multidisciplinary approach reaches beyond coordinated care. Within the framework of evidence-based practice guidelines, tumor board discussions and recommendations on an individualized patient basis, weighing the risks and benefits of various treatment modalities, are essential for best care. This multidisciplinary management has been reported to have an impact on clinical outcome in multiple cancer types.[27,28] Management of melanoma in a multidisciplinary clinic has been shown to promote not only consensus-based treatment recommendations and efficient coordinated care but also cost-efficiency, education, and research.[29,30] Multidisciplinary programs often have the added benefits of state-of-the-art oncologic specialization and access to novel treatments. Moreover, for a rare disease such as MCC, centralization of care with a unified treatment approach and ongoing prospectively collected clinical data facilitates research to answer many current best management questions.

UM Multidisciplinary MCC Program

Recognizing the increasing incidence of MCC and the benefits of a multimodality approach to treating this aggressive cutaneous malignancy, the UM Comprehensive Cancer Center multidisciplinary MCC program was established in February 2006. This program is directed by the Department of Dermatology and its strength comes from the participation and

cooperation of multiple disciplines, including dermatology, dermatopathology, surgical oncology, otolaryngology, plastic surgery, ophthalmology, radiation oncology, medical oncology, nuclear medicine, genetics, nursing, tissue procurement, and data management. Approximately 70 new patients each year are evaluated and treated in this program.

Applying NCCN Guidelines in the UM Multidisciplinary MCC Program

The UM MCC program uses NCCN Guidelines for the management of patients. When options exist, the program standardizes treatment to allow for collection of uniform data for clinical research. Preliminary workup includes review of histopathology with reporting of an MCC profile, including growth pattern, Breslow thickness, the presence or absence of ulceration and angiolymphatic invasion, mitoses per mm^2, immunostains, and margin status of the primary tumor. Patients undergo a comprehensive history and physical examination, including a complete skin and lymph node examination. Imaging studies are considered if clinically indicated, such as in the presence of a strong suspicion of distant metastatic disease or significant comorbidities that impact management, or when a cutaneous metastasis from a noncutaneous primary neuroendocrine carcinoma is being considered. Patients are clinically staged and presented at the tumor board for therapeutic recommendations.

Clinically lymph node–negative patients are considered for wide local excision (WLE) of the primary tumor with 1- to 2-cm margins and SLNB with immunohistochemistry as preferred treatment at UM, regardless of the location or size of the primary lesion. For head and neck SLNBs, per UM standard protocol, single-photon emission CT (SPECT-CT) is used (Figure 1). However, for select patients, a discussion of the risks and benefits by the tumor board or patient preference may argue against excision and/or SLNB and favor radiation as monotherapy. The surgeon, radiation oncologist, and patient all play roles in this decision-making process. The intent of WLE of the primary tumor is to obtain histologically negative margins. For SLN-negative patients with tumors less than 2 cm, histologically negative margins after WLE, and generally no other adverse factors such as angiolymphatic invasion, observation only is recommended at UM. For SLN-positive patients, lymph node dissection (LND) is the preferred treatment, although the optimal treatment for these patients is currently unknown.[31] LND is the most common initial treatment after a positive SLN reported in the literature, and a few small series show low regional lymph node recurrence rates after LND.[12,13] However, in accordance with NCCN Guidelines[24] and based on tumor board discussion and patient preferences, radiation as sole therapy for microscopic nodal metastases may be considered.

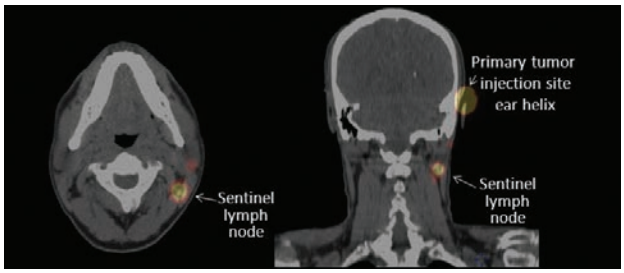

Figure 1 Head and neck SPECT-CT, prior to sentinel lymph node (SLN) excision, demonstrates a level IIb neck SLN in the submuscular triangle, deep to the sternocleidomastoid muscle and posterior to the internal jugular vein.

