REVIEW ARTICLE

Contemporary Literature Review of Clinical Characteristics and Management of Merkel Cell Carcinoma

Laraib Khan[1*], Ahmed Nadeem Abbasi[1], Sohail Rasool[2], Calogero Casà[3] and Andrea D'Aviero[4]

[1]*Department of Radiation Oncology, The Aga Khan University, Karachi, Pakistan*
[2]*General Practice Clinic, Portlaoise, County Laoise, Republic of Ireland*
[3]*Radiation Oncology Department, Gemelli ART, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuor, Milano, Italy*
[4]*Radiation Oncology Department, Mater Olbia Hospital, Olbia, Italy*

Abstract

Merkel cell carcinoma is a rare aggressive, non-melanomatous cutaneous malignancy with rising incidence. It has two distinct etiologies Merkel cell polyomavirus associated and non-associated, usually presents as painless, indurated, solitary violaceous dermal nodules on sun-exposed sites, frequently in the head and neck region followed by extremities. The workup includes dermoscopy, histopathology with immunohistochemical staining, and imaging. Treatment modalities for Merkel cell carcinoma are surgery, radiation therapy, chemotherapy, *etc.* however, the role of immunotherapy and targeted agents is emerging.

Keywords: *Merkel cell carcinoma, cutaneous malignancy, immunotherapy, tumor board, Radiation.*

INTRODUCTION

Merkel cell carcinoma (MCC) first described as "trabecular carcinoma" in 1972 [1] is a rare aggressive, non-melanomatous cutaneous malignancy of neuroendocrine origin which was recognized by the presence of neurosecretory granules in tumors as reported in an ultrastructural study in 1978 [2]. However, it is debated to be arising from skin cells of epithelial, lymphoid, or fibroblastic origin [3]. Several extensive overviews are published on this topic. This review is in series with our previous review articles [4-6] to provide the latest updates in MCC management.

EPIDEMIOLOGY AND ETIOLOGY

MCC is a rare malignancy with a rising incidence with 2488 new cases in the US in 2020, which is projected to be reaching to 3284 by 2025 as the population ages [7]. Australia has the highest incidence of MCC predominantly because of high annual UV exposure and the Caucasian population [8]. In a recent longitudinal cohort study it was concluded that part of the initially raised incidence was due to increased detection and the projection of rising incidence is likely because of the aging population [9].

Broadly, MCC has two distinct etiologies *i.e.* Merkel cell polyomavirus (MCPyV) associated, which is detected in >80% of cases [10], and non-MCV associated, usually due to Ultraviolet (UV) exposure induced genomic mutations. Due to the inactivation of the tumor suppressors RB and p53 genes, MYCL activation by the virus or gene amplification, and an attenuated neuroendocrine differentiation program driven by the atonal homolog 1 (ATOH1) transcription factor, both these forms of MCC have a high proliferative index [11]. MCPyV was later found to be detected in the skin flora of many healthy individuals and viral integration is thought to occur rarely which results in MCC oncogenesis [12]. Overall, MCC is frequently seen in older age males and fair-skinned individuals with long-term sun exposure and immunosuppressed (*e.g.* chronic lymphocytic leukemia (CLL) or organ transplant) patients [13].

CLINICAL FEATURES

MCC usually presents as painless, indurated, solitary violaceous dermal nodules on sun-exposed sites, frequently in the head and neck region followed by extremities. The important clinical features can be summarized with a mnemonic asymptomatic, expanding rapidly, immunosuppressed, older than 50 years, and UV-exposed skin (AEIOU) [14]. The National Cancer Database (NCDB) reports that the majority of patients present with local disease (66%), some of them have the nodal disease at presentation (27%), whereas metastatic disease is rare (7%) with 5-year survival rates of 64%, 39%, and 18% respectively [15]. In another study, 5-year survival rates were reported to be 51%, 35%, and 14% for local, nodal, and metastatic diseases, each [16].

DIFFERENTIAL DIAGNOSIS

Differential Diagnoses include tumors typically arising from UV-exposed areas like keratoacanthoma, squamous cell carcinoma, and basal cell carcinoma and poorly differentiated tumors such as Ewing sarcoma, small cell lung cancer, and small cell melanoma should also be ruled out [17].

