Merkel Cell Carcinoma
Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.
☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

SPECIMEN(S) SUBMITTED (select all that apply)

- ☐ Skin
- ☐ Lymph node(s), *specify sentinel lymph node, if known/ applicable*
- ☐ Other, *specify*

PROCEDURE (select all that apply) (Note 1)

- ◯ Not specified
- ☐ Excision (or resection)
- ☐ Biopsy, *specify type of biopsy, if possible (e.g., curettage, shave, punch, elliptical)*

ANATOMIC SITE

- ◯ Not specified
- ◯ *Specify site*

If applicable also indicate
- ◯ Left
- ◯ Right
- ◯ Midline

MACROSCOPIC PRIMARY LESION DESCRIPTION (Note 2)

TUMOUR SIZE (Note 3)

Maximum tumour diameter (clinical measurement) mm

Maximum tumour diameter (macroscopic measurement) mm

Maximum diameter of primary tumour (microscopic measurement) mm

- ◯ Cannot be determined *(e.g., no clinical information provided or submitted slide likely not representative)*

EXTENT OF INVASION (select all that apply) (Note 4)

- ◯ Invasion not identified (i.e., only in-situ/intra-epithelial neoplastic proliferation)
- ◯ Cannot be assessed
- ☐ Tumour invades dermis
- ☐ Tumour invades subcutis
- ☐ Tumour invades into skeletal muscle
- ☐ Tumour invades into bone
- ☐ Tumour invades cartilage
- ☐ Other, *specify*

TUMOUR THICKNESS (Note 5)

- ◯ Indeterminate

Measured thickness mm

OR mm at least

LYMPHOVASCULAR INVASION (Note 6)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present, *specify if immunohistochemistry is used*

TUMOUR-INFILTRATING LYMPHOCYTES (Note 7)

- ◯ Not identified
- ◯ Brisk
- ◯ Non-brisk

LOCOREGIONAL* CUTANEOUS METASTASES (Note 8)

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

* *Satellite or in-transit cutaneous metastasis.*

MERKEL CELL POLYOMA VIRUS (MCPV) (Note 9)

- ◯ Testing for MCPV not performed (or results not known)
- ◯ Testing for MCPV performed, *specify method & result*

MORPHOLOGICAL DIVERSITY (Note 10)

- ◯ Not identified
- ◯ Present - squamous, *specify second phenotypic element*

- ◯ Present - other (non-squamous), *specify second phenotypic element*

MARGIN/TISSUE EDGES STATUS (select all that apply) (Note 11)

Peripheral margin

- ◯ Cannot be assessed
- ◯ Not involved by carcinoma
  - Distance from margin ◯ < 1 mm OR to nearest 1 mm ____ mm
  - Location, *specify, if possible*
- ◯ Involved by carcinoma
  - Location, *specify, if possible*

Deep margin

- ◯ Cannot be assessed
- ◯ Not involved by carcinoma
  - Distance from margin ◯ < 1 mm OR to nearest 1 mm ____ mm
  - Location, *specify, if possible*
- ◯ Involved by carcinoma
  - Location, *specify, if possible*

LYMPH NODE STATUS (Note 12)

- ◯ No nodes submitted or found

OR

Sentinel nodes

- ◯ Number of sentinel lymph nodes examined ____
  - ◯ Number cannot be determined
- ◯ Number of positive sentinel lymph nodes ____
  - ◯ Number cannot be determined

Extranodal extension**

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

Maximum dimension of largest metastasis in sentinel node** ____ mm

Location of largest sentinel node metastasis**, *specify (e.g., subcapsular, parenchymal, both subcapsular and parenchymal)*

Non-sentinel lymph nodes (clinically negative)

- ◯ Number of non-sentinel lymph nodes examined ____
  - ◯ Number cannot be determined
- ◯ Number of positive non-sentinel lymph nodes ____
  - ◯ Number cannot be determined

Extranodal extension**

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

Maximum dimension of largest metastasis in regional node** ____ mm

Clinically apparent lymph nodes

- ◯ Number of non-sentinel lymph nodes examined ____
  - ◯ Number cannot be determined
- ◯ Number of positive non-sentinel lymph nodes ____
  - ◯ Number cannot be determined

Extranodal extension**

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

Maximum dimension of largest metastasis in regional node** ____ mm

** *Required only in the presence of positive nodes.*

IMMUNOHISTOCHEMISTRY (Note 13)

◯ Not performed, *explain reasons*

◯ Performed, *specify*

PATHOLOGICAL STAGING (UICC TNM 8th edition)## (Note 14)