After a negative SLNB, no radiation therapy to the nodal basin is typically recommended regardless of location. For the head and neck region, NCCN Guidelines include consideration of radiation therapy to the nodal basin because of a higher risk of a false-negative SLNB from aberrant drainage and multiple drainage basins.[24] At UM, the expertise of the head and neck surgeons in SLNB supports observation.[32]

Clinically lymph node–positive patients undergo fine needle aspiration (FNA) to confirm metastatic MCC. If this is negative in the setting of high clinical suspicion, an open lymph node biopsy is performed. For palpable nodal metastases, LND is preferred treatment at UM. Radiation therapy as sole treatment for macroscopic nodal disease is only considered in select patients who may be poor surgical candidates based on multidisciplinary tumor board discussion or in those who refuse surgery.

At UM, adjuvant radiation therapy of the primary tumor site after resection is generally reserved for tumors at least 2 cm in clinical diameter or if histologic clear margins cannot be obtained after resection. However, adjuvant radiation therapy is also considered in select patients with tumors less than 2 cm in clinical diameter if the profile of the primary

tumor is concerning (ie, extensive angiolymphatic invasion), or if the location of the tumor would require morbid surgery in the event of recurrence. Radiation as monotherapy of the primary tumor site is recommended if the multidisciplinary tumor board deems the tumor surgically unresectable or the patient refuses surgery, consistent with NCCN Guidelines.[24]

Adjuvant radiation therapy to a nodal basin after LND is generally only recommended for patients with palpable adenopathy or multiple involved lymph nodes, and/or in the presence of extracapsular extension.

For patients with distant metastatic disease, tumor board discussion includes a variety of treatment modalities, including surgery, radiation therapy, chemotherapy, and novel therapies/clinical trials to individualize patient care.

Recommendations regarding long-term clinical monitoring for recurrence in patients with MCC vary among physicians. At UM, physical examinations including total body skin and lymph node examinations are recommended every 3 to 6 months for 2 years, then every 6 to 12 months thereafter, consistent with NCCN Guidelines.[24] In general, imaging studies are performed as clinically indicated based on a review of systems. For patients at high risk for developing metastases, imaging studies, such as CT or PET/CT, may be performed every 6 to 12 months in the absence of symptoms.

The following cases have been selected to highlight the implementation of the NCCN Guidelines in the UM multidisciplinary MCC program.

Patient Presentation 1

A 71-year-old woman presented with a small (<1 cm) red "wart" on her left forearm, which was present for 3 months. Her dermatologist performed a biopsy, and the diagnosis was confirmed by UM to be a primary MCC (Table 1).

Past medical history included insulin-dependent diabetes and hypertension. Review of systems was negative for metastatic disease. Physical examination showed a 6-mm biopsy site without clinical residual lesion. Lymph node evaluation of the head and neck and supraclavicular, axillary, epitrochlear, and inguinal basins revealed no adenopathy. Her clinical stage was IB (T1cN0M0).

The tumor board recommended a WLE with 1- to 2-cm margins and SLNB in accordance with the NCCN Guidelines for the treatment of clinically lymph node–negative MCC. No imaging was recommended based on a negative history, review of systems, and physical examination. The surgical oncologist in the UM MCC program performed the surgery. Histopathology showed no residual MCC at the primary tumor site, a negative non-sentinel left axillary lymph node, and 1 of 2 left axillary SLNs positive for metastatic MCC (Table 2).

Her pathologic stage was IIIA (T1N1aM0). The tumor board recommended an LND consistent with NCCN Guideline options.[24] Forty-six lymph nodes were removed, which were negative for MCC. The tumor board did not recommend adjuvant radiation therapy to the primary site, based on a small (<2 cm), widely excised primary tumor, nor regional radiation therapy, based on micrometastasis in a

Table 1 Patient 1 Primary MCC Profile

Characteristic	Finding
Growth pattern	Circumscribed
Depth of invasion (Breslow)	≥2.20 mm
Ulceration	Absent
Angiolymphatic invasion	Not identified
Mitoses/mm^2	>30 mm^2
Immunohistochemical staining	
CK20	Positive (diffuse cytoplasmic and perinuclear dot)
TTF-1	Negative
Margins	Deep margin involved

Abbreviations: CK20, cytokeratin 20; MCC, Merkel cell carcinoma; TTF-1, thyroid transcription factor-1.

