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## Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline

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**Abstract** Merkel cell carcinoma (MCC) is a rare tumour of the skin of neuro-endocrine origin probably developing from neuronal mechanoreceptors. A collaborative group of multidisciplinary experts form the European Dermatology Forum (EDF), The European Association of Dermato-Oncology (EADO) and the European Organization of Research and Treatment of Cancer (EORTC) was formed to make recommendations on MCC diagnosis and management, based on a critical review of the literature, existing guidelines and expert's experience. Clinical features of the cutaneous/subcutaneous nodules hardly contribute to the diagnosis of MCC. The diagnosis is made by histopathology, and an incisional or excisional biopsy is

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mandatory. Immunohistochemical staining contributes to clarification of the diagnosis. Initial work-up comprises ultrasound of the loco-regional lymph nodes and total body scanning examinations. The primary tumour should be excised with 1–2 cm margins. In patients without clinical evidence of regional lymph node involvement, sentinel node biopsy is recommended, if possible, and will be taken into account in a new version of the AJCC classification. In patients with regional lymph node involvement radical lymphadenectomy is recommended. Adjuvant radiotherapy might be considered in patients with multiple affected lymph nodes of extracapsular extension. In unresectable metastatic MCC mono- or poly-chemotherapy achieve high remission rates. However, responses are usually short lived. Treatment within clinical trials is regarded as a standard of care in disseminated MCC.

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## 1. Introduction

These guidelines have been written under the auspices of the European Dermatology Forum (EDF) and the European Association of Dermato-Oncology (EADO) in order to assist clinicians in treating patients with Merkel cell carcinoma (MCC) in Europe. The paper was initiated due to advances in the histological diagnosis and the prognostic classification of MCC with implications for treatment selection. The guidelines address aspects of MCC management, from the clinical and histological diagnosis of primary tumour to the systemic treatment of advanced or metastatic disease. It is hoped that this set of guidelines will assist healthcare providers in managing their patients according to the current standards of care and evidence-based medicine. It is not intended to replace national guidelines accepted in their original country. These guidelines reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may modify the conclusions or recommendations in this report. In addition, it may be necessary to deviate from these guidelines for individual patients or under special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, deviation from them should not necessarily be deemed negligent.

## 2. Methods

To construct this EDF–EADO–European Organization for Research and Treatment of Cancer (EORTC) guideline, an extensive search with terms ‘Merkel cell carcinoma’ using the PubMed, EMBASE and Cochrane Library databases was conducted (until 31st December 2014). Articles included systematic reviews, pooled analyses and meta-analyses. The search was restricted to English-speaking language publications. We also searched for existing guidelines on Merkel cell carcinoma in the databases mentioned above as well as in relevant websites (national agencies, medical societies). A subgroup among the authors produced a working draft that was extensively discussed at a

consensus meeting and thereafter through email communication. In addition, the panel looked for concordances and differences among recently published guidelines (see [Appendix A](#)). Previous recommendations on distinct items (epidemiology, diagnosis, prognosis, treatment and follow-up) were discussed extensively in view of the available evidence-based data. Items that were agreed upon by our expert panel were adapted within our guideline proposal with appropriate reference. Items that differed from previously published guidelines or were originally recommended by our working group were clearly stated as proposed by the EADO consensus group. The guideline draft was circulated between panel members from EADO, EDF and EORTC before reaching its final form.

## 3. Definition

Merkel cell carcinoma (MCC) is a rare highly aggressive primary cutaneous carcinoma of the skin with epithelial and endocrine features. Its origin – neuroendocrine – is probably skin mechano-receptors; pluripotent stem cells or even lymphoid cells are likewise debated [3].

