Surgical Management of Merkel Cell Carcinoma

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KEYWORDS

• Merkel cell carcinoma surgery • Sentinel lymph node biopsy
• Lymph node metastases • Adjuvant radiation

KEY POINTS

- Merkel cell carcinoma is a rare aggressive cutaneous malignancy occurring most commonly in the head and neck region.
- Risk factors for development of Merkel cell carcinoma include sun exposure, age older than 65 years, immunosuppression, and infection with Merkel cell polyomavirus.
- Prognosis depends on factors, such as stage at presentation, tumor thickness, polyoma viral status, presence of tumor infiltrating lymphocytes, and lymphovascular invasion.
- Treatment of stage I and II Merkel cell carcinoma includes surgical resection and sentinel lymph node biopsy followed by the selective use adjuvant radiation.
- Treatment of stage III Merkel cell carcinoma requires multimodality treatment, including surgical resection of the primary site, lymphadenectomy, and adjuvant radiation or chemoradiation.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare aggressive neuroendocrine cutaneous malignancy that occurs most commonly in the head and neck region. Annual incidence of MCC is 0.6 cases per 100,000 persons and has been increasing.[1] The incidence of MCC in the United States, approximately 1600 cases per year, is expected to reach 3000 cases annually by 2025.[2] When analyzing characteristics of 4376 patients with MCC from the Surveillance, Epidemiology, and End Results database diagnosed between 1980 and 2008, Smith and colleagues[3] reported that most MCC tumors (48.1%) were located in the head and neck, followed by upper extremity (24.6%).

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ETIOLOGY AND RISK FACTORS

Risk factors for MCC include age greater than 65 years, sun exposure, immunosuppression, and infection with Merkel cell polyomavirus; 80% of MCCs have evidence of viral genome, whereas the rest exhibit UV-related DNA damage[2]; 98% of MCCs occur in whites; and 81% of cases occur in sun-exposed skin. MCC presents as an erythematous or violaceous dermal papule (**Figs. 1** and **2**). Up to 30% of patients present with clinical evidence of cervical or intraparotid lymph node metastases.[4]

DIAGNOSIS, STAGING, PROGNOSIS

A punch biopsy or an excisional biopsy of a suspicious skin lesion with narrow margins is preferred to shave biopsy, in order to accurately diagnose depth of invasion of the lesion. In addition to standard hematoxylin-eosin histopathologic evaluation, immunohistochemical staining plays an important role in the diagnosis of MCC. Positive immunostaining for cytokeratin 20 (CK20) in the presence of negative thyroid transcription factor 1 (TTF-1) staining suggests the diagnosis.[5] Poorly differentiated MCCs may lose the CK20 marker. Positive stains for chromogranin A, synaptophysin, or CD 56 (neural cell adhesion molecule) and the negativity for TTF-1 distinguish MCCs from small cell carcinomas.[5]

A thorough history and complete head and neck examination, including palpation of the parotid, occipital, and cervical lymph node regions, should be performed. Imaging