TNM Descriptors (only if applicable) (select all that apply)

☐ m - multiple primary tumours
☐ r - recurrent
☐ y - post-therapy

Primary tumour (pT)

◯ TX Primary tumour cannot be assessed
◯ T0 No evidence of primary tumour
◯ Tis Carcinoma in situ
◯ T1 Tumour 2 cm or less in greatest dimension
◯ T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension
◯ T3 Tumour more than 5 cm in greatest dimension
◯ T4 Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, fascia or bone

Regional lymph nodes (pN)

◯ No nodes submitted or found
◯ NX Regional lymph nodes cannot be assessed
◯ N0 No regional lymph node metastasis
◯ N1 Regional lymph node metastasis
◯ N2 In-transit metastasis *without* lymph node metastasis
◯ N3 In-transit metastasis *with* lymph node metastasis

Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley Blackwell.

Scope

The dataset has been developed for the reporting of the pathologic findings of primary cutaneous Merkel cell carcinoma in excision (resection) specimens containing tumour. It does not apply to partial superficial biopsies or re-excisions with no residual primary tumour. It also does not apply to cytology specimens. For small partial biopsies and cytology specimens, reporting the tumour diagnosis per se is usually sufficient. If there is no residual tumour seen in a re-excision, it suffices to say so. The features of the tumour seen in prior biopsies or excisions do not need to be repeated. In situations in which an initial partial (incisional or excisional) biopsy contains a substantial amount of tumour, completion of the data set may require synthesizing the findings of both the biopsy and subsequent excision with residual tumour.

Back

Note 1 – Procedure (Core)

Reporting expectations vary depending on procedure type. The full set of staging features can only be captured by an excision with primary tumour.

Back

Note 2 - Macroscopic primary lesion description (Non-core)

The macroscopic description provides valuable information on the dimensions of the resected tissue and the size of the tumour. On rare occasion it may also help document the presence of a satellite. It is also helpful for assessing the margin status.

Back

Note 3 - Tumour size (Core)

Tumour diameter is a staging parameter.[1,2]

Tumour diameter has historically been determined by clinical measurements. If that measurement is available, it should be reported as such. If clinical tumour diameter is unavailable, macroscopic and/or microscopic measurements should be used (largest diameter of tumour).

Back

Note 4 - Extent of invasion (Core)

Relevant to document extent of disease and for staging (invasion of bone, muscle, fascia or cartilage constitutes pT4; except for superficial facial muscle involvement).[1,2]

Back

Note 5 - Tumour thickness (Non-core)

Tumour thickness is a reproducible/measurable parameter of potential prognostic significance.[3]

When possible, if the specimen includes epidermis and dermis, tumour thickness is to be measured according to the method of Breslow and quantified in mm (rounded to the nearest 0.1 mm).

When a substantial amount of tumour was removed by a prior procedure, the final report of residual tumour should include a combined tumour measurement taking the findings from both procedures into account.

Back

Note 6 - Lymphovascular invasion (Core)

Lymphovascular invasion (LVI) is prognostically relevant.[4]

When lymphatic invasion is suspected, but not unequivocal on H&E, the use of immunohistochemistry (2.g., D2-40) is recommended for final determination on the presence or absence of LVI.

Back

Note 7 - Tumour-infiltrating lymphocytes (Non-core)

Potentially prognostically significant, if further stratified by immunophenotypic findings. Details on the immunophenotyped of the tumour microenvironment may also be predictive of response to checkpoint blockade inhibitors. However, currently it is not practical to perform such studies routinely.[5-7]

If tumour-infiltrating lymphocytes (TILS) are reported, we suggest to do so in analogy to melanoma for reasons of familiarity and reproducibility.

TILs not identified: No lymphocytes present, or lymphocytes present but do not infiltrate tumour at all.

TILs non-brisk: Lymphocytes infiltrate tumour only focally or not along the entire base of the vertical growth phase.

TILs brisk: Lymphocytes diffusely infiltrate the entire base of the dermal tumour (Figure 1, A) or the entire invasive component of the tumour (Figure 1, B).