### 3.1. Epidemiology and aetiology

MCC annual age standardised incidence rate per million ranges from 2 to 4 in Europe and in the United States (US) to 8/million PY in Australia. It increased from 1980 to 2000 in US and in Europe [4–7]. This can be related to a true increased incidence by itself or caused by ageing of the population, increased sun exposure and/or improvement of diagnostic immunohistochemical tools as well as improved registration. MCC predominates in men (61.5%) and in the elderly with a median age at diagnosis around 76 years, 71.6% of patients being older than 70 [5,7]. MCC is an aggressive disease with an overall 10-year survival for patients estimated to 57.3% in US [7] and 47% in Europe [5].

The main factors known to be involved in MCC pathogenesis are:

- UV radiation attested by a eight times higher incidence in white compared to black, a correlation between incidence and UVB irradiation index, highest incidence rates in Australia and predominance on sun-exposed skin [8].
- Immunosuppression attested by a significantly increased risk in HIV patients and transplant recipients [9–11] and recent suggestion that high intra-tumoral T-lymphocyte infiltrates are associated with better survival [12,13]. So far no studies on the specific management of the immunosuppressive therapy in transplant-recipients diagnosed with MCC are available and minimisation of immunosuppressive drugs should be discussed on an individual basis.
- Merkel cell polyomavirus (MCPyV) DNA is a ubiquitous virus which can be detected in up to 80% cases using molecular techniques [14–17] and in 97% using a recently available monoclonal anti large T antigen antibody [18].

## 4. Diagnosis

### 4.1. Clinical features of primary tumour

MCC is a rapidly growing asymptomatic solitary, firm, non-tender, flesh-coloured to red tumour with nodular or plaque features, rarely ulcerated at first presentation. [19] The predominant sites are head and neck (53%) and extremities (34–35%); whereas trunk and oral and genital mucosa are involved in less than <10%. [7]

### 4.2. Histopathology [20]

Diagnosis is based on incisional tumour biopsy. MCC generally consists in a solid nodular lesion in the dermis and subcutis. On haematoxylin examination MCC is characterised by a proliferation of uniform small round blue undifferentiated cells with large lobulated nuclei and scant cytoplasm, high mitotic rate and apoptotic bodies and occasional necrosis. Immunohistochemistry is required for diagnosis (Table 1) and MCC is characterised by expression of both epithelial markers such as

cytokeratin 20 with a characteristic paranuclear dot-like staining but also AE1/AE3 and CAM5.2 and by expression of neuroendocrine markers such as neuron-specific enolase (very sensitive but expressed by other neuroendocrine tumours), synaptophysin and chromogranin A (more specific for MCC). The latter is the most commonly used marker with a diffuse cytoplasmic staining pattern. By contrast the following markers are generally negative: S-100 and HMB-45 expressed by melanoma, leucocyte common antigen and other lymphocyte markers expressed by lymphomas, CK7 and carcinoembryonic antigen expressed by sweat gland carcinomas and thyroid transcription factor 1 (TTF-1) important for differential diagnosis with metastatic small cell lung cancer (SCLC) (see Table 1). The diagnostic value of Merkel cell polyomavirus detection using either molecular or immunohistochemical techniques is currently investigated [20]. In clinical practice a characteristic histopathological report complemented with positive CK-20 and TTF-1 immunostainings is considered sufficient for the diagnosis of MCC.

## 5. Prognostic classification

### 5.1. Clinical features (demography, primary tumour)

Clinical unfavourable factors are male gender, location in head and neck or trunk as compared to upper limbs, size of the primary tumour [7,5] and the presence of immunosuppression [21,22].

### 5.2. Histological prognosis markers of the primary tumours

So far there is no convincing demonstration of any histological prognosis marker in MCC. The favourable prognostic value of low tumour depth, absence of lymph vascular invasion and more recently tumour infiltrating immune cells have been suggested and deserves further evaluation [13,23,24]. However it is well known from clinical practice that even a superficial MCC can metastasise and in the AJCC classification tumour depth is not regarded as a high risk feature [25].

Table 1  
Immunohistochemistry, adapted from Becker et al. [1].