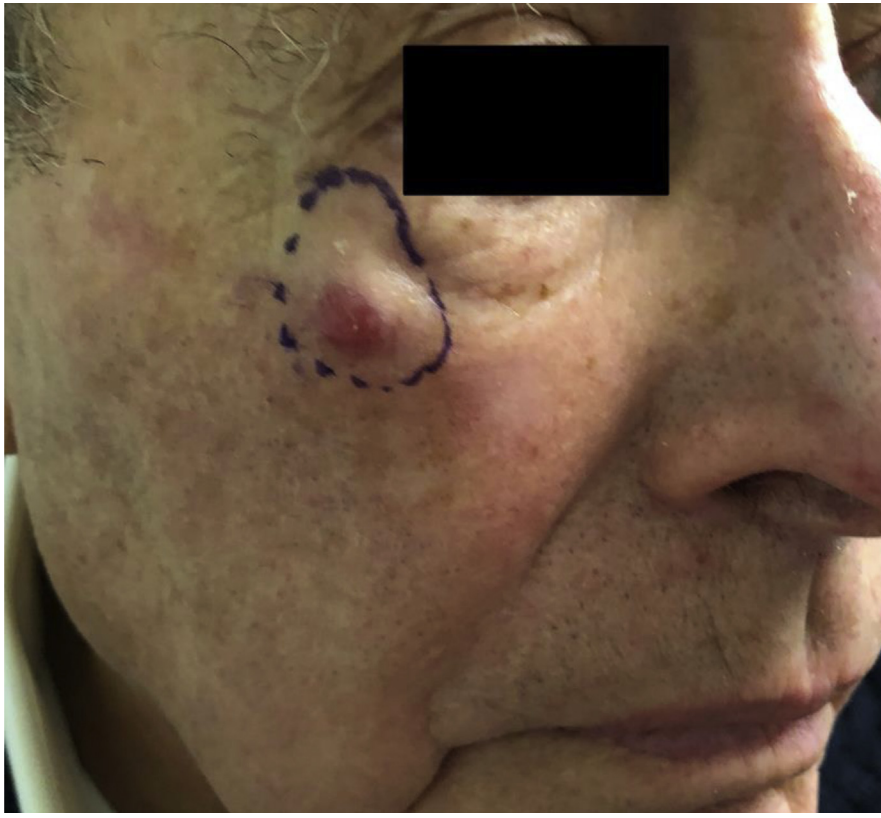

Fig. 1. MCC of the right malar region.

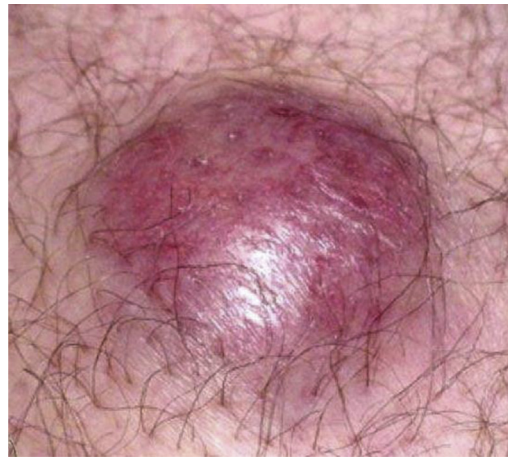

Fig. 2. MCC appears as an erythematous or violaceous dermal papule.

of the neck is a helpful adjunct to clinical staging. Lymphoscintigraphy with sentinel lymph node biopsy (SLNB) plays a critical role in staging MCCs and facilitates treatment planning. Up to one-half of patients with early-stage disease are reclassified as having late-stage disease following SLN biopsy. According to the National Comprehensive Cancer Network (NCCN) guidelines, SLNB is recommended for all patients with clinically node-negative disease who are fit for surgery.

Staging

The American Joint Committee on Cancer staging system incorporates well-established prognostic factors in MCC. In TNM staging, T classification is determined primarily by tumor diameter (**Table 1**). N classification is determined by the presence of lymph node metastases as well as dermal lymphatic metastases. Staging for MCC distinguishes lymph node metastases, which are identified clinically or radiographically versus those identified pathologically. Similar to melanoma, MCC is upstaged from stage I–II to stage IIIA, if clinically occult lymph nodes yield pathologic evidence of nodal metastases. Clinically positive nodal disease is considered at least stage IIIB, except T0/unknown primary (UP) MCCs, which are considered IIIA despite the presence of clinical nodal disease.

Dermal lymphatic metastases, or in-transit metastases, are features of MCCs and other cutaneous malignancies, which can complicate treatment. At a minimum, the presence of in-transit disease increases overall stage to III. In-transit disease located at a site distant from the primary tumor alters overall staging to M1a or stage IV.

Other, less well established clinicopathologic or immunologic factors have been investigated as independent predictors of prognosis, including tumor site,[3] tumor thickness,[6–9] growth pattern,[7,8] MCC viral status,[10,11] tumor-infiltrating lymphocytes,[7,12,13] and lymphovascular invasion (LVI).[7,14–16]

Prognostic Factors

The rates of metastatic spread of MCCs are far higher than those of most other cutaneous malignancies and upstage patients with clinical stage I–II to pathologic stage IIIA disease.[3,17,18] MCCs arising in head and neck sites have been linked to higher rates of occult nodal disease. In analyzing characteristics of 4376 patients with MCC, male sex, location of the primary tumor in the lip, intermediate tumor size