**Corresponding author: Laraib Khan, Department of Radiation Oncology, The Aga Khan University, Karachi, Pakistan, laraib94.lk@gmail.com*
Received: December 15, 2022; Revised: January 13, 2023; Accepted: January 27, 2023
DOI: https://doi.org/10.37184/lnjcc.2789-0112.4.12

DIAGNOSTIC AND STAGING EVALUATION

The initial step in diagnosis is a thorough clinical examination of skin and lymph nodes. For a definitive diagnosis punch or full-thickness skin biopsy with hematoxylin-eosin (H&E) staining and immunopanel is required [17].

Dermoscopy

MCC has no specific dermoscopic features but certain common characteristics are useful to differentiate it from other skin lesions. The most common dermoscopic findings of MCC include Milky red areas with polymorphous, linear irregular vessels [18].

Histopathology

The histopathologic features of MCC include nests of packed round blue cells with finely granular 'salt and pepper' chromatin patterns, indistinct nucleoli, scant cytoplasm, and frequent mitotic figures [19].

Immunohistochemistry

It is useful in differentiating MCC from extracutaneous neuroendocrine tumors, as cytokeratin-20 is positive in up to 95% of cases and thyroid transcription factor 1 (TTF-1) is usually negative. Besides these, MCC is found to express other markers like neurofilament NF, ATOH1, and special AT-rich sequence-binding protein 2 (SATB2) [20].

Imaging

The role of imaging as a part of staging workup is debated in the literature and is indicated whenever the metastatic or locally advanced disease is suspected based on examination findings as per National cancer comprehensive cancer network (NCCN) recommendations [21]. In 12%–20% of MCC patients presenting without suspicious clinical findings, occult metastasis resulted in upstaging of the disease [22]. Most reported imaging modalities in MCC include CT scan with contrast, Whole-body PET CT, MRI, and ultrasound [23].

Sentinel Lymph Node Biopsy

Once diagnosed with MCC, Sentinel lymph node biopsy (SNLB) should be performed as a staging procedure. SNLB has a prognostic value in MCC therefore, it is recommended in clinically negative regional nodes and it has been associated with a significant survival advantage [24].

STAGING

Staging is based on American Joint Committee on Cancer (AJCC) staging system 8th edition (**Table 1**) [20]. An alternative and relatively simpler system can also be used for stage grouping: Stage I: patients with localized disease; with a tumor of less than 2cm are considered stage 1A, whereas 2cm or more are considered stage 1B, Stage II is consistent with regional lymph node metastasis and Stage III: signifies distant metastasis. The former has put forth six clinical-stage groups 0, I, IIA, IIB, III, IV, and seven pathological-stage groups 0, I, IIA, IIB, IIIA, IIIB, and IV (**Table 2**) [6].

Table 1 (a, b, c, d): Definitions for T, N, M AJCC Cancer Staging Manual, Eighth Edition (2017) [20].

(a) T Primary Tumor

TX	Primary tumor cannot be assessed (*e.g.*, curetted)
T0	No evidence of a primary tumor
Tis	*In situ* primary tumor
T1	Maximum clinical tumor diameter ≤2 cm
T2	Maximum clinical tumor diameter >2 but ≤5 cm
T3	Maximum clinical tumor diameter >5 cm
T4	Primary tumor invades fascia, muscle, cartilage, or bone

(b) Clinical (N)

NX	Regional lymph nodes cannot be clinically assessed (*e.g.*, previously removed for another reason, or because of body habitus).
N0	No regional lymph node metastasis was detected on clinical and/or radiologic examination.
N1	Metastasis in regional lymph node(s).
N2	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) without lymph node metastasis.
N3	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) with lymph node metastasis.