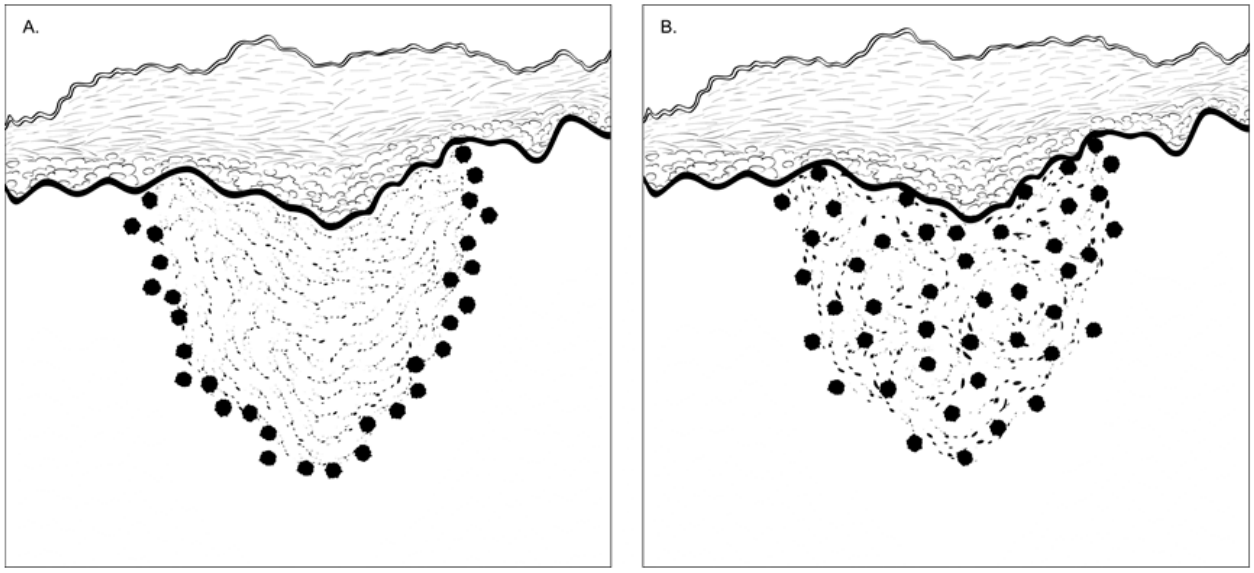

Figure 1. Brisk tumour-infiltrating lymphocytes. A. Lymphocytes diffusely infiltrate the entire base of the invasive tumour. B. Lymphocytes infiltrate the entire invasive component of the carcinoma. Copyright College of American Pathologists.

Back

Note 8 - Locoregional cutaneous metastases (Core)

The presence of an in-transit metastasis indicates stage N2.[1,2]

Locoregional cutaneous metastases are metastatic tumour deposits affecting the anatomic region located between the primary tumour and regional lymph node basin. They may be detected clinically or only after microscopic examination. The metastatic deposits may involve the dermis, subcutis or skeletal muscle. In analogy to melanoma, metastases have historically been designated as *microscopic satellite*, *satellite* or *in-transit* lesions. *Satellites* have been defined as metastases occurring within an arbitrarily chosen radius of less than 2 cm of the primary tumour. The term *microscopic satellite* has been used for metastases adjacent to the primary tumour detected upon microscopic examination. Metastatic lesions detected outside a radius of 2 cm are described as *in-transit* metastases. Since there is no apparent prognostic difference between these arbitrary subtypes of metastases, they are grouped together herein as locoregional cutaneous metastases. Diagnostic problems can sometimes occur. An in-transit lesion may be confused with a second primary melanoma. A microscopic satellite lesion may be confused with part of the primary tumour that was artifactually separated from the mother lesion by surgery or regression. Thus, for a suspected microscopic satellite to be accepted as bonafide metastasis it must be clearly separated from the main tumour by intervening normal tissue devoid of evidence of prior surgery or regression to avoid overdiagnosis.

Back

Note 9 - Merkel cell polyoma virus (Core)

The presence or absence of Merkel cell polyoma virus segregates Merkel cell carcinomas into those of viral pathogenesis (the majority) and those due to UV-mediated genetic damage (the minority).[8] These tumour subsets differ from one another genetically[8,9], immunohistochemically[10] and biologically.[11] Merkel cell polyomavirus-negative tumours are more aggressive, hence this factor is of prognostic importance.[11] Immunohistochemistry, employing the CM2B4 antibody, is recommended as a reliable method of viral detection.[11]

Back

Note 10 - Morphological diversity (Core)

Most Merkel cell carcinomas exhibit a pure small cell/neuroendocrine phenotype but a minority display morphological diversity. The latter, termed combined Merkel cell carcinomas, are usually characterized by admixed neuroendocrine and squamous elements, identifiable on routine microscopy (e.g., Merkel cell carcinoma intimately associated with Bowen's disease or invasive squamous cell carcinoma, or focal squamous differentiation in a Merkel cell carcinoma). Combined Merkel cell carcinomas are uniformly Merkel cell polyoma virus-negative[12-14] and thus belong in an adverse prognostic category.[11]

Back

Note 11 - Margin/Tissue edges status (Core)

As a core dataset item for all cancers, Cancer Outcomes and Services Dataset (COSD)[15] records whether tumour excision margins are clear by more than 5 mm, clear by greater than 1 mm but less than or equal to 5 mm, or present less than or equal to 1 mm, but without tumour reaching the margin. Skin cancer margins should therefore be measured in relation to both 1 mm and 5 mm breakpoints.

