Merkel Cell Carcinoma: Local Recurrence Rate Versus Radiation Dose Study from a 949-Patient Database

Patricia Tai *, Michael Veness, Vimal Prajapati, Aoife Jones Thachuthara, Jidong Lian, Avi Assouline, Edward Yu, Kurian Joseph

Posted Date: 6 February 2025

doi: 10.20944/preprints202502.0339.v1

Keywords: Merkel cell carcinoma; local recurrence; radiotherapy dose; pattern of spread; skin; database

Invited Review

Merkel Cell Carcinoma: Local Recurrence Rate Versus Radiation Dose Study from a 949-Patient Database

Patricia Tai [1,*], Michael Veness [2], Vimal H Prajapati [3], Aoife Jones Thachuthara [4], Jidong Lian, MD [5], Avi Assouline [6], Edward Yu [7] and Kurian Joseph [8]

1. U. Saskatchewan, Saskatoon, SK, Canada; ptai2@yahoo.com
2. U. Sydney, Sydney, Australia; michael.veness@health.nsw.gov.au
3. U. Calgary, Calgary, AB, Canada; vimal.h.prajapati@dermatologyphilosophy.com
4. Cork University Hospital, Cork, Ireland; aoifejones.05@gmail.com
5. U. Toronto, Toronto, ON, Canada; Jidong.lian@thp.ca
6. Oncologue Radiothérapeute, Centre de Cancérologie de la Porte de Saint-Cloud (CCPSC), France; aviassouline@aol.com
7. Western U., London, ON, Canada; eyu@uwo.ca
8. U. Alberta, Edmonton, AB, Canada; Kurian.joseph@ahs.ca

* Correspondence: Correspondence: ptai2@yahoo.com

Abstract: (1) Background: Optimal radiotherapy doses for Merkel cell carcinoma are unknown. (2) Methods: After a PubMed literature search, we analyzed data by Equivalent Dose in **2-Gy** fractions (EQD2). (3) Results: 939/949 data were evaluable: 728/939 (77.5%) presented with localized disease, of which 171 were irradiated alone, with a median primary EQD2 of 50 (14.0-72.0) Gy2. Local recurrence (LR) was 23.4% (40/171). The remaining patients were controlled with a median EQD2 of 50 (23.3-72.0) Gy2. Thirteen patients were given *definitive* radiotherapy EQD2<50 vs ≥50 Gy2 to gross primaries: LR were 23.1% (3/13) vs 12.5% (1/8)(*P*=0.0004). Few patients received ≥60 Gy2. After *adjuvant* radiotherapy <50 vs ≥50 Gy2 to 156 primaries, LR were 18.8% (6/32) vs 12.8% (12/124); for <60 vs ≥60 Gy2, 15.5% (16/103) vs 8.7% (2/23)(*P*=0.52). LR after <50 Gy2 was 25% (3/12) for positive margins versus 17.4% (4/23) for negative margins; for ≥50 Gy2: 15% (3/20) versus 4.8% (3/62), respectively (*P*=0.36). (4) Conclusions: For definitive radiotherapy, EQD2<50 Gy2 demonstrates significant higher LR than ≥50 Gy2 (*P*=0.0004). For adjuvant radiotherapy, a trend of higher LR with < 50 Gy2 was seen. Large prospective multicenter studies are required to define the optimal doses for definitive and adjuvant MCC treatment.

Keywords: Merkel cell carcinoma; local recurrence; radiotherapy dose; pattern of spread; skin; database

1. Introduction

Merkel cell carcinoma (MCC) is an aggressive radiosensitive cutaneous neuroendocrine malignancy arising predominantly in older (70+ year olds) Caucasians. Many (30-40%) will die from MCC despite treatment, usually from distant metastases. The incidence is increasing rapidly, and lesions can arise anywhere on the body with the head and neck involved in 40-50% of cases [1]. The etiology of MCC is associated with a highly prevalent virus, the Merkel cell polyomavirus, as well as chronic ultraviolet radiation. MCC has a high propensity to spread to draining lymph nodes. It is relevant to establish the extent of a patient's MCC at diagnosis as this will impact both on management and prognosis. Most (50-60%) patients present with a primary lesion only but there is a need to investigate draining lymph nodes (LN), so called sentinel lymph nodes (SLN)) as the incidence of subclinical spread is high (30-50%). A further 20-30% will present with nodal metastases.

 doi:10.20944/preprints202502.0339.v1

Traditionally, node-positive disease in MCC patients had been treated with lymph nodal dissection (LND), but radiotherapy is a definite or adjuvant treatment option.