Table 2 Patient 1 Positive SLN Profile

Characteristic	Finding
Site	Left axilla
Diagnosis	Positive
H&E	Positive
CK20	Positive
CK	Positive
Tumor burden	1%–2% surface area involved
Location of metastasis	Subcapsular sinus and parenchyma
Extracapsular extension	Absent

Abbreviations: CK, cytokeratin; H&E, hematoxylin-eosin staining; SLN, sentinel lymph node.

single SLN without extracapsular extension. The patient remained disease-free 4 years after diagnosis.

Patient Presentation 2

An 83-year-old man presented with a 3-month history of a slow-growing, hyperkeratotic lesion on the left preauricular cheek. His dermatologist performed a biopsy, and the diagnosis was confirmed by UM to be a primary MCC (Table 3).

The patient's medical history included coronary artery disease, myocardial infarction, defibrillator/pacemaker placement, cardiac stent, insulin-dependent diabetes, and hypertension. Review of systems was negative for metastatic disease. Physical examination showed a 1.2-cm crusted biopsy site on the left preauricular cheek without clinical residual lesion. No lesions were concerning for in-transit or satellite metastases, and no regional lymphadenopathy was palpated. His clinical stage was IB (T1cN0M0).

The tumor board recommended a WLE with 1- to 2-cm margins and SLNB according to NCCN Guidelines for the treatment of clinically lymph node–negative MCC. WLE with a 1.5-cm margin, SLNB, and delayed reconstruction were performed. Histopathology showed residual MCC 3.15 mm in depth with angiolymphatic invasion. Planar lymphoscintigraphy showed a single left retromandibular (level II) lymph node. However, 2 SLNs were noted intraoperatively in the left neck and removed, with one showing fibroadipose tissue only and the other positive for metastatic MCC (Table 4).

The patient's pathologic stage was IIIA (T1N1aM0). After surgery, the patient experienced a transient ischemic attack. Given his medical comorbidities and a single SLN that was positive according to immunohistochemistry only, radiation therapy as primary treatment to the nodal basin was recommended by the tumor board, consistent with NCCN Guideline options.[24] Adjuvant radiation therapy to the primary tumor site was also recommended, despite a relatively small (<2 cm) primary lesion with widely free surgical margins, given the presence of angiolymphatic invasion seen in the primary tumor and that the location could be easily incorporated into the radiation field for the regional nodal basin. He remains disease-free 2.5 years after diagnosis.

Patient Presentation 3

A 64-year-old man presented with a lesion on the right hip/buttock that had been growing for 1 year.

Table 3 Patient 2 Primary MCC Profile

Characteristic	Finding
Growth pattern	Circumscribed
Depth of invasion (Breslow)	≥2.07 mm
Ulceration	Absent
Angiolymphatic invasion	Not identified
Mitoses/mm^2:	84/mm^2
Immunohistochemical staining	
CK20	Positive (dot-like)
CK (CAM-5.2 and AE1/AE3)	Positive (dot-like)
CK7	Positive (dot-like)
TTF-1	Negative
Margins	Moderate lesion to all margins

Abbreviations: CK, cytokeratin; MCC, Merkel cell carcinoma; TTF-1, thyroid transcription factor-1.

It was diagnosed clinically as a cyst and treated with antibiotics, followed by an attempt at incision and drainage. Two weeks later an excision was performed on this 4-cm mass. Histopathology revealed a primary MCC with positive cytokeratin 20 (CK20) immunostaining in a dot-like perinuclear pattern, Breslow depth of 25 mm, and no angiolymphatic invasion. Thyroid transcription factor-1 (TTF-1) immunostaining was not performed; however, chest radiograph was negative.

The patient's medical history included chronic renal insufficiency and bilateral hip replacements. Review of systems was negative for metastatic disease. Physical examination showed a 10-cm incision on the right hip/buttock without clinical residual lesion. Palpation of the draining lymphatics and the right inguinal nodal basin revealed no surrounding in-transit or satellite metastases or lymphadenopathy. His clinical stage was IIB (T2cN0M0).

