

Merkel Cell Carcinoma: Call for Wide Surgical Margins Plus Adjuvant Radiation

BY MARK FUERST

SAN FRANCISCO—Wider surgical margins reduce local recurrence in Merkel cell carcinoma primary lesions that are not treated with radiation therapy, according to a new study presented here at the American Academy of Dermatology (AAD) Annual Meeting.

Merkel cell carcinoma is a rare and aggressive cutaneous neuroendocrine cancer with local recurrence rates up to 62 percent. Current National Comprehensive Cancer Network (NCCN) guidelines recommend excising primary Merkel cell carcinomas with margins of one to two centimeters. For the new study, researchers from the Department of Dermatology at Stanford University investigated the

Clinical Management

In another presentation, Christopher Bichakjian, MD, Clinical Associate Professor in the Division of Cutaneous Surgery and Oncology and Director of the Multidisciplinary Merkel Cell Carcinoma Program at the University of Michigan, said that clinical management of patients with Merkel cell carcinoma should focus on local control “without excessively wide surgical margins and selective use of adjuvant radiation therapy.”

“Even small primary tumors may have nodal metastases,” he noted. “Microscopic metastasis can be a precursor of disease progression and poor outcome.”

The NCCN recommends obtaining



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effect of surgical margin size on local recurrence rates in 148 patients with stages I, II, or IIIA Merkel cell carcinoma.

Teresa Fu, MD, a resident in the Stanford Department of Dermatology, who presented the study, explained that patients were categorized by surgical margin size (whether less than or more than one centimeter) and by whether they received radiation therapy to the primary site. Among the 42 patients who did not receive radiation therapy to the primary site, 30 percent (9 of 30) with surgical margins smaller than one centimeter had a local recurrence, while none of the 12 patients with surgical margins larger than that did.

Among patients who did receive radiation therapy to the primary site, surgical margin size was not significantly associated with risk of local recurrence: Only four percent of patients (2/48) with less than a one centimeter margin and 12 percent of patients (7/58) with more than a one centimeter margin recurred locally.

“These findings suggest that in the treatment of cutaneous Merkel cell carcinoma, radiation therapy may nullify the impact of surgical margin size on local recurrence rates,” she concluded. In cases where postoperative radiotherapy is planned, surgical margins should be minimized to reduce morbidity and avoid delays in initiating radiation due to postoperative wound healing.”

histologically negative margins when clinically feasible. “Surgical margins should be balanced with morbidity of surgery. If appropriate, one should avoid undue delay in proceeding to radiation therapy.”

He recommended attempting a wide excision with margins of one to two centimeters, is feasible, and when tissue sparing is of critical importance, techniques for more exhaustive histologic margin assessment may be considered, he added.

“Try to get comfortably clear surgical margins, generally ranging from one to two centimeters based on location. Tissue sparing should not be a primary goal. Merkel cell carcinoma is a very radiosensitive tumor. When reasonable excision margins reveal microscopically positive margins, strongly consider deferring more surgery and pursuing adjuvant radiation therapy.”

The available literature on the adjuvant use of radiation therapy is “very confusing,” he said. Several large studies based on National Cancer Data Base (NCDB) or NCI Surveillance Epidemiology and End Results (SEER) data have reported a correlation between adjuvant radiation therapy and

improved overall survival. “However, incomplete information in these datasets limits the ability to draw meaningful conclusions about clinical management.

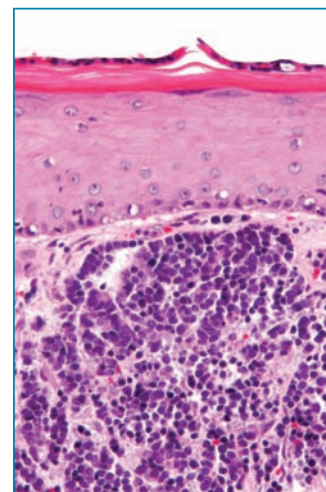
Examples of critically important missing information from NCDB data include the location of the radiation field—primary site versus nodal basin—and sentinel lymph node [SLN] status. Moreover, overall survival is a highly inadequate outcomes measure in elderly patients with Merkel cell carcinoma, whose mortality is heavily influenced by their comorbidities.”