As to date, there is limited research on the optimal radiotherapy doses for microscopic and macroscopic diseases, and hence researchers have given different recommendations [NCCN ref]. Based on a 54-patient study from M. D. Anderson Cancer Center, authors recommended a dose of 56-60 Gy for *gross* disease and 46-50 Gy for *adjuvant* radiotherapy, both in 2 Gy fractions [2]. Two analyses of the American National Cancer Database showed different results for adjuvant radiotherapy dose. Doses from 40 to <50 Gy appears to be sufficient for extremities and/or trunk with stage I to III MCC, with overall survival (OS) equivalent to that of higher-dose regimens (≥50-70 Gy) [3]. However, another study published in 2020 supported doses of 50-57 Gy for most stage I/II Merkel cell carcinoma receiving *adjuvant* radiotherapy if 2 Gy per fraction is used and strongly recommended ≥ 50 Gy for patients with nodal presentations irrespective of tumor site [4]. This corroborates with *adjuvant* radiotherapy dose of 50-56Gy for local control of MCC, as demonstrated by meta-analysis and a large epidemiological study [5]. The updated German S2k guideline in 2023 states that the standard dose for *adjuvant* radiotherapy remains 50 Gy [6]. An *adjuvant* dose of 50 to 60 Gy was recommended for the tumor bed in another review [7].

When combined with chemotherapy, a clinical trial employed 50 Gy in 25 fractions over 5 weeks for with disease localized to the *gross* primaries and nodes (involved in 14/18, i.e. 77% of patients), and at least one of the following high-risk features: recurrence after initial therapy, involved nodes, primary size greater than 1 cm, gross residual disease after surgery, or occult primary with nodes [8,9]. But combination chemo-radiation has fallen out of favor due to toxicities and the theoretical concern of immunosuppression induced by chemotherapy adversely impacting prognosis. Research on immunotherapy in MCC is the trend nowadays.

Next issue is the effect of dose-fractionation. The group at Dana-Farber/Brigham & Women's Cancer Center studied 241 patients with non-metastatic MCC, treated with conventional (conv-RT) or hypo-fractionated radiotherapy (hypo-RT) [10]. The hypo-RT cohort was older (≥73 years at diagnosis: 78.0 % vs 41.5 %, $p < 0.01$), and received a lower equivalent total RT dose in 2 Gy per fraction (<50 Gy: 58.0 % vs 5.2 %, $p <0.01$). Median follow-up was 65.1 (range: 1.2-194.5) months for conv-RT and 25.0 (range: 1.6-131.3) months for hypo-RT cohorts. Two-year cumulative incidence of in-field locoregional relapse was low in both groups (1.1 % conv-RT vs 4.1 % hypo-RT, P=0.114). While two-year OS was lower for the hypo-RT group (62.6 % vs 84.4 %, P=0.0008), two-year MCC-specific survival was similar (84.7 % vs 86.6 %, P=0.743).

With the above-mentioned radiation dose controversies, our research team decided to examine the optimal dose-fractionation for MCC using the EQD2 concept, i.e. the equivalent dose if converted to 2-Gy fractions based on the linear-quadratic formula [11].

2. Materials and Methods

We have built a 949-patient aggregated database from records of our institutions and individual patient data from the literature for the period March 1982 to Feb 2015. This includes retrospective chart review of data from the six jurisdictions ofFrance, Canada and Australia. A PubMed search was also conducted to secure adequate database. A Microsoft excel datasheet was designed. There were no exclusion criteria for patients. The following were compiled for patients after ethics approval: baseline information of age, sex, initial clinical and pathological stages, site, time delay before seeing doctors, other concurrent tumor(s), maximum dimension of the primary tumor, LNM and DM, histological details, history of immunosuppression/co-morbidities/previous radiotherapy. We recorded the treatment(s) received: surgery (e.g. Mohs microsurgery, nodal dissection or excision alone, and resection margin), radiotherapy (doses, field coverage, response), chemotherapy (specific chemotherapy drugs, number of cycles, response) and outcome such as recurrence (timing, site and subsequent treatments), and final disease status. MCC polyomavirus status was not included due to non-availability at the time of study.