	Merkel cell carcinoma (MCC)	Lymphoma	Melanoma	SCLC*
CK 20	+	–	–	–
Neuron-specific-enolase	+	–	–	+/-
Chromogranin A (CgA)	+/-	–	–	+/-
Huntingtin interacting protein 1 (HIP1)	+	+/-	–	–
Vimentin	–	+	+	–
Melan-A/MART-1	–	–	+	–
Leucocyte common antigen (LCA)	–	+	–	–
Thyroid transcription factor-1 (TTF-1)	–	–	–	+

\* SCLC small cell lung cancer.

### 5.3. Distant involvement

The main prognostic factors are related to distant involvement. MCC tumours of localised stage carry the best prognosis (71% survival rate) [7]. In regional and distant disease five-year survival was 52% and 17%, respectively in a large European registry [5]; and 47.8% and 20.1% in the SEER study [7].

Lymph node status is the most important independent predictor [26] including occult microscopic nodal involvement which occurs in around one third of patients [2,27]. Therefore the new AJCC classification based on 5823 prospectively enrolled MCC cases from the US National Cancer Data Base includes sentinel lymph node status which is considered as an important procedure in MCC management. Before sentinel lymph node biopsy, regional lymph node ultrasonography (US) [28] is recommended as well as initial work up with computerised tomography scanner (CT scan) or positron emission tomography–computed tomography (PET–CT).

### 5.4. AJCC classification [2]

T1 are characterised by tumour size <2 cm (T1) while T2 (between 2 and 5 cm) and T3 (more than 5 cm) carry the same prognostic. The T4 category includes deeply invasive tumours (invading bone, muscle, fascia or cartilage) as in other AJCC staging systems.

Patients with nodal disease detected by pathologic examination but without detectable clinical involvement have micrometastatic or N1a nodal disease. Those who have clinically apparent regional lymph node disease, confirmed by pathologic evaluation, have macrometastatic or N1b nodal disease. N2 refers to the presence of in transit lesions. There are 3 categories of distant metastatic disease (M status) as in melanoma staging: M1a-distant skin, distant subcutaneous tissues, or distant lymph nodes; M1b-lung; and M1c-all other visceral

sites. The stage and sub stage groups are summarised in Table 2 with corresponding prognosis values.

## 6. Patient management

### 6.1. Preoperative staging

Full body skin examination by an expert dermato-oncologist should be conducted. Lymph nodal clinical examination of all main nodal basins is done with particular carefulness to the loco regional nodes.

Ultrasound of the loco regional nodes and total body PET-CT will complete the instrumental staging.

### 6.2. Primary and adjuvant treatment for clinically N0 disease

There is no formal evaluation of excision margins in the literature, however the EADO/EORTC recommends a 1 to 2 cm excision margin taking into account functional considerations in the head/neck region and with complete histological inspection of the margins of the excised material using microscopically controlled surgery; however, it should be kept in mind, that the safety margin is more intended to remove microscopic satellite metastases than to ensure clear resection margins of the primary tumour. The benefit on survival of adjuvant radiotherapy of the tumour region (50 Gy and 10 more Gy on tumour bed) is highly suggested from retrospective studies and is therefore recommended [29–32]. Reconstruction should take into account further adjuvant radiotherapy.

Sentinel lymph node biopsy is recommended if possible, whatever the size of the tumour. If micro-metastasis is demonstrated, a therapeutic lymph node dissection is proposed although there are no prospective studies demonstrating its benefit in the literature.

If a sentinel node biopsy cannot be performed, regional follow up with ultrasound and clinical examination every 4 months should be planned.

Adjuvant irradiation (50 Gy) of the lymphatic drainage area has been shown in a prospective study to improve local control without improving survival [33]. Retrospective data from the US National cancer database on 6955 patients conclude on the absence of survival benefit from adjuvant radiotherapy in stage III patients [32]. Therefore adjuvant radiotherapy of the lymphatic drainage area cannot be recommended in general after therapeutic node dissection but could be discussed in a multidisciplinary approach to improve local disease control mainly in the case of extracapsular nodal involvement.