Guidelines on the surgical margins recommended for Merkel cell carcinoma are based on evidence utilising clinical margins. These are either 10 or 20 mm for this cancer. Histological margins are widely used as a surrogate marker for clinical margins.

Back

Note 12 - Lymph node status[16] (Core and Non-core)

Metastatic Merkel cell carcinoma 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 COSD items.[15]

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.[1]

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.

<u>A) Diameter of largest deposit:</u> this is regarded by AJCC as a site-specific prognostic factor.[17] 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 used. The single largest maximum dimension (measured in millimetres to the nearest 0.1 mm using an ocular micrometer) of the largest discrete metastatic Merkel cell carcinoma 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.[18] 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.

Back

Note 13 – Immunohistochemistry (Non-core)

The use of immunohistochemistry (IHC) is recommended to confirm the diagnosis of Merkel cell carcinoma. It is invaluable, whenever the clinical and histopathologic findings are such that other tumours need to be considered in the differential diagnosis (e.g., lymphoma, metastatic neuroendocrine carcinoma of extracutaneous origin, Ewing's sarcoma). IHC is also helpful for the detection of micrometastatic tumour deposits in sentinel lymph nodes.[19] Various antibodies can be used including, but not limited to cytokeratin 20, CAM 5.2, AE1/AE3, chromogranin, synaptophysin, CM2B4, INSM1 and neurofilament. Positivity can be variable between antibodies and can be perinuclear dot-like, cap-like, cytoplasmic or cell membranous. The tumour should be negative for lymphoid and melanoma markers. Strong and diffuse labelling for thyroid transcription factor (TTF-1) favours metastatic neuroendocrine carcinoma of extracutaneous origin.

Merkel cell carcinoma has the ability to reflect the biological heterogeneity of normal Merkel cells and accordingly there is no one immunohistochemical profile that applies to all Merkel cell carcinomas. For example, cytokeratin 20 is considered to have a sensitivity of approximately 90%, whereas others claim a greater sensitivity for neurofilament.

Back

Note 14 – Pathological staging (UICC TNM 8th edition)[1,2] (Core)

Those patients with Merkel cell carcinoma (MCC) in whom the primary tumour cannot be assessed (eg, curetted) should be categorized as TX. Merkel cell carcinoma in situ (ie, completely limited to epidermis or adnexal epithelium) is categorized as Tis. The T category of MCC is classified primarily by measuring the maximum dimension of the tumour with a threshold of ≤2 cm (T1), >2 cm but ≤5 cm (T2), or >5 cm (T3). Extracutaneous invasion by the primary tumour into bone, muscle, fascia, or cartilage is classified as T4.

Regional metastases most commonly present in the regional lymph nodes. Nodal staging is primarily based on nodal tumour burden: microscopic versus macroscopic. Therefore, patients without clinical or radiologic evidence of lymph node metastases, but who have pathologically documented nodal metastases, are defined by convention as exhibiting “microscopic” or “clinically occult” nodal metastases. In contrast, MCC patients with both clinical evidence of nodal metastases *and* pathologic examination confirming nodal metastases are defined by convention as having “macroscopic” or “clinically apparent” nodal metastases.

Distant metastases are defined as metastases that have spread beyond the draining lymph node basin, including cutaneous, nodal, and visceral sites.

Back

References

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

2 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours, 8th Edition*, Wiley-Blackwell.

3 Harms KL, Healy MA, Nghiem P, Sober AJ, Johnson TM, Bichakjian CK and Wong SL (2016). Analysis of Prognostic Factors from 9387 Merkel Cell Carcinoma Cases Forms the Basis for the New 8th Edition AJCC Staging System. *Ann Surg Oncol* 23(11):3564-3571.

4 Fields RC, Busam KJ, Chou JF, Panageas KS, Pulitzer MP, Allen PJ, Kraus DH, Brady MS and Coit DG (2011). Five hundred patients with Merkel cell carcinoma evaluated at a single institution. *Ann Surg* 254(3):465-473; discussion 473-465.