The primary outcome was local recurrence (LR). Equivalent doses in 2-Gy fractions (EQD2) = total dose × [(dose per fraction + α/β)/(2 + α/β)] was calculated to compare different dose-fractionations, assuming α/β=10 [11].

 doi:10.20944/preprints202502.0339.v1

2.1. Statistical Analysis

Pattern of recurrence was analyzed as the primary outcome, with survival rate as a secondary outcome. CSS was defined as the time interval from diagnosis to death from MCC, or censored at the last follow-up date if the patient was still alive at the time of analysis. OS was defined as the time interval from diagnosis to death regardless of the cause, or last follow-up date for censoring as described above. Kaplan-Meier method was used to generate survival curves [12]. Cox-Proportional Hazards model was used to identify risk factors for DM [13].

3. Results

Altogether 939/949 data were evaluable with sufficient radiotherapy information: 50.8% male, median age 73 (range: 31-96) years and median follow-up 21 (0-272) months. 728/939 (77.5%) presented with localized disease (stages I and II) and 176/939 (18.7%) with nodal disease (stage III). A median dose of 50 (range: 14-70) Gy2 were used for both micro-/macroscopic tumors.

Among 171 stages I and II patients who were irradiated without chemotherapy, median primary EQD2 was 50 (14.0-72.0) Gy2, and nodal EQD2 was 50 (15.9-71.9) Gy2. Five-year Kaplan-Meier cause-specific survival was 56.5%; overall survival was 43.8%; and LR was 23.4% (40/171) after a median EQD2 of 50 (14.0-70.0) Gy2. The remaining 131 patients achieved local control with median EQD2 of 50 (23.3-72.0) Gy2. Table 1 shows that 13 patients received definitive radiotherapy for gross primary disease: LR for EQD2<50Gy2 vs ≥50Gy2 were 23.1% (3/13) vs 12.5% (1/8) (P=0.0004, unpaired t-test). Comparison for <60 Gy2 vs ≥60 Gy2 was not performed due to few patients receiving ≥60 Gy2.

Adjuvant radiotherapy was given to 156 patients to the primary site, LR for <50Gy2 vs ≥50Gy2 were 18.8% (6/32) vs 12.8% (12/124); for <60Gy2 vs ≥60Gy2, 15.5% (16/103) vs 8.7% (2/23) (P=0.52, Fisher exact test). After treatment with <50Gy2 to positive margin, LR was 25% (3/12) and to negative margin, 17.4% (4/23) vs ≥50Gy2: 15% (3/20) and 4.8% (3/62), respectively (P=0.36, chi-square statistic with Yates correction).

Table 1. Radiation doses for stage I/II Merkel cell carcinoma for primary disease only without nodes at presentation.

MCC presenting with skin primary disease only	No. of patients, Total ***definitive*** dose (median) Gy and Gy2	No. of patients, Total ***adjuvant*** dose (median) Gy and Gy2	
		Margin -ve	**Margin +ve**
Primary tumor	N=23 16.0-60.0 (42.5) 31.3-60.0 (48.8)	N=81 25.0-66.0 (50.0) 32.5-56.4 (55.6)	N=23 16.0-60.0 (42.5) 31.3-60.0 (48.8)
		Margin -ve	**Margin +ve**
Nodal region	Not applicable for node-negative cases	N=54 16.2-70.0 (50.0) 15.9-70.0 (50.0)	N=54 16.2-70.0 (50.0) 15.9-71.9 (50.0)

Abbreviation: -ve, negative; +ve, positive; Gy2, equivalent doses in 2-Gy fractions.

4. Discussion

To our knowledge, this MCC database is one of the most comprehensive in the literature with a lot of treatment details. Although our data on adjuvant radiotherapy of LR for <50Gy2 vs ≥50Gy2

 doi:10.20944/preprints202502.0339.v1

were 18.8% vs 12.8%; for <60Gy2 vs ≥60Gy2, 15.5% vs 8.7% turned out to have *P*=0.52, the results are in the right direction demonstrating the benefit of adequate radiotherapy dose by 32% and 44% reduction. In addition, LR after <50Gy2 to positive surgical margins was 25% vs 17.4%; after ≥50Gy2: 15% vs 4.8% (3/62) again point towards benefit of a higher dose despite *P*=0.36. Radiotherapy doses should be individualized to achieve the best outcome taking into account the body sites, e.g. the shin tolerates radiation poorly with the scanty subcutaneous tissue and its location is exposed to trauma with poor circulation. Cosmetic outcome is another important consideration for the face and hands. Functional outcome is important for hands and feet. Relevant literature review for radiotherapy of MCC is presented below.

