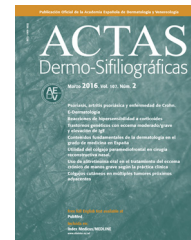




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## REVIEW

# Merkel Cell Carcinoma: An Update of Key Imaging Techniques, Prognostic Factors, Treatment, and Follow-up<sup>☆</sup>



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### PALABRAS CLAVE

Carcinoma de células de Merkel;  
Factores pronóstico;

**Abstract** Merkel cell carcinoma, though rare, is one of the most aggressive tumors a dermatologist faces. More than a third of patients with this diagnosis die from the disease. Numerous researchers have attempted to identify clinical and pathologic predictors to guide prognosis, but their studies have produced inconsistent results. Because the incidence of Merkel cell carcinoma is low and it appears in patients of advanced age, prospective studies have not been done and no clear treatment algorithm has been developed. This review aims to provide an exhaustive, up-to-date account of Merkel cell carcinoma for the dermatologist. We describe prognostic factors and the imaging techniques that are most appropriate for evaluating disease spread. We also discuss current debates on treating Merkel cell carcinoma.

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**Actualización en el carcinoma de células de Merkel: claves de las técnicas de imagen, factores pronóstico, tratamiento y seguimiento**

**Resumen** El carcinoma de células de Merkel es un tumor muy poco frecuente, pero es uno de los más agresivos a los que se puede enfrentar un dermatólogo. Más de un tercio de los pacientes fallece por esta enfermedad. Numerosos investigadores han intentado identificar los posibles

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t factores clínico-patológicos relacionados con el pronóstico de este carcinoma. Sin embargo, los resultados obtenidos en estos estudios son discordantes. Debido a la baja frecuencia y la edad avanzada de los pacientes, no se dispone de estudios prospectivos, y en consecuencia, no existe un claro algoritmo en el tratamiento. Este artículo pretende realizar una exhaustiva y comprensiva revisión del carcinoma de células de Merkel que suponga al dermatólogo una puesta al día en este tumor. Detallamos los factores pronósticos, se revisan las técnicas de imagen que resultan más adecuadas para el estudio de extensión y las controversias actuales relacionadas con el tratamiento.

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## Introduction

Merkel cell carcinoma (MCC) is a rare, highly aggressive tumor, and local or regional disease recurrence is common, as is metastasis. Because of the low incidence of this tumor and the advanced age of patients, prospective studies comparing treatment protocols for different stages have not been done. At present we lack consensus on how to manage the treatment of MCC once diagnosed.

This review aims to provide an exhaustive, up-to-date account of MCC for the dermatologist. We describe prognostic factors and the imaging techniques that are most appropriate for evaluating disease spread. We also discuss current debates on how to treat MCC.

## Imaging Studies of MCC Extension

No clinical management guidelines reflecting consensus on the most appropriate test batteries and imaging studies to establish MCC tumor extension and guide follow-up have emerged.<sup>1</sup>

The entire surface of the patient's skin must be examined and regional lymph nodes palpated to detect evidence of spread.<sup>1</sup>

An exhaustive blood workup including a full blood count and biochemistry for alkaline phosphatases and coagulation factors should be done.<sup>2</sup> A baseline serum test for the Merkel cell polyomavirus (MCPyV) should be ordered if possible. High antibody titers are specific indicators of recent disease and changes in blood levels reflect response to treatment; thus, increases are considered markers of recurrence.<sup>3</sup>

An imaging study must be obtained for initial staging in order to rule out distant metastasis. Computed tomography (CT) and magnetic resonance imaging are usually recommended.<sup>4</sup> New generation positron emission (PET) CT provides simultaneous capture of images of metabolic activity and the anatomical location of lesions<sup>5-7</sup> (Fig. 1). This information is of great importance because it can affect staging: Concannon et al.<sup>6</sup> found that stage classification changed in 33% of patients based on fluorodeoxyglucose PET-CT and that the approach to management changed in 43%.

When tumors appear localized on clinical examination, showing no evident sign of metastasis, it is important to firmly establish whether regional lymph nodes are involved or not (Fig. 1), given that nodal spread is associated with a worse prognosis.<sup>4</sup>

There is ample evidence of the usefulness of ultrasound imaging to explore spread to lymph nodes in melanoma. However, the use of this technique in MCC is still limited. Zager et al.<sup>8</sup> proposed ultrasound imaging to study the lymph node basins draining MCCs in patients at high surgical risk who cannot undergo sentinel lymph node biopsy (SLNB) as well as to follow patients in whom node involvement is uncertain. Along that line, Righi et al.<sup>9</sup> recently suggested a protocol that combined ultrasound imaging with fine-needle aspiration as a step prior to SLNB in selected patients. When there are palpable nodes (stage III), this approach can confirm regional metastasis. In the absence of palpable lymph nodes (stages I and II), ultrasound exploration and fine-needle aspiration can be followed by cytology and immunohistochemistry (Fig. 1) to detect cells positive for cytokeratin (CK) 20.<sup>1</sup> Patients with positive results of cytology are referred for lymph node dissection. This approach circumvents SLNB in at-risk patients, and those in whom nodal spread is not suspected based on ultrasound imaging are not referred for SLNB. The sensitivity of this approach was 85.7% and specificity was 90% in the study of Righi and colleagues.

## Prognostic Factors

Many have tried to identify factors that might affect prognosis in MCC, but studies have produced inconsistent results. The main clinical, histologic, and immunohistochemical indicators of prognosis are summarized in Table 1.<sup>10</sup>

Most agree that overall survival in MCC depends mainly on stage at clinical diagnosis.<sup>11-14</sup> In a study of 251 patients, Allen et al.<sup>15</sup> reported an 81% survival rate for patients diagnosed in stage I (67% for stage II, 52% for stage III, and 11% for stage IV).

Reported clinical predictors of poor prognosis are advanced age (>70 years)<sup>16</sup>; male sex<sup>17</sup>; immunocompromised status<sup>14</sup>; tumor size of more than 2 cm on diagnosis<sup>18</sup>; and a tumor location on the trunk,<sup>13</sup> buttocks, legs, or mucosal tissues.<sup>19</sup> MCC may also start in the lymph nodes without a skin tumor. Such primary nodal tumors account for 8% to 12% of all MCCs and are associated with a better prognosis.<sup>20,21</sup>

The largest case series to analyze histologic factors was reported by Andea et al.<sup>22</sup> The factors they initially found to be related to a poor prognosis were tumor size, thickness, and depth; an infiltrative growth pattern; the presence of lymphatic and vascular invasion; and the absence of a peritumoral lymphocytic infiltrate. However, only an infiltrative

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