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EDITORIAL – ENDOCRINE TUMORS

# Management of Regional Lymph Nodes in Patients with Merkel Cell Carcinoma Following a Positive Sentinel Node Biopsy: Less May be More, But is Either Enough?

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Merkel cell carcinoma (MCC) is an aggressive cutaneous tumor that is generally regarded as rare, but population-based data indicate a rapidly increasing incidence in many parts of the world, including the US, Australia, New Zealand, and Europe.[1–6] Current clinical practice guidelines recommend sentinel lymph node (SLN) biopsy for clinically node-negative MCC patients, and completion lymph node dissection (CLND) and/or radiation therapy (RT) for those found to be SLN-positive.

This edition of the journal includes two articles[7] that shed further light on the options for management of regional nodes in patients with MCC who are found to be SLN-positive. In the first, from the Moffitt Cancer Center in Tampa, Florida, 71 SLN-positive MCC patients treated over a 17-year period were reviewed. It was found that there were no statistically significant differences in regional control, disease-free survival (DFS), or overall survival for SLN-positive patients managed with CLND, nodal basin RT or both. In the second report, also comparing outcomes for CLND and RT in SLN-positive patients with MCC, 163 patients treated over an 11-year period at the University of Michigan in Ann Arbor, Michigan, were studied.[8] Again, there were no significant differences in regional control or DFS, nor were there differences in distant recurrence-free survival or MCC-specific survival for patients managed with CLND, CLND + adjuvant RT, or nodal RT alone. Importantly, these two reports are the largest in the literature to date that have examined the efficacy of RT to the node basin as monotherapy in SLN-positive MCC patients, with 40 of 71 and 26 of 163 SLN-positive patients having been treated with RT alone following their initial SLN biopsy in the Florida and Michigan studies, respectively.

Detailed morbidity data were not reported in the Michigan study, but, in the Florida study, CLND followed by adjuvant RT was more morbid than CLND alone or RT alone, with higher rates of surgical site infection and lymphedema. This finding is not unexpected since the morbidity from combining two radical modalities tends to be supra-additive, and this 'double trouble' has been well-documented in the breast and melanoma literature.

The Michigan series adds an additional dimension to our knowledge of the prognosis for SLN-positive MCC patients by demonstrating that those with one or more positive non-SLNs at the time of CLND ($n = 44$) had significantly worse 5-year MCC-specific survival (39%) than those with negative non-SLNs (87%). Thus, CLND has important prognostic implications in MCC, as it does in melanoma, and may be useful in determining eligibility for adjuvant systemic therapy.

As well as the limitations inherent in single-institution retrospective studies, and additional limitations acknowledged by the authors of both studies, there are further caveats. In both studies, median follow-up times were short, (22 and 23 months), and statistical power was

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limited not only by modest patient numbers (always an issue with rare tumors such as MCC) but also by the competing risk of death from other causes (reflecting the aged cohort typical of this disease entity). In the Florida study, at the time of analysis, 25 of the 71 patients had died, but only 4 due to MCC. With longer follow-up, this ratio would be expected to change as a further 12 patients had already developed distant disease. The competing risk of mortality may also explain the apparently improved nodal control in the RT arm of the Michigan report as patients in the RT group were considerably older and had more comorbidities (since only patients considered to be at high perioperative risk or who declined CLND were offered just RT to the nodal basin).

In these reports, there were fewer patients with head and neck MCC than is typical of MCC, perhaps reflecting a reluctance to perform SLNB in the head and neck where lymphatic pathways are often complex and false-negative results are a particular concern.[9,10] Alternatively, RT may have been preferred in head and neck MCC patients to manage both the primary tumor site and the neighbouring lymph node basin, due to their proximity.

In the Michigan study, details of RT dose and fractionation schedules were not provided. However, in the Florida study, the 'median' dose/fractionation schedule was reported and was appropriate for MCC,[11] but there is no documentation of the quality of treatment contouring, planning, and fields delivered on an individual patient basis. Geographical miss due to poor contouring and field design is the predominant cause of RT failure. Although all CLND procedures were performed at the Florida authors' institution, the RT was likely to have been delivered at community facilities closer to home (as it was in two-thirds of their RT monotherapy patients). Comparing CLND where all cases are treated at a center of excellence, with RT monotherapy delivered by generalists (in 66% of cases), may explain the higher absolute recurrence rate in the RT monotherapy group.

Finally, a major omission in both studies was information about the extent of staging investigations. This may be particularly relevant as recent prospective data from Australia indicated that routine FDG-PET imaging upstaged 26% of patients presenting with stage 2A–3B MCC who were managed with chemoradiotherapy.[3] In the Florida study, no data were available regarding primary tumor diameter, which is today a requirement for American Joint Committee on Cancer (AJCC) staging.

Based on their finding that only 23% of those who underwent CLND were found to have a positive non-sentinel node, the Florida group suggested that perhaps "some patients require no further treatment". A more radical suggestion would be to question whether it is necessary to perform SLN biopsy at all? The ratio of distant to regional recurrence in their series was 12:4, indicating that there is a need to better identify those patients likely to suffer distant relapse (above and beyond those who prove to be SLN+ve). This becomes more pertinent in the era of immunotherapy, where impressive and, importantly, sustained responses in metastatic MCC have been documented in both the polyoma virus-associated and UV-associated subtypes of the disease, with higher response rates seen in patients naïve to chemotherapy.[12–14]

In melanoma patients with resected nodal disease, adjuvant anti-PD1 therapy has recently been shown to substantially improve outcomes,[15] and the value of neoadjuvant treatment is being assessed. Similarly, there may be advantages from administration of immunotherapy in early MCC to eradicate or suppress micrometastatic disease. Neoadjuvant nivolumab is being tested in patients with resectable AJCC stage II–IV MCC, and a 47% pathological complete response rate was seen on central review in the initial 17 patients treated in this way.[16]

A further tantalizing possibility is to combine immune checkpoint blockade with RT, where the latter 'primes' the immune system, leading to an enhanced adaptive immune response. The net result might be that RT and immunotherapy act synergistically, not only achieving regional control equivalent to that achieved by CLND but also improving disease-specific survival. Ultimately, the goal should be to identify the subgroup of patients at high risk of metastatic spread who will benefit from early use of systemic immunotherapy.

The authors of both studies are to be congratulated for demonstrating that 'less may be more' in MCC patients who are found to be SLN+ve when it comes to preventing regional recurrence, and reduced morbidity may result. However, the real issue going forward is how best to identify and manage those at risk of distant disease (and therefore death) from MCC. Less may indeed be more, but we must question whether either is really enough?

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