4.1. Sentinel Lymph Node Biopsy (SLNB) and Adjuvant Radiotherapy

Conservative surgery can be performed for both primary and nodal MCC. SLNB can be seen as a form of selective lymphadenectomy of involved nodes which is followed by radiation, being used in most American centers, for example the University of Washington [14].

4.2. Effectiveness of Radiotherapy for Gross Disease

MCC has an excellent response to radiotherapy highlighting its unique radio-responsiveness among skin cancers. In a series from the Peter MacCallum Cancer Institute, Australia, complete responses of measurable tumors were observed in 22 out of 23 sites (96%) and 1 partial response (4%), i.e., an overall response rate of 100%. There was only 1 recurrence in an irradiated site (after a low radiation dose) [15]. More examples of success stories were found in the older literature [16], including a 26 cm tumor with excellent response [17]. Other studies have shown similarly excellent results on longer follow-up: 75% at 49 months [18] and 85% at 2 years [19]. Modern radiotherapy technique with stereotactic radiosurgery allows a higher dose to be achieved for gross tumor while sparing surrounding norma tissues. This can be performed for liver, bone and brain metastases < 3 cm in general [20].

In 2015, the Peter MacCallum Cancer Centre, Melbourne, Australia published its 15-years of experience of positron emission tomography (PET) scans [21] and reported post-treatment metabolic response in 1-6 months to be significantly associated with improved overall survival. The 24/37) patients achieving a complete metabolic response had an 88% 2-year overall survival (95% CI, 0.75-1.00) and a 68% 5-y overall survival (95% CI, 0.49-0.95). Patients without a complete metabolic response had a 15% 1-year overall survival (95% CI, 0.04-0.55). PET scans are also useful to identify locoregional recurrence which can be salvaged by multi-modality treatment [22,23]. In this study, 4 of the 9 patients with locoregional recurrence were successfully salvaged by further treatment with long-term follow-up, median 6.5 years.

4.3. Dose-Response to Radiotherapy

As to date, the optimum radiation doses for MCC are only estimated in the adjuvant, microscopic and macroscopic settings. There is limited radiotherapy dose response data but an Australian study documented a dose response for patients with macroscopic disease and recommending 55 Gy as a minimum dose [23]. In that study no patient with macroscopic MCC disease developed in-field relapse at doses >56 Gy [24]. The majority of patients treated with definitive RT had out-of-field relapse with in-field control.

A systematic review of the literature reported an almost 90% in-field control rate following definitive radiotherapy with a mean dose delivered of just under 50 Gy, with no apparent association between RT dose and incidence of recurrence [25], likely due to radiosensitivity of MCC. In an analysis of 2093 patients from the NCDB with MCC located on the trunk or extremities, all patients underwent surgery (88% achieved negative margins and 12% had microscopic or gross residual MCC) followed by adjuvant RT. Using overall survival as the outcome, patients receiving between 40-50 Gy had an equivalent survival to those receiving >50-70 Gy. Patients receiving <40 Gy had a worse survival [26].

Patients of poor performance status should be considered for shorter hypo-fractionated regimes such as 20-30Gy in 5-10 fractions. At least one study has documented 45% complete response using

 doi:10.20944/preprints202502.0339.v1

an 8 Gy singe fraction (including large tumors up to 16 cm) and almost 80% in-field lesion control [27]. Whether the larger doses per fraction compensate for a lower total dose is unclear but is an alternative approach in selected patients of poor performance status.

With combination treatment, chemotherapy appears to be effective with 50 Gy [8,9]. A phase II trial randomized 50 patients to nivolumab 240 mg intravenously every 2 weeks plus ipilimumab 1 mg/kg intravenously every 6 weeks (group A) or the same drug schedule with the addition of stereotactic radiotherapy to at least one tumour site (24 Gy in three fractions at week 2; group B) to gross tumor [28]. 22 patients naïve to immune checkpoint inhibitors all showed response to combined nivolumab and ipilimumab, of which 9 (41%) were complete responses. The authors concluded that addition of stereotactic radiotherapy did not improve efficacy of combined nivolumab and ipilimumab. We felt that the radiation dose was only 36 Gy2, a higher dose may have a different conclusion. More research with combination immunotherapy and radiotherapy is needed to clarify the optimal dose.