Table 1
Merkel cell carcinoma staging

Clinical Primary Tumor (T)	
TX	Primary tumor cannot be assessed (eg, curetted)
T0	No evidence of primary tumor
Tis	In situ primary tumor
T1	Maximum clinical tumor diameter, ≤2 cm
T2	Maximum clinical tumor diameter >2 but ≤5 cm
T3	Maximum clinical tumor diameter >5 cm
T4	Primary tumor invades fascia, muscle, cartilage, or bone
Clinical lymph node metastases (N)	
NX	Regional lymph nodes cannot be clinically assessed (eg, previously removed for another reason, or because of body habitus)
N0	No regional lymph node metastasis detected on clinical and/or radiologic examination
N1	Metastasis in regional lymph node(s)
N2	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) without lymph node metastasis
N3	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) with lymph node metastasis
Pathologic regional metastases (pN)	
pNX	Regional lymph nodes cannot be accessed (eg, previously removed for another reason or not removed for pathologic evaluation)
pN0	No regional lymph node metastasis detected on pathologic evaluation
pN1	Metastasis in regional lymph node(s)
pN1a(sn)	Clinically occult regional lymph node metastasis identified only by sentinel lymph node biopsy
pN1a	Clinically occult regional lymph node metastasis following lymph node dissection
pN1b	Clinically and/or radiologically detected regional lymph node metastasis, microscopically confirmed
pN2	In-transit metastasis (discontinuous from primary tumor, located between primary tumor and draining regional nodal basin, or distal to the primary tumor) without lymph node metastasis
pN3	In-transit metastasis (discontinuous from primary tumor, located between primary tumor and draining regional nodal basin, or distal to the primary tumor) with lymph node metastasis

Overall stage: clinical TNM	**T classification**	**N classification**	**M classification**
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2–T3	N0	M0
Stage IIB	T4	N0	M0
Stage III	T0–T4	N1–3	M0
Stage IV	T0—T4	Any N	M1

Overall stage: pathologic TNM	T classification	N classification	M classification
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2–T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	T1–T4	N1a(sn) or N1a	M0
	T0	N1b	M0
Stage IIIB	T1–T4	N1b–3	M0
Stage IV	T0–T4	Any N	M1

Data from NCCN Clinical Practice Guidelines in Oncology. Merkel Cell Carcinoma. Version 1.2020. October 2, 2019, 1-66.

2 cm to 5 cm, increasing tumor extension beyond the dermis, nodal metastasis, and distant metastasis each were independently associated with an increased risk of death from MCC.[3] The investigators found high frequency of lymph node metastases, 30.6% in non–head and neck MCC and 43.6% in head and neck MCC, even in small tumors less than 2 cm in size, indicating aggressiveness of MCC located in the head and neck region.

LVI, believed to be an early event in MCC pathogenesis,[19] has been associated with even higher rates of microscopic nodal disease and worse survival, independent of other factors.[7,15,16] LVI in the primary tumor has been associated with a 65% rate of occult metastases.[16]

Immunologic markers also have been investigated as prognostic biomarkers, based on observations of greater susceptibility and worse survival in immunosuppressed groups. Intratumoral $CD8^+$ lymphocyte infiltration has been shown to provide independent prognostic information.[12] Studies of predictive biomarkers of response to immunotherapy are ongoing.[20,21] For example, patients with an absence of Merkel cell polyomavirus oncoprotein (MCPyV) antibodies to a virus-related MCCs may be subject to higher recurrence rates. Currently, MCPyV serology may be included in the initial work-up as well as post-treatment surveillance of MCC patients.[22]

Imaging in Merkel Cell Carcinoma

Imaging plays an important role in the initial staging of MCC, due to MCC's propensity for early metastasis. Anatomic imaging, such as computerized tomography (CT) scan or magnetic resonance imaging and/or whole-body PET with fused axial imaging, may be useful to identify regional and distant metastases.[23] PET-CT scan is most useful for advanced disease. Imaging is less reliable for identifying occult metastatic disease in clinically stage I–II cases than is SLNB.[24] SLNB frequently has been utilized in the staging of MCC,[16,17,25] but there is no absolute consensus on the independent survival benefit of SLNB.[15] It facilitates, however, tailoring of the radiotherapy (RT) treatment to the disease[16] and provides a rationale for systemic therapy use, off or on protocol.