The tumor board recommended a WLE with a 2-cm margin and SLNB followed by adjuvant radiation therapy to the primary tumor site based on the clinical diameter of the lesion (≥ 2 cm). The surgical oncologist in the UM MCC program performed the surgery. Resection of the primary tumor site showed no residual MCC and a single positive SLN (Figure 2; Table 5).

His pathologic stage was IIIA (T2N1aM0). The tumor board recommended an LND consistent with NCCN Guideline options[24]; 14 lymph nodes were negative for MCC. The patient received adjuvant radiation therapy to the primary tumor site. The tu-

Table 4 Patient 2 Positive SLN Profile

Characteristic	Finding
Site	Left neck
Diagnosis	Positive
H&E	Negative
CK20	Positive
CK	Positive
Tumor burden	<1% surface area involved
Location of metastasis	Subcapsular sinus and parenchyma
Extracapsular extension	Absent

Abbreviations: CK, cytokeratin; H&E, hematoxylin-eosin staining; SLN, sentinel lymph node.

mor board did not recommend adjuvant radiation therapy to the nodal basin because of a single positive SLN and no extracapsular extension, consistent with NCCN Guidelines.[24]

A year later, the patient developed a cutaneous in-transit metastasis on the right hip just outside the radiation field of the primary tumor site. This was excised with a negative margin and he remained disease-free at 4 years after diagnosis.

Patient Presentation 4

An 82-year-old man presented to a local surgeon with a tender left preauricular swelling. A maxillofacial CT revealed a fluid collection or lymph node in the subcutaneous tissue of the left cheek. An FNA was nondiagnostic and he underwent a left superficial parotidectomy. UM confirmed a small cell neuroendocrine carcinoma within the parotid gland, periparotid adipose tissue, and 2 lymph nodes. Immunostains were positive for CK20 in a perinuclear dot-like pattern and negative for TTF-1 consistent with metastatic MCC. A PET/CT revealed FDG-avid adenopathy in the left neck.

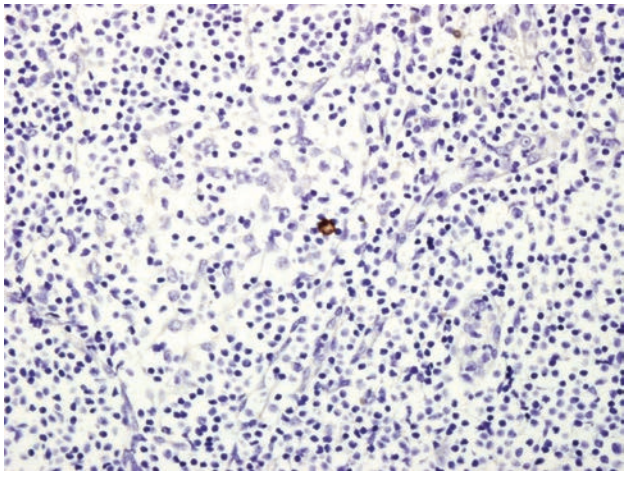

Figure 2 Cytokeratin-20 immunostain identifies Merkel cell carcinoma micrometastasis with an isolated single cell in a sentinel lymph node section (x400).

Table 5 Patient 3 Positive SLN Profile

Characteristic	Finding
Site	Right inguinal
Diagnosis	Positive
H&E	Positive
CK20	Positive
CK	Positive
Tumor burden	<1% surface area involved (≈9 cells)
Location of metastasis	Subcapsular sinus
Extracapsular extension	Absent

Abbreviations: CK, cytokeratin; H&E, hematoxylin-eosin staining; SLN, sentinel lymph node.

The patient's medical history included hypertension, non–insulin-dependent diabetes, and a hip replacement. Review of systems was negative except for a new tender, pink papule on the left forehead noted a few weeks before the preauricular swelling. Physical examination revealed a 4-mm pink-red dome-shaped papule on the left forehead (Figure 3). A well-healed incision was present with mild swelling on the left preauricular cheek extending to the mandibular angle. Lymph node evaluation revealed no significant lymphadenopathy. Biopsy results of the left forehead lesion confirmed a primary MCC (Table 6).