(c) Pathological (pN)

pNX	Regional lymph nodes cannot be assessed (*e.g.*, previously removed for another reason or not removed for pathological evaluation).
pN0	No regional lymph node metastasis was detected on pathological evaluation.
pN1	Metastasis in regional lymph node(s):
	pN1a(sn) Clinically occult regional lymph node metastasis identified only by sentinel lymph node biopsy.
	pN1a Clinically occult regional lymph node metastasis following lymph node dissection.
	pN1b Clinically and/or radiologically detected regional lymph node metastasis, microscopically confirmed.
pN2	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) without lymph node metastasis.
pN3	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) with lymph node metastasis.

(d) M Distant Metastasis

Clinical (M)	
M0	No distant metastasis was detected on clinical and/or radiologic examination.
M1	Distant metastasis detected on clinical and/or radiologic examination.
	M1a Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s).
	M1b Metastasis to the lung.
	M1c Metastasis to all other visceral sites.
Pathological (pM)	
M0	No distant metastasis was detected on clinical and/or radiologic examination
pM1	pM1 Distant metastasis microscopically confirmed.

	pM1a Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s), microscopically confirmed.
	pM1b Metastasis to lung, microscopically confirmed.
	pM1c Metastasis to all other distant sites, microscopically confirmed.

Table 2: AJCC Cancer Staging Manual, Eighth Edition (2017) Prognostic Groups.

Clinical (cTNM)			
Stage	**T**	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2-T3	N0	M0
IIB	T4	N0	M0
III	T0-T4	N1-3	M0
IV	T0-T4	Any N	M1
Pathological (pTNM)			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2-T3	N0	M0
IIB	T4	N0	M0
IIIA	T1-T4	N1a(sn) or N1a	M0
	T0	N1b	
IIIB	T1-T4	N1b-3	M0
IV	T0-T4	Any N	M1

PROGNOSTICATION

Multiple factors including age, tumor size (*i.e.* maximum tumor diameter), presence of nodal or distant metastases, lymphovascular invasion (LVI), immunosuppression, the positivity of p53 and p63, *etc.* are implicated in the prognostication of MCC [25]. In a recent study, a positive SLN and LVI were reported to be independently associated with worse disease-related outcomes, warranting consideration for investigational studies [26]. Baseline MCPyV oncoprotein antibody titer can also be taken into regard as a tumor marker for prognostic significance [27].

MANAGEMENT

To provide quality healthcare multidisciplinary team (MDT) discussion plays a vital role [28]. Therefore, after relevant workup, optimal MCC management requires site-specific MDT discussion involving a dermatologist, surgeon, radiation oncologist, medical oncologist, histopathologist, and radiologist. Park *et al.* shared their experience of modifications in the initial treatment plan in more than 50% of cases after MDT discussion [27].

Surgery

In absence of any baseline high-risk features (larger primary tumor, chronic T-cell immunosuppression, head & neck primary site, and LVI), surgical excision with clear margins and SLNB is the preferred treatment option in clinically node-negative disease as per NCCN guidelines. However, the extent of resection should be balanced with the morbidity of surgery [21]. Re-excision is to be considered in cases of positive surgical margins, as negative surgical margins are associated with improved survival [29, 30]. Mohs micrographic surgery (MMS) is a useful technique and is widely used. It has shown no survival difference as compared to wide local excision in stage I and II diseases [29]. In cases of clinically positive lymph nodes with non-metastatic disease, complete lymph nodal dissection (CLND) can be considered [21]. However, there is very limited data available to suggest the extent of lymph nodal surgery.

Radiation

Radiation therapy (RT) in MCC can be incorporated in adjuvant and definitive settings. Several studies have reported poorer disease-related outcomes in patients who were managed non-surgically [31, 32]. Nevertheless, in locoregionally advanced MCC or in patients who are unfit for surgery or refuse surgical management, initial treatment with definitive RT can be offered [33, 34]. It is still unclear if surgery or RT is more effective as the initial part of management for lymph nodal-positive MCC. Wright *et al.* showed better overall survival with surgery (with or without adjuvant RT) as compared with definitive RT (median 30 *vs.* 15 months, P < .001) [31]. Two recent retrospective studies evaluated outcomes in lymph node-positive MCC patients treated with CLND *versus* RT and found low rates of regional recurrence in both treatment options [35, 36].