For elderly patients with poor performance status for whom surgery is not feasible, radiotherapy of tumours and positive lymph node can be discussed in a multidisciplinary approach.

Table 2

Staging classification of MCC (adapted from Lemos et al. [2]).

Stage	T	N	M	5 years survival (%)
O	TIS	N0	M0	
IA	T1	pN0	M0	79
IB	T1	cN0	M0	60
IIA	T2/T3	pN0	M0	58
IIB	T2/T3	cN0	M0	49
IIC	T4	N0	M0	47
IIIA	Any T	N1a	M0	42
IIIB		N1b/N2	M0	26
IV		Any N	M1	18

TO, no primary tumour, TIS (in situ).

T1 primary tumour diameter <2 cm, T2 comprise between 2 and 5 cm, T3 more than 5 cm.

NO, no regional node metastasis, cNO, nodes not clinically detectable but no pathologic examination, pNO, nodes negative both clinically and by pathologic examination.

N1a micrometastasis, N1b macrometastasis, N2 in transit metastasis.



### 6.3. Primary and locoregional approach followed by adjuvant therapy for clinically N+ node (with cytological or histological confirmation and negative TDM or TEP CT imaging)

The combination of surgery and radiotherapy of the tumour region will be performed as described below. Therapeutic node dissection of the basin will be performed eventually followed by adjuvant radiotherapy if indicated. As already stated retrospective data strongly suggest that adjuvant radiotherapy does not impact overall survival but only local disease control. Therefore it will be discussed in extensive disease on a case by case multidisciplinary approach [32]. Adjuvant immunotherapeutic trials have been initiated and whenever possible patients should be treated within a clinical trial. For elderly patients with poor performance status for whom surgery is not feasible, radiotherapy of tumours and lymph node can be discussed in a multidisciplinary approach.

### 6.4. Treatment of extra-nodal locoregional disease: surgery/radiation therapy/ electrochemotherapy/isolated limb infusion

Satellite or in-transit metastases around the primary site should be removed surgically if the number, size and location allow a complete removal of the metastatic sites. RT alone or in combination with chemotherapy may be used as an alternative option when surgery is not feasible. RT is particular helpful as a palliative treatment, in order to relieve pain.

Electrochemotherapy is a relatively new treatment modality which can find indication in locally advanced lesions [34].

Isolated hyperthermic limb perfusion represents an important therapeutic option when the local progression could include in the treatment proposals the indication for amputation [35,36]. In solid tumours with such a locoregional diffusion on limbs, isolated limb perfusion with tumour necrosis factor and alkeran has demonstrated in most solid tumours to save as much as 70% of limbs otherwise undergoing amputation. A less invasive approach to treat locally advanced disease in the limbs is represented by isolated limb infusion. The efficacy is usually 10–15% less beneficial than with the classic approach but less invasive with reduced complications.

### 6.5. Follow up

There is no evaluation of the best follow-up strategy. Once loco regional disease is under control from the surgical point of view, the proposal can be characterised by clinical examinations and nodal ultrasound every

4 months during the first 3 years then every 6 months for up to 5 years.

CT or PET CT might be proposed every year for 5 years.

### 6.6. Metastatic stage

Except for surgery of isolated metastasis, there is no established curative treatment for metastatic MCC. In a recent American registry study chemotherapy was not associated with MCC relapse or survival [37] and no therapy is currently approved in this situation by FDA or EMEA.

