Lymph node status[1] (Core and Non-core)

Metastatic Merkel cell carcinoma (MCC) to lymph nodes is usually readily identified, but the detection of rare tumour cells may on occasion be difficult in routine H&E-stained sections. The use of immunohistochemistry (IHC) has been shown to increase the sensitivity of identifying occult lymph node metastases. With the bread-loaf dissection technique it is recommended that each slice of lymph node is examined by one H&E-stained section and if negative, by IHC. If the primary tumour is known to express CK20, one immunostain for CK20 per lymph node tissue block is sufficient. If the immunophenotype of the primary tumour is not known, one may apply two immunostains (e.g., CK20 and NF1 or CK20 and Cam5.2) to reduce the risk of false-negatives. If the primary tumour is known to be negative for CK20, the stain is to be used for which the primary tumour is most strongly and diffusely positive (e.g., Cam5.2, AE1:AE3, INSM1 and CM2B4).

In order to apply pN staging for involved lymphadenectomy specimens, the pathologist needs to know if clinical examination and imaging were negative (so-called microscopic disease in the context of completion/elective lymphadenectomy specimens) or if clinical or radiological examination were positive (so called macroscopic disease in the context of therapeutic lymphadenectomy specimens). A positive node with microscopic disease is stage pN1a and with macroscopic disease pN1b. Only basic pN1 staging can be provided if this clinical and imaging information is not available to the pathologist at the time of reporting.

The number of nodes isolated and number involved by malignancy are core Cancer Outcomes and Services Dataset (COSD) items.[2]

The number involved and maximum diameter of a metastatic deposit are not staging criteria. *Lymph node involvement is the principal nodal staging determinant.*

<u>Lymph node extracapsular invasion and margin status</u>

For consideration of potential adjuvant radiotherapy, extracapsular invasion and margin status of the whole specimen are listed as core items. Both are widely regarded as adverse prognostic features.

Extracapsular invasion is regarded by American Joint Commission on Cancer (AJCC) as a site-specific prognostic factor.[3]

Adjuvant radiotherapy is considered in the presence of extracapsular invasion.

Extracapsular invasion is present when tumour cells are seen outside the lymph node capsule, typically in perinodal adipose tissue, in contiguity with intranodal disease (e.g., not related to contamination of perinodal tissue with tumour cells during processing of the tissue specimen in the pathology laboratory). Matted nodes (defined as two or more nodes adherent to one another through involvement by metastatic disease, identified at the time the specimen is examined macroscopically in the pathology laboratory) often suggest the presence of extranodal extension but the latter must be confirmed microscopically.

A) <u>Diameter of largest deposit</u> is regarded by AJCC as a site-specific prognostic factor.[4] To date, however, this has no proven staging importance, and the reproducibility of assessing this parameter is not known. It is recommended that guidelines provided for the measurement of sentinel node tumour burden in the AJCC Melanoma Staging System be use.[4] The single largest maximum dimension (measured in millimetres to the nearest 0.1 mm using an ocular micrometer) of the largest discrete metastatic MCC deposit in sentinel nodes should be measured and recorded. To be

considered a discrete deposit, the tumour cells must be in direct continuity with adjacent tumour cells. In some instances, multiple small tumour aggregates may be disbursed within a lymph node and separated by lymphoid cells. In this circumstance, the size of the largest discrete single deposit (not the nodal area over which the multiple deposits are contained) should be recorded. In addition, a descriptive comment on the distribution of tumour cells would also be appropriate. The measurement may be made either on H&E-stained sections or on sections stained immunohistochemically.

B) Extranodal extension is defined as the presence of a nodal metastasis extending through the lymph node capsule and into adjacent tissue, which may be apparent macroscopically but must be confirmed microscopically.[5] Matted nodes (defined as two or more nodes adherent to one another through involvement by metastatic disease, identified at the time the specimen is examined macroscopically in the pathology laboratory) often suggest the presence of extranodal extension, but the latter must be confirmed microscopically.

C) Clinically apparent lymph nodes are defined as those detected on palpation (clinical examination) or on radiological investigations.

References

1 Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, Johnson TM, Liegeois-Kwon NJ, Otley CC, Paulson KG, Ross MI, Yu SS, Zeitouni NC, Byrd DR, Sondak VK, Gershenwald JE, Sober AJ and Nghiem P (2010). Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol* 63(5):751-761.

2 National Cancer Intelligence Network (NCIN) (2011). *Cancer Outcomes and Services Dataset – 0.5.0. Skin.* Available at: http://www.ncin.org.uk/search/cancer+outcomes+and+services+dataset+version+0+5+0. (Accessed 8th April 2019).

3 Amin MB, Edge SB and Greene FL et al (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.

4 Gershenwald JE, Scolyer RA and Hess KR et al (2017). Melanoma of the Skin. In: *AJCC Cancer Staging Manual. 8th ed* Amin MB, Edge SB and Greene FL et al (eds), Springer New York, 563-585.

5 Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, Lazar AJ, Faries MB, Kirkwood JM, McArthur GA, Haydu LE, Eggermont AMM, Flaherty KT, Balch CM and Thompson JF (2017). Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 67(6):472-492.