The role of postoperative adjuvant RT is well-established in patients with positive surgical margins and pathologically positive lymph nodes. A systematic review and meta-analysis suggested survival and disease-free survival (DFS) benefits for postoperative radiation of MCCs [37].

RT in MCC can be given in the form of external beam radiation therapy with electrons, photons, or protons, depending on tumor location and equipment availability. For superficial lesions or tumor boost electrons and deeper invasion or lymph nodal RT photons are commonly used. In lesions with nearby critical structures, such as the eye, treatment using protons is preferred [38].

Adjuvant RT when indicated, should be expedited as soon as wound healing allows. Bolus is usually used to achieve adequate skin dose. A 5 cm margin around the primary site should be used. Doses with conventional fractionation (2 Gy/fraction) for negative margins resection (R0) are 50–56 Gy, for microscopically positive margins resection (R1) 56–60 Gy dose is recommended and for grossly positive margins resection (R2) where re-resection is not an option or in definitive setting, 60–66 Gy dose is advised. With clinically positive lymph nodes without a CLND dose of 60-66, Gy to the nodal basin is advised and for positive lymph nodes at SLNB, the recommended dose is 50-56 Gy, which can be escalated to 60 Gy in cases of extracapsular extension after CLND, as per NCCN [21]. Preliminary data from a prospective study evaluating the outcomes of single-fraction RT (SFRT) of 8 Gy for MCC in the head and neck region, suggests favorable in-field locoregional control, which needs further exploration [39].

Contact skin high-dose-rate brachytherapy as another treatment option can also be explored in MCC management. It has shown optimal results in the management of other non-melanoma skin cancers in several studies [40-43].

Chemotherapy

The role of chemotherapy in the adjuvant setting is controversial and it is not routinely recommended. Its utilization is limited to systemic disease. Several studies suggested no improved disease outcomes with adjuvant chemotherapy [44-46]. However, it can be offered on a case-by-case basis if indicated in high-risk patients (R2 resection, large tumors). The most commonly used agents include cisplatin, carboplatin, and etoposide [21].

Immunotherapy

Because of the immunogenic nature of MCC, the recent advancements in immune checkpoint inhibitors (ICIs) have tremendously improved the prognosis in disseminated MCC. It has resulted in changing practice patterns [47]. Data from recent prospective clinical trials support the use of the ICIs including anti-PD-L1/P-1 monoclonal antibodies like avelumab, pembrolizumab, and nivolumab. Data from the JAVELIN Merkel 200 trial, an open-label multicenter trial testing avelumab in patients with stage IV MCC, showed survival benefits as compared with chemotherapy [48]. Likewise, the recommendation for the use of pembrolizumab is supported by a phase II, single-arm multicenter trial testing pembrolizumab in patients with stage III/IV MCC [49]. Checkmate 358 phase I/II trial included 39 patients with resectable MCC and evaluated the role of neoadjuvant nivolumab. Among 36 patients who underwent surgery, 47.2% achieved a pathologic complete response [50]. However, some patients with advanced-stage MCC do not respond to PD-1 inhibitors or PD-L1 inhibitors, which has led to the use of agents like ipilimumab, which is an anti-CTLA-4 monoclonal antibody but due to its toxicity and lesser efficacy, the data does not currently support its use [51].

Targeted Molecular Therapy

With recent advancements and a better understanding of the pathogenesis of MCC, the role of targeted molecular therapies is emerging in patients who do not respond well to immunotherapies or who are immunocompromised. Positivity for certain immunohistochemical markers like VEGF-A, VEGFR-2/3, VEGF-C, PDGF-alpha/beta,c-kit, Mcl-1, Bmi-1, HIF-1alpha, Glut-1, *etc.* has directed towards the use of Pazopanib and cabozantinib in metastatic MCC patients [25]. Also, somatostatin analog (SSA) therapy can benefit a subset of MCC patients with somatostatin receptor expression [52].