Various regimen used to treat small cell lung cancer thought to be a neuroendocrine tumour, have been evaluated in small series or case reports and are summarised in Desch et al. [38]. These regimens combine in various ways carboplatin, cisplatin and etoposide, cyclophosphamide with vincristine, doxorubicin, prednisone, bleomycin or 5-fluorouracil. Initial regression is frequent with a response rate up to 75% [38–41] but of short duration with a median overall survival rate of 9 months and high toxicity in elderly patients. Among these regimens, one of the most frequently used for patients with good performance status is a combination of cisplatin and etoposide (cisplatin 60–80 mg/m<sup>2</sup> IV on day 1 plus etoposide 80–120 mg/m<sup>2</sup> IV on days 1–3 every 21–28 days or carboplatin AUC 5 IV on day 1 plus etoposide 80–100 mg/m<sup>2</sup> IV on days 1–3 every 28 days: ([http://www.nccn.org/professionals/physician\\_gls/pdf/sclc.pdf](http://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf)).

On the other hand monotherapies using anthracyclines, liposomal anthracyclines or etoposide have also led to anecdotal responses with less toxicity and can also be considered in a case by case approach. Best supportive care or palliative radiotherapy can be discussed in patients with poor performance status.

Enrolment in clinical trials should be encouraged and should aim to evaluate innovative therapies such as immunotherapy including anti CTLA4 and anti PDL1/PD-1, pan tyrosine kinase inhibitors and somatostatin analogues. If the physicians, patients or family members need detailed information about the ongoing clinical trials in MCC, the following site provides this immediately: [http://ec.europa.eu/research/health/medical-research/cancer/fp7-projects/immomec\\_en.html](http://ec.europa.eu/research/health/medical-research/cancer/fp7-projects/immomec_en.html).

## 7. Summary

The present EDF–EADO–EORTC guidelines represent a European consensus-based interdisciplinary set of recommendations (S2 level) addressing all aspects of management of MCC, from the diagnosis of primary tumour to the systemic treatment of locally advanced or metastatic disease. The recommendations are based on current standards of care, existing guidelines and

Table 3

Summary of management recommendations on Merkel cell carcinoma (MCC) by European Dermatology Forum (EDF)–European Association of Dermato-Oncology (EADO)–European Organization for Research and Treatment of Cancer (EORTC) expert panel.

*Diagnostic and staging recommendations:*

- The diagnosis of MCC is primarily based on histological and immunohistochemical features
- A biopsy and histologic confirmation should be performed in all clinically suspicious lesions
- The diagnosis of MCC should prompt a complete examination of the entire skin and palpation of the regional lymph nodes for nodal involvement
- Initial work up consists in ultrasound of the loco regional nodes as well as computerised tomography scanner (CT scan) or Positron Emission Tomography–Computed Tomography (PET–CT)

- Sentinel lymph node biopsy is recommended if possible and is taken into account in the new AJCC classification

*Treatment recommendations:*

- Surgical excision with 1–2 cm margins taking into account functional considerations in the head/neck region is recommended followed by adjuvant therapy of the tumour region
- In case of lymph node involvement, the preferred treatment is a regional lymph node dissection. Adjuvant RT will be discussed in cases where multiple nodes are affected or if extracapsular involvement is observed
- Satellite or in-transit metastases around the primary site should be removed surgically if a complete removal of the metastatic sites is feasible. Electrochemotherapy or RT with or without chemotherapy may be used as an alternative option when surgery is not feasible
- Mono- or polychemotherapy can be used in metastatic MCC; however, there is no established standard regimen and responses are usually short-lived. The standard of care is enrolment in clinical trials

expert panel opinion. A summary of these guidelines is provided in [Table 3](#).

## 8. Validity period

These guidelines are planned to be updated at least every three years.

