Box 2 Summary of 'The Oxford levels of evidence 2' (adapted from the Oxford Centre for Evidence-Based Medicine levels of evidence working group)

Level 1
Systematic review or meta-analysis.
Level 2
Randomized trial or observational study with dramatic effect.
Level 3
Non-randomized, controlled cohort, or follow-up study.
Level 4
Case series, case–control, or historically controlled study.
Level 5
Mechanism-based reasoning.

Evidence supporting panel recommendations was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group, 'The Oxford Levels of Evidence 2' (2016 version). A summary of the OCEBM grading scale may be found above (box 2). The level of evidence (LE) for a given recommendation is expressed in parentheses following the recommendation (eg, LE:1). Recommendations without an associated LE were based on expert consensus.

MERKEL CELL CARCINOMA

MCC is a rare tumor of neuroendocrine differentiation with incidence rates on the rise in the US.[19] The main characteristics associated with MCC include immunosuppression, advanced age, UV exposure, and MCPyV positivity,[2] the latter two being the most common etiological factors, each associated with distinct tumor genotypes and phenotypes.[20]

MCC is an aggressive tumor that can grow quickly and may metastasize to additional sites on the skin, lymph nodes, and distant organs.[21] More advanced disease at presentation is associated with worse survival outcomes, with one analysis of the National Cancer Database (n=9,387) reporting 5-year overall survival (OS) rates for local, nodal, and metastatic MCC of 51%, 35%, and 14%, respectively.[22] Of note, this study assessed patients in the database with follow-up and staging data collected between 1998 and 2012 (prior to the FDA approval of ICIs for MCC). Furthermore, disease-specific survival (DSS) was not assessed. The DSS rates for MCC are estimated to be higher due to a high rate of death due to intercurrent disease in patients of advanced age.[23]

Surgical excision is the standard of care for resectable primary MCC tumors, and adjuvant radiation therapy is often used to reduce the risk of recurrence.[21 23] Unresectable tumors or tumors that are challenging to resect fully are sometimes treated with primary radiation.[24] For patients with tumors that are not amenable to surgery or radiation, treatment options have historically been limited. Systemic chemotherapy offers high initial response rates, but responses are not durable, with a median time to progression of merely 3 months.[25] MCC is known to be an immunogenic tumor,[26] and ICIs have demonstrated safety, efficacy, and clinical benefit in many patients with advanced disease. The FDA has approved two anti-PD-(L)1 agents for treatment of advanced MCC (for the purpose of this guideline, 'advanced MCC' encompasses tumors that are recurrent, locally advanced, and/or metastatic, and not amendable to curative surgery or radiation; see box 1), and numerous ongoing studies are evaluating ICIs both in earlier stages of the disease or as components of novel combination strategies.

Optimal care of patients with MCC ideally involves a multidisciplinary team approach that may include surgical oncology, radiation oncology, medical oncology, interventional radiology, dermatology, palliative care, and any other pertinent specialties, as appropriate. Comprehensive management recommendations for non-immunotherapeutic treatment of MCC of any stage are outside the scope of this guideline but can be found in other published guidelines.[27]

Diagnosis, workup, and initial staging for MCC

Proper diagnosis and initial staging of MCC are key components of determining the risk of systemic metastases and, hence, eligibility for systemic therapy. Like other cancers, the staging system is largely determined by anatomical features including size of the primary tumor, presence and size of lymph node metastases, and presence of distant metastases.

Diagnosis and initial staging for MCC

The diagnosis of MCC routinely involves immunohistochemistry (IHC) in addition to histopathological analysis of a tumor biopsy. The histological characteristics of MCC often resemble other small-cell neoplasms such as BCC, small-cell lung cancer, small-cell melanoma, and others;[28 29] therefore, the differential diagnosis frequently involves IHC staining for MCC-specific markers. A useful marker for MCC is cytokeratin 20 (CK20),[30 31] which is reported to be positive in 87.4% of MCCs.[29] CK20 staining in a perinuclear dot-like pattern is highly suggestive of MCC. Positive IHC staining for additional neuroendocrine markers such as synaptophysin,[32] neuron-specific enolase,[33] neurofilament,[34 35] and chromogranin A,[36 37] and/or negative staining for thyroid transcription factor-1 (TTF-1)[36] can also aid in the differential diagnoses, particularly for CK20-negative MCC.

In 2010, the American Joint Committee on Cancer (AJCC) adopted a consensus system to stage MCC,[38] and the Tumor, Node, Metastasis (TNM) system forms the basis of modern MCC staging.[22 39] Now in the 8th edition, the updated AJCC staging system was informed by an analysis of 9,387 MCC cases. Noted updates include a distinction between clinical and pathological assessment of nodal involvement, as well as new stage classifications for tumors with nodal disease and metastatic disease with an 'unknown primary' (discussed later in this section).[22] A summary of the AJCC (8th edition) staging system for MCC can be found in table 1.