Others

Literature has supported the use of hyperthermic isolated limb perfusion (HILP) or isolated limb infusion (ILI) as safe alternatives to amputation in cases of isolated, unresectable extremity MCC [53]. In an institutional experience, HILP proved to provide excellent locoregional control in selected patients with MCC in-transit metastasis [54].

CONCLUSION

MCC being a rare malignant entity with nonspecific clinical history, not yet clearly defined pathogenesis and high relapse rates have attracted the interest of clinicians and researchers. Recent advancements in the understanding of its molecular basis, have led to evaluate the responsiveness of MCC to different therapeutic agents and their combinations. It is commendable that a new era for successful MCC treatment strategies can be anticipated in near future. Consequently, the best care of MCC can be achieved by multidisciplinary tumor board discussion before treatment initiation.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

None.

AUTHOR'S CONTRIBUTION

All the authors contributed equally to the publication of this article.

REFERENCES

1. Toker C. Trabecular carcinoma of the skin. Arch Dermatol 1972; 105(1): 107-10. DOI: https://doi.org/10.1001/archderm.1972.01620040075020
2. Tang CK, Toker C. Trabecular carcinoma of the skin. An ultrastructural study. Cancer 1978; 42(5): 2311-21. DOI: https://doi.org/10.1002/1097-0142(197811)42:5%3C2311::aid-cncr2820420531%3E3.0.co;2-l
3. Sunshine JC, Jahchan NS, Sage J, Choi J. Are there multiple cells of origin of Merkel cell carcinoma? Oncogene 2018; 37(11): 1409-16. DOI: https://doi.org/10.1038/s41388-017-0073-3
4. Abbasi AN. Clinical features and management of Merkel Cell Carcinoma. J Pak Med Assoc 2007; 57(7): 368-71.
5. Abbasi AN, Zahid S. Latest update on the clinical features and management of Merkel cell carcinoma. J Pak Med Assoc 2012; 62(3): 262.
6. Abbasi AN, Ahmed SM, Qureshi BM. Recent updates in the management of Merkel cell carcinoma. J Pak Med Assoc 2019; 69(11): 1693-9. DOI: https://doi.org/10.5455/jpma.286585
7. Paulson KG, Park SY, Vandeven NA, Lachance K, Thomas H, Chapuis AG, *et al.* Merkel cell carcinoma: current US incidence and projected increases based on changing demographics. J Am Acad Dermatol 2018; 78(3): 457-63e2. DOI: https://doi.org/10.1016%2Fj.jaad.2017.10.028
8. Schadendorf D, Lebbé C, Zur Hausen A, Avril MF, Hariharan S, Bharmal M, *et al.* Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 2017; 71: 53-69. DOI: https://doi.org/10.1016/j.ejca.2016.10.022
9. Jacobs D, Huang H, Olino K, Weiss S, Kluger H, Judson BL *et al.* Assessment of age, period, and birth cohort effects and trends in Merkel cell carcinoma incidence in the United States. JAMA Dermatol 2021; 157(1): 59-65. DOI: https://doi.org/10.1001/jamadermatol.2020.4102

10. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008; 319(5866): 1096-100. DOI: https://doi.org/10.1126/science.1152586
11. DeCaprio JA. Molecular pathogenesis of Merkel cell carcinoma. Annu Rev Pathol 2021; 16: 69-91. DOI: https://doi.org/10.1146/annurev-pathmechdis-012419-032817
12. Martel-Jantin C, Pedergnana V, Nicol JT, Leblond V, Trégouët DA, Tortevoye P, *et al.* Merkel cell polyomavirus infection occurs during early childhood and is transmitted between siblings. J Clin Virol 2013; 58(1): 288-91. DOI: https://doi.org/10.1016/j.jcv.2013.06.004
13. Walsh NM, Cerroni L. Merkel cell carcinoma: A review. J Cutan Pathol 2021; 48(3): 411-21. DOI: https://doi.org/10.1111/cup.13910
14. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol 2008; 58: 375-81. DOI: https://doi.org/10.1016/j.jaad.2007.11.020
15. Hughes MP, Hardee ME, Cornelius LA, Hutchins LF, Becker JC, GaoL. Merkel Cell Carcinoma: Epidemiology, Target, and Therapy. Curr Dermatol Rep 2014; 3(1): 46-53. DOI: https://doi.org/10.1007%2Fs13671-014-0068-z
16. Harms KL, Healy MA, Nghiem P, Sober AJ, Johnson TM, Bichakjian CK, *et al.* Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th edition AJCC staging system. Ann Surg Oncol 2016; 23(11): 3564-71. DOI: https://doi.org/10.1245/s10434-016-5266-4
17. Amaral T, Leiter U, Garbe C. Merkel cell carcinoma: epidemiology, pathogenesis, diagnosis and therapy. Rev Endocr Metab Disord 2017; 18(4): 517-32. DOI: https://doi.org/10.1007/s11154-017-9433-0
18. Argenziano G, Zalaudek I, Corona R, Sera F, Cicale L, Petrillo G, *et al.* Vascular structures in skin tumors: a dermoscopy study. Arch Dermatol 2004; 140(12): 1485-9. DOI: https://doi.org/10.1001/archderm.140.12.1485
19. Coggshall K, Tello TL, North JP, Siegrid SY. Merkel cell carcinoma: an update and review: pathogenesis, diagnosis, and staging. J Am Acad Dermatol 2018; 78(3): 433-42. DOI: https://doi.org/10.1016/j.jaad.2017.12.001
20. Kervarrec T, Tallet A, Miquelestorena-Standley E, Houben R, Schrama D, Gambichler T, *et al.* Diagnostic accuracy of a panel of immunohistochemical and molecular markers to distinguish Merkel cell carcinoma from other neuroendocrine carcinomas. Mod Pathol 2019; 32(4): 499-510. DOI: https://doi.org/10.1038/s41379-018-0155-y
21. National cancer comprehensive cancer network. NCCN clinical practice guidelines in oncology: Merkel cell carcinoma 2022. Accessed January 23, 2023. https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf
22. Singh N, Alexander NA, Lachance K, Lewis CW, McEvoy A, Akaike G, *et al.* Clinical benefit of baseline imaging in Merkel cell carcinoma: Analysis of 584 patients. J Am Acad Dermatol 2021; 84(2): 330-9. DOI: https://doi.org/10.1016/j.jaad.2020.07.065
23. Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Blitzblau R, *et al.* Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2018; 16(6): 742-74. DOI: https://doi.org/10.6004/jnccn.2018.0055
24. Kachare SD, Wong JH, Vohra NA, Zervos EE, Fitzgerald TL. Sentinel lymph node biopsy is associated with improved survival in Merkel cell carcinoma. Ann Surg Oncol 2014; 21(5): 1624-30. DOI: https://doi.org/10.1245/s10434-013-3434-3
25. Hernandez LE, Mohsin N, Yaghi M, Frech FS, Dreyfuss I, Nouri K. Merkel cell carcinoma: An updated review of pathogenesis, diagnosis, and treatment options. Dermatol Ther 2022; 35(3): e15292. DOI: https://doi.org/10.1111/dth.15292
26. Harounian JA, Molin N, Galloway TJ, Ridge D, Bauman J, Farma J, *et al.* Effect of sentinel lymph node biopsy and LVI on Merkel cell carcinoma prognosis and treatment. The Laryngoscope 2021; 131(3): E828-35. DOI: https://doi.org/10.1002/lary.28866
27. Park SY, Doolittle-Amieva C, Moshiri Y, Akaike T, Parvathaneni U, Bhatia S, *et al.* How we treat Merkel cell carcinoma: within and beyond current guidelines. Future Oncol 2021; 17(11): 1363-77. DOI: https://doi.org/10.2217/fon-2020-1036
