

## 46. Merkel Cell Carcinoma

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### Emerging Prognostic Factors for Clinical Care

#### Lymphovascular Invasion and Other Histopathologic Parameters

Lymphovascular invasion (LVI), also referred to as angiolymphatic invasion, is defined as the presence of tumor cells within the endothelium-lined spaces without distinguishing between lymphatic channels and blood vessels. Although LVI generally is considered a poor prognostic indicator in melanoma and other malignancies, inconsistent data regarding this parameter exist for MCC<sup>1-3</sup> (AJCC Level of Evidence: III). Moreover, nonuniform detection methods, including the use of immunohistochemical staining of endothelial cells, and inconsistent reporting limit the ability to draw definitive conclusions about the prognostic value of this parameter from larger datasets. Consistent synoptic reporting of LVI is strongly encouraged. Other parameters not routinely collected include ulceration, mitotic rate, and the presence of tumor-infiltrating lymphocytes. Consistent recording of such variables is strongly encouraged to validate or refute prognostic correlations identified in smaller, single-institution cohorts.

#### Merkel Cell Polyomavirus (MCPyV)

The association between MCC and the novel virus MCPyV was first described in 2008.<sup>4</sup> Since then, mounting evidence has emerged that MCPyV viral proteins have a causal role in MCC development.<sup>5,6</sup> However, a subset of MCCs consistently are MCPyV negative, suggesting alternate mechanisms of tumorigenesis.<sup>7</sup> It has been suggested that a geographic variation in contributions of causative factors for MCC may exist. UV radiation may be a more prevalent factor in the development of MCPyV-negative MCCs, in which a higher overall mutation burden with a prominent UV-signature pattern has been identified.<sup>8,9</sup> Although a trend may suggest a more favorable outcome for patients with virus-positive tumors, the prognostic significance of MCPyV status remains unclear and controversial<sup>10-12</sup> (AJCC Level of Evidence: III).

#### p63

Recently, relatively small studies suggested a strong correlation between immunohistochemical expression of p63 and worse outcome in patients with MCC.<sup>11,13</sup> However, other studies could not confirm the correlation with prognosis and did not report the high rate of p63 positivity previously observed.<sup>9,14</sup> The prognostic value and clinical utility of this marker with variable expression remain unclear (AJCC Level of Evidence: III).

#### Imaging

Several new and emerging imaging modalities are described in the recent literature. With regard to lymphoscintigraphy for sentinel lymph node detection, the use of single-photon emission CT/CT imaging

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may contribute to improved detection of radiolabeled lymph nodes close to the primary tumor/radiotracer injection site (e.g., primary tumors located in the head/neck region).<sup>15</sup> In addition, the use of intraoperative gamma camera technology may further assist surgeons in the intraoperative detection and localization of sentinel lymph nodes during surgery, as well as verify the excision of sentinel lymph node(s).<sup>16</sup> The use of [indium-111]-pentetretotide scintigraphy and [gallium-68 (<sup>68</sup>Ga)]-DOTATATE, -DOTATOC, and -DOTANOC PET/CT imaging has been described based on expression of somatostatin receptor (SSTR) in MCC.<sup>17,18</sup> Somatostatin analogs labeled with PET radioisotopes (e.g., <sup>68</sup>Ga, copper-64) may offer additional diagnostic imaging information about the sites and extent of MCC involvement throughout the body beyond the typical anatomic information provided by CT and MR imaging or the metabolic information of FDG PET.<sup>19</sup> Further clinical trials are needed to compare these emerging imaging approaches with standard imaging methods.

### Risk Assessment Models

The AJCC recently established guidelines that will be used to evaluate published statistical prediction models for the purpose of granting endorsement for clinical use.<sup>20</sup> Although this is a monumental step toward the goal of precision medicine, this work was published only very recently. Therefore, the existing models that have been published or may be in clinical use have not yet been evaluated for this cancer site by the Precision Medicine Core of the AJCC. In the future, the statistical prediction models for this cancer site will be evaluated, and those that meet all AJCC criteria will be endorsed.

### Recommendations for Clinical Trial Stratification

The following stratification criteria stem from the prognostic factor analyses suggested for use in MCC trials, depending on the specific objectives of the study, the cancer stage(s), and the population under study (including the sample size). These recommended criteria for clinical trials are listed by stage in approximate order of their statistical power.

<b>Stage I/II</b>	Largest tumor diameter ( $\leq 2$ cm, $> 2$ cm and $\leq 5$ cm, $> 5$ cm)
	Tumor thickness (millimeters)
<b>Stage III</b>	Clinically occult versus clinically detected regional nodal disease
	Unknown primary status (if applicable)
<b>All (including Stage IV)</b>	Profound immunosuppression
	MCPyV status
	Patient age ( $< 65$ vs. $\geq 65$ years)
	Patient sex

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