SURGICAL MANAGEMENT: EARLY-STAGE DISEASE (STAGES I AND II)

Wide local excision (WLE) of the primary MCC tumor with 1-cm to 2-cm margins, or to the level of investing fascia or periosteum, is the mainstay of treatment.[22] For early-stage T1 and T2 primary MCC tumors of the head and neck region, Mohs micrographic surgery (MMS) also has been utilized successfully, with overall survival outcomes comparable to those of WLE.[25] Although used infrequently overall, MMS is

more likely to be utilized for small MCCs in head and neck sites, followed by adjuvant radiation[25,26] and performed less often in conjunction with an SLNB.[26] If MMS is chosen as a treatment, then SLNB should be performed prior to MMS, in order not to cause alteration in lymphatic drainage of the primary MCC. SLNB ideally should be performed at the time of the WLE of the primary tumor.[22,26]

Absence of SLNB precludes complete pathologic staging and impedes targeted adjuvant radiation planning.[16] Synoptic reporting of pathologic findings after MMS is underutilized, which also may affect staging and additional treatment. According to the NCCN guidelines, the following elements have to be included in the pathology report: largest tumor diameter (centimeters); peripheral and deep margin status; LVI; and extracutaneous extension to bone, muscle, fascia, or cartilage.[22] Additional clinically relevant factors to be included are Breslow depth (millimeters), tumor-infiltrating lymphocytes (not identified, brisk, nonbrisk), tumor growth pattern (nodular or infiltrative), and presence of secondary cutaneous malignancy in the specimen, such as squamous cell or basal cell carcinoma.[22]

SURGICAL MANAGEMENT: STAGE III

Stage IIIA

The surgical management of stage III is distinguished based on the presence of microscopic (stage IIIA) or clinically positive lymph node metastases (stage IIIB). Stage I–II MCCs without clinically or radiographically apparent nodal metastases that are found to have lymph node metastases postoperatively are reclassified as pathologic stage IIIA. A positive SLNB prompts additional treatment. The NCCN guidelines recommend nodal dissection and/or RT to the nodal basin, based on 2 small single-institution studies that suggested equivalent nodal control and survival after RT or completion lymph node dissection (CLND).[27,28] A larger study of more than 400 SLN-positive MCC patients from the National Cancer Database (NCDB) showed that patients treated with RT with or without CLND conferred a survival benefit compared with completion nodal dissection alone. The investigators recommended a personalized approach to adding CLND to adjuvant RT based on age, comorbidities, lymph node basin, and burden of disease.[29]

Stage IIIB

Early studies suggested aggressive treatment that included WLE, lymph node dissection, and adjuvant RT improved the survival of MCC patients.[30–32] Surgery and radiation have remained the mainstay in the treatment of MCCs with clinically apparent lymph node metastases without evidence of distant metastatic spread.[33] Chemotherapy (etoposide, and cisplatin or carboplatin) frequently is added, although the survival benefit of cytotoxic chemotherapy has not been demonstrated. Multimodality treatment has yielded 5-year overall survival rates of 30% to 40%.[34,35] RT to the primary site and nodal basin improved locoregional control[36–38] and disease-free[39] and overall survival.[40,41] Although primary RT in the setting of clinically positive nodal disease has been reported, locoregional control appears to be better with combined lymphadenectomy and postoperative RT.[42] The number of clinically involved lymph nodes[43] and immune-suppressed status[44] influence recurrence-free and disease-specific survival rates.