Deducing from the literature, clinicians may consider a higher dose for lesions with a greater concern for recurrence, e.g. multiple positive resection margins, recurrent lesions, multiple recurrent episodes and patients who may not attend future follow-up, etc. All treatment decisions should be individualized to achieve the best outcome. This study is meant to help clinicians who have few experiences on this rare tumor.

5. Conclusions

In summary, our work shows that standard fractionated radiotherapy doses $\geq$50 Gy2 and perhaps $\geq$60 Gy2 resulted in improved locoregional control, although statistically insignificant due to small patient numbers. Deducing from the literature, clinicians may consider a higher dose for lesions with a greater concern for recurrence, e.g. multiple positive resection margins, recurrent lesions, multiple recurrent episodes and patients who may not attend future follow-up, etc. All treatment decisions should be individualized to achieve the best outcome. This study is meant to help clinicians who have few experiences on this rare tumor.

Author Contributions: Conceptualization, P.T., E.Y. and K.J.; methodology, P.T., E.Y. and K.J.; software, P.T..; validation, P.T., E.Y. and K.J.; formal analysis, P.T., E.Y. and K.J.; investigation, P.T., E.Y. and K.J.; data curation, all; writing— P.T., E.Y. and K.J.; writing—review and editing, P.T., E.Y. and K.J.; supervision, P.T., E.Y. and K.J.; project administration, P.T., E.Y. and K.J. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the University of Saskatchewan Biomedical Research Ethics Board (Bio-REB). "It has reviewed the above- named research study. The study was found to be acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized study is carried out according to governing law. This approval is valid for the specified period provided that there is no change to the approved protocol or the consent process (protocol code: Bio# 16-06; date of approval: 5 July 2017)".

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is unavailable to the public due to privacy (restrictions by the ethics committee above).

Acknowledgments: Data and research support from Saskatchewan Cancer Agency. In this publication, the results and conclusions, if any, are the sole responsibility of the researcher and that no endorsement by the Agency or by any third party, is to be inferred.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

 doi:10.20944/preprints202502.0339.v1

The following abbreviations are used in this manuscript:

ADMEC-O	Adjuvant immunotherapy with nivolumab versus observation
ADT	Androgen deprivation therapy
CSS	Cause-specific survival
CT	Computerized tomography
DFS	Disease-free survival
DM	Distant metastases
Gy2	Equivalent doses in 2-Gy fractions
LNM	Lymph node metastases
LR	Local recurrence
MCC	Merkel cell carcinoma
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
SLNB	Sentinel lymph node biopsy
-ve	Negative
+ve	Positive

References

1. Paulson KG, Park SY, Vandeven NA, et al. Merkel cell carcinoma: Current US incidence and projected increases based on changing demographics. J Am Acad Dermatol. 2018;78(3):457-63.
2. Morrison WH, Peters LJ, Silva EG, Wendt CD, Ang KK, Goepfert H. The essential role of radiation therapy in securing locoregional control of Merkel cell carcinoma. Int J Radiat Oncol Biol Phys. 1990 Sep;19(3):583-91.
3. Patel SA, Qureshi MM, Sahni D, et al. Identifying an optimal adjuvant radiotherapy dose for extremity and trunk Merkel cell carcinoma following resection: an analysis of the National Cancer Database. JAMA Dermatol. 2017;153(10):1007-14.
4. Yusuf M, Gaskins J, Wall W, et al. Optimal adjuvant radiotherapy dose for stage I, II or III Merkel cell carcinoma: an analysis of the National Cancer Database. Jpn J Clin Oncol. 2020;50(2):175-84.
5. Hennequin C, Rio E, Quéro L, Clavère P. Radiation therapy of cutaneous cancers. Cancer Radiother. 2022 Feb-Apr;26(1-2):397-403.
6. Vordermark D, Höller U. The role of radiotherapy in the updated German S2k guideline for management of Merkel cell carcinoma. Strahlenther Onkol. 2023;199(5):433-5.
7. Alonso RS, Lahbabi I, Ben Hassel MB, et al. Merkel cell carcinoma: outcome and role of radiotherapy. Cancer Radiother. 2008 Sep;12(5):352-9.
8. Poulsen M, Rischin D, Walpole E, et al. Analysis of toxicity of Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group study. Int J Radiat Oncol Biol Phys. 2001;51(1):156-63.
9. Poulsen M, Walpole E, Harvey J, et al. Weekly carboplatin reduces toxicity during synchronous chemoradiotherapy for Merkel cell carcinoma of skin. Int J Radiat Oncol Biol Phys. 2008;72(4):1070-4.
10. Liu KX, Milligan MG, Schoenfeld JD, Tishler RB, Ng AK, Devlin PM, et al. Characterization of clinical outcomes after shorter course hypofractionated and standard-course radiotherapy for stage I-III curatively-treated Merkel cell carcinoma. Radiother Oncol. 2022;173:32-40.
11. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989;62(740):679-94.
12. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc.1958;53:457-82.
13. Cox DR. *Regression Models and Life-Tables. J Royal Statistical Soc. 1972; Series B 34(2):187–220.*
14. Singh N, McClure EM, Akaike T, Park SY, Huynh ET, Goff PH, et al. The Evolving Treatment Landscape of Merkel Cell Carcinoma. Curr Treat Options Oncol. 2023;24(9):1231-58.