5 Feldmeyer L, Hudgens CW, Ray-Lyons G, Nagarajan P, Aung PP, Curry JL, Torres-Cabala CA, Mino B, Rodriguez-Canales J, Reuben A, Chen PL, Ko JS, Billings SD, Bassett RL, Wistuba, II, Cooper ZA, Prieto VG, Wargo JA and Tetzlaff MT (2016). Density, Distribution, and Composition of Immune Infiltrates Correlate with Survival in Merkel Cell Carcinoma. *Clin Cancer Res* 22(22):5553-5563.

6 Miller NJ, Church CD, Dong L, Crispin D, Fitzgibbon MP, Lachance K, Jing L, Shinohara M, Gavvovidis I, Willimsky G, McIntosh M, Blankenstein T, Koelle DM and Nghiem P (2017). Tumor-Infiltrating Merkel Cell Polyomavirus-Specific T Cells Are Diverse and Associated with Improved Patient Survival. *Cancer Immunol Res* 5(2):137-147.

7 Giraldo NA, Nguyen P, Engle EL, Kaunitz GJ, Cottrell TR, Berry S, Green B, Soni A, Cuda JD, Stein JE, Sunshine JC, Succaria F, Xu H, Ogurtsova A, Danilova L, Church CD, Miller NJ, Fling S, Lundgren L, Ramchurren N, Yearley JH, Lipson EJ, Cheever M, Anders RA, Nghiem PT, Topalian SL and Taube JM (2018). Multidimensional, quantitative assessment of PD-1/PD-L1 expression in patients with Merkel cell carcinoma and association with response to pembrolizumab. *J Immunother Cancer* 6(1):99.

8 Wong SQ, Waldeck K, Vergara IA, Schroder J, Madore J, Wilmott JS, Colebatch AJ, De Paoli-Iseppi R, Li J, Lupat R, Semple T, Arnau GM, Fellowes A, Leonard JH, Hruby G, Mann GJ, Thompson JF, Cullinane C, Johnston M, Shackleton M, Sandhu S, Bowtell DD, Johnstone RW, Fox SB, McArthur GA, Papenfuss AT, Scolyer RA, Gill AJ, Hicks RJ and Tothill RW (2015). UV-Associated Mutations Underlie the Etiology of MCV-Negative Merkel Cell Carcinomas. *Cancer Res* 75(24):5228-5234.

9 Goh G, Walradt T, Markarov V, Blom A, Riaz N, Doumani R, Stafstrom K, Moshiri A, Yelistratova L, Levinsohn J, Chan TA, Nghiem P, Lifton RP and Choi J (2016). Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy. *Oncotarget* 7(3):3403-3415.

10 Pasternak S, Carter MD, Ly TY, Doucette S and Walsh NM (2018). Immunohistochemical profiles of different subsets of Merkel cell carcinoma. *Hum Pathol* 82:232-238.

11 Moshiri AS, Doumani R, Yelistratova L, Blom A, Lachance K, Shinohara MM, Delaney M, Chang O, McArdle S, Thomas H, Asgari MM, Huang ML, Schwartz SM and Nghiem P (2017). Polyomavirus-Negative Merkel Cell Carcinoma: A More Aggressive Subtype Based on Analysis of 282 Cases Using Multimodal Tumor Virus Detection. *J Invest Dermatol* 137(4):819-827.

12 Busam KJ, Jungbluth AA, Rekthman N, Coit D, Pulitzer M, Bini J, Arora R, Hanson NC, Tassello JA, Frosina D, Moore P and Chang Y (2009). Merkel cell polyomavirus expression in merkel cell carcinomas and its absence in combined tumors and pulmonary neuroendocrine carcinomas. *Am J Surg Pathol* 33(9):1378-1385.

13 Ly TY, Walsh NM and Pasternak S (2012). The spectrum of Merkel cell polyomavirus expression in Merkel cell carcinoma, in a variety of cutaneous neoplasms, and in neuroendocrine carcinomas from different anatomical sites. *Hum Pathol* 43(4):557-566.

14 Martin B, Poblet E, Rios JJ, Kazakov D, Kutzner H, Brenn T and Calonje E (2013). Merkel cell carcinoma with divergent differentiation: histopathological and immunohistochemical study of 15 cases with PCR analysis for Merkel cell polyomavirus. *Histopathology* 62(5):711-722.

15 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).

16 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.

17 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.

18 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.

19 Allen PJ, Busam K, Hill AD, Stojadinovic A and Coit DG (2001). Immunohistochemical analysis of sentinel lymph nodes from patients with Merkel cell carcinoma. *Cancer* 92(6):1650-1655.