Bichakjian presented data on the use of SLN biopsy for Merkel cell carcinoma at the University of Michigan, reporting successful identification of the sentinel lymph node in 93 of 97 cases (96%), including primary tumors of the head and neck.

“SLN positivity is significantly associated with clinical tumor

size, tumor thickness, mitotic rate, and infiltrating tumor growth pattern,” he said. Overall SLN positivity in the entire cohort was 45 percent. Importantly, among patients with the lowest-risk tumors measuring less than one centimeter in size, up to two millimeters in thickness, and with a mitotic rate of less than 10/mm², the SLN positivity rate ranges from 23.1 to 36.4 percent.

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Bichakjian defined optimal management of primary Merkel cell carcinoma as excision of the primary tumor with negative margins with or without adjuvant radiation therapy, as indicated, and SLN biopsy followed by appropriate treatment of nodal basin, as indicated.

Emerging Therapies for Merkel Cell Carcinoma

Also at the meeting, Isaac Brownell, MD, PhD, an investigator in the Dermatology Branch at the National Cancer Institute, discussed emerging therapies for Merkel cell carcinoma, noting that the neuroendocrine tumor is associated with advanced age, immunosuppression, ultraviolet radiation, and fair skin, and that Merkel cell polyomavirus is found in 80 percent of tumors.

Standard treatment consists of surgical excision, which is curative for local disease; SLN biopsy and complete lymph node dissection, which is prognostic; radiotherapy, which improves relapse-free survival; and chemotherapy, which is palliative, but lacks durable response. "There is no effective treatment for advanced Merkel cell carcinoma," he stated. "There is a need for novel treatments."

The rare status of Merkel cell carcinoma and unclear molecular mechanisms have impeded drug development. "The targeted therapies that have been tried are largely unsuccessful. Immunotherapy remains hopeful," Brownell said.

Targeted molecular therapies for Merkel cell carcinoma include kinase inhibitors. Trials of the tyrosine kinase inhibitor imatinib show KIT expression, but not activation, he said. Pazopanib, a multikinase inhibitor, shows mixed case reports, and controlled trials are ongoing. Trials are also active with cabozantinib, a c-Met, and



ISAAC BROWNELL, MD, PHD:

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vascular endothelial growth factor receptor (VEGFR)-2 inhibitor.

Because Merkel cell carcinoma expresses somatostatin receptor 2, there have been multiple trials of somatostatin analogues, Brownell noted. Combinations are also in the works with cixutumumab (insulin-like growth factor-1R inhibitor), everolimus (mTor inhibitor), and octreotide acetate, as well as everolimus and vatalanib (VEGFR, platelet-derived growth factor receptor, and c-Kit inhibitor).

Apoptotic pathways have been with oblimersen, a B-cell lymphoma-2 antisense oligonucleotide, as well as neural cell adhesion molecule, the immunotoxin BB-10901, and the DM1 conjugated antibody tubulin cytotoxin, which shows some complete responses in a small trial, he added.

Immunotherapy for Merkel cell carcinoma is rational, Brownell said. "It should respond to immunotherapy. There is a higher incidence and worse prognosis in immunocompromised populations, improved prognosis with CD8-positive tumor-infiltrating lymphocytes, spontaneous regression, and responses to dinitrochlorobenzene, tumor-necrosis factor alpha, and

interferon. Similar observations predicted the immune responsiveness of melanoma."

Reversing T-cell inhibition with immune checkpoint modulators is under investigation. Active immunotherapy trials for Merkel cell carcinoma include those with anti-PD-L1, anti-PD-1, adoptive T cells, interleukin (IL)-12 DNA vaccine, GLA-SE (a synthetic toll-like receptor 4 agonist), F16-IL2 antibody-cytokine, and adjuvant ipilimumab (anti-cytotoxic T-lymphocyte-associated protein-4).

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Upcoming immunotherapy trials for Merkel cell carcinoma will include an anti-4-1BB agonist and a combination of ipilimumab and nivolumab, which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2.

In conclusion, Brownell emphasized that effective treatment for advanced Merkel cell carcinoma is needed: "Targeted molecular approaches have been largely ineffective in small trials. Merkel cell carcinoma is a good candidate for immunotherapy. Multiple ongoing and upcoming trials will test immunotherapy for Merkel cell carcinoma." ■