28. Abbasi AN. Establishment and maintenance of quality of sitespecific multidisciplinary tumor boards in Pakistan. J Coll Physicians Surg Pak 2016; 26(10): 805-7.
29. Singh B, Qureshi MM, Truong MT, Sahni D. Demographics and outcomes of stage I and II Merkel cell carcinoma treated with Mohs micrographic surgery compared with wide local excision in the National Cancer Database. J Am Acad Dermatol 2018; 79(1): 126-34.e3. DOI: https://doi.org/10.1016/j.jaad.2018.01.041
30. Bajetta E, Celio L, Platania M, Lo Vullo S, Patuzzo R, Maurichi A, *et al.* Single-institution series of early-stage Merkel cell carcinoma: long-term outcomes in 95 patients managed with surgery alone. Ann Surg Oncol 2009; 16(11): 2985-93. DOI: https://doi.org/10.1245/s10434-009-0615-1
31. Wright GP, Holtzman MP. Surgical resection improves median overall survival with marginal improvement in long-term survival when compared with definitive radiotherapy in Merkel cell carcinoma: A propensity score matched analysis of the National Cancer Database. Am J Surg 2018; 215(3): 384-7. DOI: https://doi.org/10.1016/j.amjsurg.2017.10.045
32. Liang E, Brower JV, Rice SR, Buehler DG, Saha S, Kimple RJ. Merkel cell carcinoma analysis of outcomes: a 30-year experience. PLoS One 2015; 10(6): e0129476. DOI: https://doi.org/10.1371/journal.pone.0129476
33. Sridharan V, Muralidhar V, Margalit DN, Tishler RB, DeCaprio JA, Thakuria M, *et al.* Merkel cell carcinoma: a population analysis on survival. J Natl Compr Canc Netw 2016; 14(10): 1247-57. DOI: https://doi.org/10.6004/jnccn.2016.0134
34. Gunaratne DA, Howle JR, Veness MJ. Definitive radiotherapy for Merkel cell carcinoma confers clinically meaningful in-field locoregional control: a review and analysis of the literature. J Am Acad Dermatol 2017; 77(1): 142-8. DOI: https://doi.org/10.1016/j.jaad.2017.02.015
35. Perez MC, Oliver DE, Weitman ES, Boulware D, Messina JL, Torres-Roca J, *et al.* Management of sentinel lymph node metastasis in Merkel cell carcinoma: completion lymphadenectomy, radiation, or both? Ann Surg Oncol 2019; 26(2): 379-85. DOI: https://doi.org/10.1245/s10434-018-6810-1
36. Lee JS, Durham AB, Bichakjian CK, Harms PW, Hayman JA, McLean SA, *et al.* Completion lymph node dissection or radiation therapy for sentinel node metastasis in Merkel cell carcinoma. Ann Surg Oncol 2019; 26(2): 386-94. DOI: https://doi.org/10.1245/s10434-018-7072-7
37. Petrelli F, Ghidini A, Torchio M, Prinzi N, Trevisan F, Dallera P, *et al.* Adjuvant radiotherapy for Merkel cell carcinoma: A systematic review and meta-analysis. Radiother Oncol 2019; 134: 211-9. DOI: https://doi.org/10.1016/j.radonc.2019.02.015
38. Steier C, Bragerton-Nasert S, Kornegay T. Merkel Cell Carcinoma. Radiation Therapist 2020; 29(2): 139-52.
39. Cook MM, Schaub SK, Goff PH, Fu A, Park SY, Hippe DS, *et al.* Postoperative, single-fraction radiation therapy in Merkel cell carcinoma of the head and neck. Adv Radiat Oncol 2020; 5(6): 1248-54. DOI: https://doi.org/10.1016%2Fj.adro.2020.07.003
40. Lancellotta V, D'Aviero A, Fionda B, Di Stefani A, Casà C, Del Regno L, *et al.* Contact skin radiotherapy (brachytherapy) for the treatment of non-melanoma skin cancers during COVID-19 pandemic. Dermatol Ther 2022; 35(3): e15276. DOI: https://doi.org/10.1111/dth.15276
41. Tagliaferri L, Ciardo FG, Fionda B, Casà C, Di Stefani A, Lancellotta V, *et al.* Non-melanoma skin cancer treated by contact high-dose-rate radiotherapy (brachytherapy): a mono-institutional series and literature review. In Vivo 2021; 35(4): 2313-19. DOI: https://doi.org/10.21873/invivo.12505
42. Casey S, Awotwi-Pratt J, Bahl G. Surface mould brachytherapy for skin cancers: The British Columbia cancer experience. Cureus 2019; 11(12): e6412. DOI: https://doi.org/10.7759/cureus.6412