The use of immunotherapy, in particular, programmed cell death-1 inhibitors, as neoadjuvant treatment prior to surgical management of advanced resectable MCC is promising. The CheckMate 358 trial, which recently was published, showed notable antitumor efficacy in patients with advanced MCC. Administration of nivolumab prior

to surgery in 39 MCC patients with predominantly stage IIIB disease resulted in pathologic complete responses (pCRs) in 47%, with at least a major pathologic response in 61.5% of patients. Recurrence-free survival rates at 12 months and 24 months postoperatively were 77.5% (95% CI, 58.4% to 88.7%) and 68.5% (95% CI, 47.5% to 82.6%), respectively, comparing favorably with historical controls. The 12-month and 24-month recurrence-free survival rates of patients with pCRs were 100% and 89%, respectively.[45] The investigators suggested that patients with pCRs may not require adjuvant RT. Response to therapy was determined more reliably with surgery, using pathologic review rather than radiographic restaging. Given these impressive results, it seems likely that immunotherapy will be incorporated into the standard treatment of locoregionally advanced MCC. Moreover, these responses appear to be durable in nature. Historically, overall survival for all patients with MCC of the head and neck was reported as low as 54% at 5 years and 37% at 10 years,[46] due to high rates of local recurrence as well as regional lymph node metastases.

SURGICAL MANAGEMENT OF UNKNOWN PRIMARY MERKEL CELL CARCINOMA

In 5% to 20% of MCCs, the primary cutaneous origin of metastatic MCC in the lymph nodes never is identified.[47,48] A full-body dermatologic survey and whole-body PET-CT scan are helpful in staging and work-up (**Fig. 3**).

UP MCC is characterized by infrequent intradermal metastases and portends a more favorable survival than other MCCs with similar nodal disease burden levels.[49] UP MCC has a lower association with MCC polyomavirus than with cutaneous MCC.[50] Other clinically distinctive characteristics have been identified, including decreased frequency of preexisting immunosuppression and higher tumor mutational burdens with UV-specific genetic signatures. Stronger underlying immune response against MCC is believed to contribute to regression of the primary lesion and improved survival associated with UP MCC.[51,52] Despite these distinctive features, there is no evidence that these represent a separate entity, such as primary lymph node MCC.[51,53]

The NCCN guidelines recommend that after multidisciplinary consultation, patients with MCC lymph node metastases undergo lymphadenectomy and adjuvant RT. Primary RT may be considered in some cases.[48] Surgery for UP MCC in the head and neck frequently involves parotidectomy and neck dissection. The lymphadenectomies approximate those performed for other cutaneous malignancies that include removal of external jugulodigastric, suboccipital, and/or postauricular lymphatics, due to the presumed cutaneous origin of these cancers.[51,53]

ROLE OF ADJUVANT RADIOTHERAPY

Surgical treatment of MCC often is followed by adjuvant radiation to the primary tumor bed with or without regional radiation to the lymph node basin.

For localized MCC (stages I and II), surgery followed by adjuvant RT has been shown to improve locoregional control[38,40] and overall survival[40,54] over surgery alone. Many studies do not distinguish between the utilization of local RT and regional RT, making it more difficult to assess the impact of the treatment on outcomes. Adjuvant local RT is employed far more commonly than elective nodal RT, particularly in the setting of a negative SLNB.[16] Indications for adjuvant local RT with or without regional RT include close or positive margins but other factors may be considered, such as larger primary tumor size and the presence of LVI or immunosuppression, at the discretion of the multidisciplinary treatment team. The NCCN recommends timely initiation of postoperative RT.[22] An NCDB review of 5952 patients with stage I–II MCC