 doi:10.20944/preprints202502.0339.v1

15. Pacella J, Ashby M, Ainslie J, et al. The role of radiotherapy in the management of primary cutaneous neuroendocrine tumors (Merkel cell or trabecular carcinoma): experience at the Peter MacCallum Cancer Institute (Melbourne, Australia). Int J Radiat Oncol Biol Phys. 1988;14(6):1077-84.
16. Alexander E 3rd, Rossitch E Jr, Small K, et al. Merkel cell carcinoma. Long term survival in a patient with proven brain metastasis and presumed choroid metastasis. Clin Neurol Neurosurg. 1989;91(4):317-20.
17. Kasraei F, Roach M, Lee MT. Merkel Cell Carcinoma: When Does Size Matter for Radiotherapy? Cureus. 2015;7(12):e443.
18. Veness M, Foote M, Gebski V, Poulsen M. The role of radiotherapy alone in patients with merkel cell carcinoma: reporting the Australian experience of 43 patients. Int J Radiat Oncol Biol Phys. 2010;78(3):703-9.
19. Sundaresan P, Hruby G, Hamilton A, et al. Definitive radiotherapy or chemoradiotherapy in the treatment of Merkel cellcarcinoma. Clin Oncol (R Coll Radiol). 2012;24(9):e131-6.
20. Jacob AT, Alexandru-Abrams D, Abrams EM, Lee JY. Stereotactic radiosurgery for merkel cell carcinoma brain metastases. J Clin Neurosci. 2015;22(9):1499-502.
21. Byrne K, Siva S, Chait L, et al. 15-Year Experience of 18F-FDG PET Imaging in Response Assessment and Restaging After Definitive Treatment of Merkel Cell Carcinoma. J Nucl Med. 2015;56(9):1328-33.
22. Grotz TE, Tarantola TI, Otley CC, Weaver AL, McGree ME, Jakub JW. Natural history of Merkel cell carcinoma following locoregional recurrence. Ann Surg Oncol. 2012;19:2556-62.
23. Eng TY, Naguib M, Fuller CD, Jones WE III, Herman TS. Treatment of recurrent Merkel cell carcinoma: an analysis of 46 cases. Am J Clin Oncol. 2004;27:576-83.
24. Foote M, Harvey J, Porceddu S et al. Effect of radiotherapy dose and volume on relapse in Merkel cell cancer of the skin. Int J Radiat Oncol Biol Phys. 2010;77:677-84.
25. Gunaratne D, 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.
26. Patel SA, Qureshi MM, Sahni D, Truong MT. Identifying an optimal adjuvant radiotherapy dose for extremity and trunk Merkel cell carcinoma: an analysis of the National Cancer Database. JAMA Dermatol. 2017;153(10):1007-14.
27. Iyer JG, Parvathaneni U, Gooley T et al. Single-fraction radiation therapy in patients with metastatic Merkel cell carcinoma. Cancer Med. 2015;4:1161-70.
28. Kim S, Wuthrick E, Blakaj D, Eroglu Z, Verschraegen C, Thapa R, et al. Combined nivolumab and ipilimumab with or without stereotactic body radiation therapy for advanced Merkel cell carcinoma: a randomised, open label, phase 2 trial. Lancet. 2022;400(10357):1008-1019.