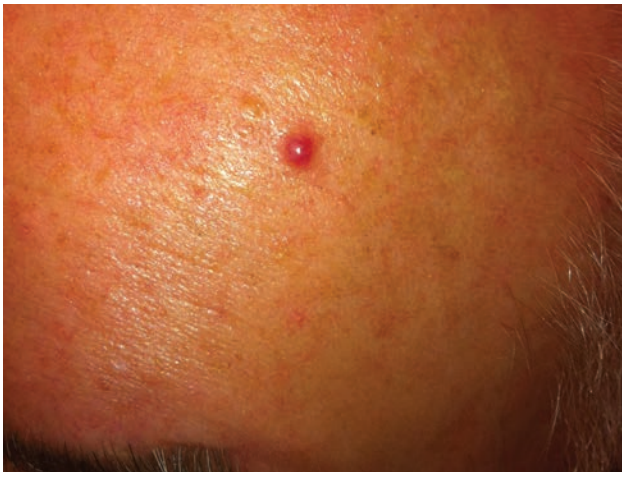

Figure 3 Primary Merkel cell carcinoma on the forehead.

Table 6 Patient 4 Primary MCC Profile

Characteristic	Finding
Growth pattern	Circumscribed
Depth of invasion (Breslow)	≥2.45 mm
Mitoses/mm^2	105/mm^2
Ulceration	Absent
Angiolymphatic invasion	Equivocal
Immunohistochemical staining	
CK20	Positive(cytoplasmic and dot-like)
TTF-1	Negative
Margins	Extends to deep margin

Abbreviations: CK, cytokeratin; MCC, Merkel cell carcinoma; TTF-1, thyroid transcription factor-1.

The patient's pathologic stage was IIIB (T1N1b/N2M0). The tumor board recommended a WLE with a 1-cm margin and left neck LND consistent with NCCN Guideline options for clinically lymph node–positive MCC.[24] This was performed by a head and neck surgeon in the UM MCC program and revealed no residual MCC at the primary tumor site and 6 of 20 lymph nodes positive for metastatic MCC, in addition to multiple positive matted lymph nodes. The tumor board recommended adjuvant radiation therapy to the left forehead, left parotid, and left neck nodal basin.

Five months after completion of adjuvant radiation, PET/CT showed an FDG-avid submental lymph node. CT-guided FNA confirmed metastatic MCC. The tumor board recommended resection of the metastatic node, which was performed by the head and neck surgeon.

PET/CT performed 6 months later showed left postauricular parotid and left retropectoral FDG-avid foci concerning for metastases. A core biopsy of the left retropectoral lymph node confirmed metastatic MCC. The tumor board recommended resection of the left parotid recurrence and a left axillary LND for macroscopic oligometastatic disease, performed concurrently by the head and neck surgeon and surgical oncologist. Of 25 left axillary lymph nodes, 8 were positive for metastatic MCC. The tumor board recommended adjuvant radiation therapy to both the left postauricular neck and left axilla. However, PET/CT before initiation revealed disease in the right neck and right axilla, and an FNA confirmed stage IV metastatic disease. Following input from surgical, medical, and radiation oncology, it was the consensus of the tumor board to recommend surgery for the right neck and right axillary disease. Right neck and right axillary LNDs were performed, revealing 1 of 32 right neck and 1 of 33 right axillary lymph nodes positive for metastatic MCC. Adjuvant radiation therapy was discussed; however, in the setting of stage IV resected disease, was not recommended by the tumor board.

A 4-month PET/CT showed an FDG-avid right adrenal nodule suspicious for metastatic MCC, and the patient received fractionated stereotactic radiotherapy as recommended by the tumor board. A 6-month PET/CT showed him to be disease-free, without evidence of metastatic disease.

The complexity of MCC management is evident in this case. Although the patient presentations have been chosen to illustrate various pathways within the NCCN Guidelines, the advantage of a multidisciplinary approach with tumor board consensus recommendations is most evident in complex advanced disease, for which treatment pathways cannot easily be captured in standardized guidelines.

Conclusions

NCCN Guidelines are available for most cancer types and provide a framework for treatment based on current evidence-based medicine. They provide a valuable tool that, when combined with multidisciplinary management, leads to optimal patient care. In the NCCN Guidelines for MCC, the current lack of high-level evidence in the medical literature contributes to the array of treatment options. The UM multidisciplinary MCC program brings together specialists with diverse training and interests to tailor these guidelines for individualized patient care. This provides tremendous benefit in terms of improving patient care, outcomes, efficiency, costs, education, and research.

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