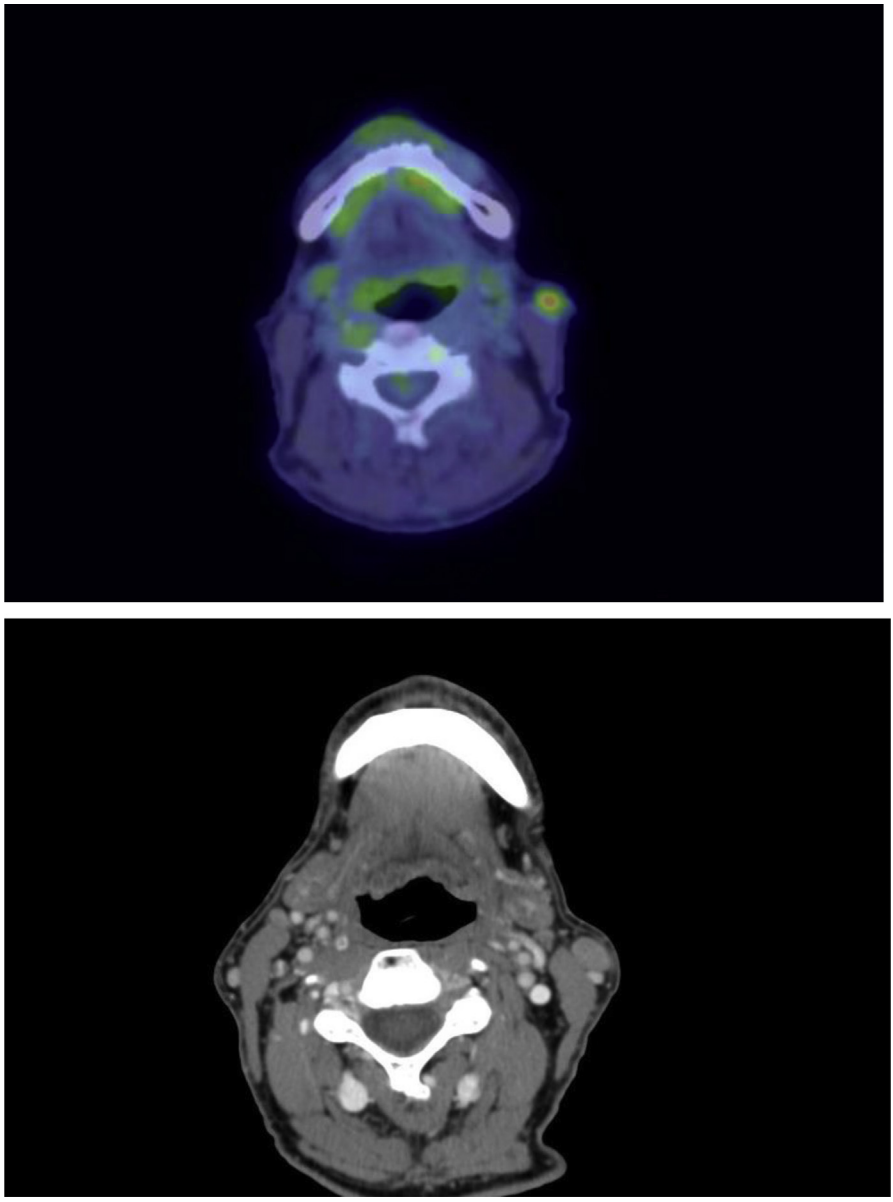

Fig. 3. PET-CT (*upper*) and CT with contrast (*lower*) both reveal a single metastatic lymph node within the left external jugular/parotid tail region, in a patient with MCC of UP. Complete skin examination failed to identify the primary tumor source. The patient underwent left parotidectomy with facial nerve preservation and selective neck dissection followed by adjuvant RT. He has no evidence of disease 3 years later.

revealed no detrimental effect of delays from completion of surgical treatment to initiation of adjuvant RT on overall survival, ranging from 4 weeks to 24 weeks. In this study, however, predictors of worse overall survival included advanced age, greater comorbidities, male sex, lower regional income, earlier year of diagnosis, more advanced tumor and nodal staging, positive margins, head and neck location, and treatment at community facilities.[55]

In patients with regional nodal metastases (stage III), adjuvant RT improves locoregional control but may not improve overall survival.[54] Patients are subject to rapid recurrences at locoregional and distant sites. High-risk patients should be considered for participation in clinical trials.

ROLE OF SYSTEMIC THERAPY

In the primary treatment of nondisseminated MCC, adjuvant cisplatin or carboplatin with or without etoposide may be considered in patients with regional disease. According to the NCCN guidelines, adjuvant chemotherapy should not be recommended routinely, because no overall survival benefit has been demonstrated in retrospective studies; it may be considered in select cases. A retrospective analysis of 2065 stage III MCC patients from the NCDB failed to show statistically significant improvement in overall survival with addition of adjuvant chemotherapy.[54] Cytotoxic chemotherapies no longer are recommended first-line treatments of disseminated disease. They largely have been replaced by immune checkpoint inhibitors (avelumab, pembrolizumab, and nivolumab) but may be considered second-line treatment. The NCCN recommends enrolling high-risk patients in clinical trials.

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DISCLOSURES

None.

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