43. Delishaj D, Rembielak A, Manfredi B, Ursino S, Pasqualetti F, Laliscia C, *et al.* Non-melanoma skin cancer treated with high-dose-rate brachytherapy: a review of literature. J Contemp Brachytherapy 2016; 8(6): 533-40. DOI: https://doi.org/10.5114%2Fjcb.2016.64112

44. Hui AC, Stillie AL, Seel M, Ainslie J. Merkel cell carcinoma: 27-year experience at the Peter MacCallum Cancer Centre. Int J Radiat Oncol Biol Phys 2011; 80(5): 1430-5. DOI: https://doi.org/10.1016/j.ijrobp.2010.04.061

45. Chen MM, Roman SA, Sosa JA, Judson BL. The role of adjuvant therapy in the management of head and neck merkel cell carcinoma: an analysis of 4815 patients. JAMA Otolaryngol Head Neck Surg 2015; 141(2): 137-41. DOI: https://doi.org/10.1001/jamaoto.2014.3052

46. McAfee WJ, Morris CG, Mendenhall CM, Werning JW, Mendenhall NP, Mendenhall WM. Merkel cell carcinoma: treatment and outcomes. Cancer 2005; 104(8): 1761-4. DOI: https://doi.org/10.1002/cncr.21355

47. Esposito A, Jacobs D, Ariyan S, Galan A, Kluger H, Clune J, *et al.* Merkel cell carcinoma: changing practice patterns and impact on recurrence-free and overall survival at a single institution and nationally. Ann Surg Oncol 2022; 29(1): 415-24. DOI: https://doi.org/10.1245/s10434-021-10727-2

48. D'Angelo SP, Lebbé C, Mortier L, Brohl AS, Fazio N, Grob JJ, *et al.* First-line avelumab in a cohort of 116 patients with metastatic Merkel cell carcinoma (JAVELIN Merkel 200): primary and biomarker analyses of a phase II study. J Immunother Cancer 2021; 9(7): e002646. DOI: https://doi.org/10.1136/jitc-2021-002646

49. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, *et al.* Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 2019; 37(9): 693-702. DOI: https://doi.org/10.1200/jco.18.01896

50. Topalian SL, Bhatia S, Amin A, Kudchadkar RR, Sharfman WH, Lebbé C, *et al.* Neoadjuvant nivolumab for patients with resectable Merkel cell carcinoma in the CheckMate 358 trial. J Clin Oncol 2020; 38(22): 2476-87. DOI: https://doi.org/10.1200/jco.20.00201

51. Becker JC, Hassel JC, Menzer C, Kähler KC, Eigentler TK, Meier FE, *et al.* Adjuvant ipilimumab compared with observation in completely resected Merkel cell carcinoma (ADMEC): A randomized, multicenter DeCOG/ADO study. J Clin Oncol 2018; 36(15_ suppl): 9527.

52. Akaike T, Qazi J, Anderson A, Behnia FS, Shinohara MM, Akaike G, *et al.* High somatostatin receptor expression and efficacy of somatostatin analogues in patients with metastatic Merkel cell carcinoma. Br J Dermatol 2021; 184(2): 319-27. DOI: https://doi.org/10.1111/bjd.19150

53. Zeitouni NC, Giordano CN, KANE JM. In-Transit Merkel Cell Carcinoma Treated with Isolated Limb Perfusion or Isolated Limb Infusion: A Case Series of 12 Patients. Dermatol Surg 2011; 37(3): 357-64. DOI: https://doi.org/10.1111/j.1524-4725.2011.01883.x

54. Thiels CA, Gonzalez AB, Gray RJ, Jakub JW. Isolated limb perfusion in Merkel cell carcinoma offers high rate of complete response and durable local–regional control: Systematic review and institutional experience. J Surg Oncol 2016; 114(2): 187-92. DOI: https://doi.org/10.1002/jso.24289