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## Conflict of interest statement

Dr. Bastholt reports personal fees from Astra-Zeneca, personal fees from Bristol Myers Squibb, personal fees from Roche, personal fees from Merck, outside the submitted work; Dr. Becker reports personal fees from Amgen, personal fees from LEO, personal fees from MSD, personal fees from Merck Serono, personal fees from Roche, personal fees from Glaxo Smith Kline, outside the submitted work; Dr. Garbe reports personal fees from Amgen, grants and personal fees from Bristol Myers Squibb, grants and personal fees from Glaxo Smith Kline, personal fees from Merck, personal fees from Novartis, grants and personal fees from Roche, outside the submitted work; Dr. Grob reports personal fees from Meda, personal fees from LEO, personal fees from Galderma, personal fees from Almirall, personal fees from Roche, outside the submitted work; Dr. Lebbe reports personal fees from Bristol Myers Squibb, personal fees from Merck, personal fees from Roche, personal fees from Novartis, personal fees from Glaxo Smith Kline, personal fees from Amgen, outside the submitted work; Dr. Malvey reports personal fees from LEO, personal fees from Almirall, personal fees from MEDA, personal fees from ISDIN, outside the submitted work; Dr. del Marmol reports personal fees from LEO, personal fees from Roche, personal fees

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## Appendix A.

### *Addendum 1: Surgical aspects of lymph node dissection in nodal disease*

The neck dissection consists in the ablation of the nodes of the five levels. The parotid gland is included into the specimen when the MCC originates on the face

or on the scalp between the eye and the mastoid regions. But not all investigators proceed with the dissection of the five levels of nodes if the metastatic nodes are not directly in the parotid gland. Similarly the indication of performing the dissection of the submental mandibular (levels I–II) nodes can be avoided when the metastases lie in the posterior triangle (V level) nodes.

There are three levels of dissection in the groin. Superficial groin dissection captures node-bearing tissue between the superficial fascia and the fascia lata, in a triangular area bound by the adductor longus medially, the Sartorius laterally and the inguinal ligament superiorly, also called the Scarpa triangle. The fascia lata is continuous with the fascia overlying the Sartorius and adductors, an easily identifiable plane defining the deep border of dissection and the roof of the femoral canal. The tissue superficial to the fascia lata has the greatest number of inguinal nodes, draining most of the cutaneous portion of the lower extremity. A deep groin dissection includes the same areas, but also encompasses the tissue within the femoral sheath, deep to the fascia lata, containing few more deep inguinal nodes, as well as several lymphatic channels. This requires skeletonisation of the femoral vessels and increased associated morbidity. Both areas of dissection include excision of Cloquet's node at the superior end of the dissection along the femoral canal, usually located between the femoral vein and the Cooper's ligament. The saphenous vein is usually sacrificed in both cases, but surgeons may also decide to preserve it as usually it does not compromise the approach of radical surgery. The iliac and obturator dissection accompanies the groin dissection, it involves the dissection of both the obturator and the nodes along the external iliac vessels from the inguinal ligament to the origin of the internal iliac artery. This technique requires skeletonisation of the external iliac vessels until the bifurcation of the common iliac vessels.

The dissection in this area is associated with significant morbidity. Overall morbidity rates have been reported between 17% and 90%, with incidence of wound infection of 13–33%, seroma formation, skin flap necrosis and long lasting limb lymphedema. It is important to mention that this wide range for morbidity can be also due to lack of uniform evaluation criteria.

The axillary dissection is characterised by the dissection of the nodes lying between the medial aspect of the dorsal muscle, to the lateral aspect of the minor pectoralis muscle representing the first level of Berg nodes, followed by the dissection of the nodes lying below the minor pectoralis muscle representing the second level of Berg nodes and concluding the dissection of the nodes lying between the medial aspect of the minor pectoralis muscle and the subclavian tendon which is just in correspondence of the axillary vein entering in the chest wall and representing the limit of the third level of Berg nodes. The minor pectoralis muscle can be easily preserved without compromising the quality of the radical

surgery. The procedure should be completed by excising the Rotter nodes located in the space in between the two pectoralis muscles and the nodes between the axillary vein and the subclavian fossa.

## References

- [1] Becker JC, Assaf C, Vordermark D, Reske SN, Hense J, Dettenborn T, et al. Brief S2k guidelines–Merkel cell carcinoma. *J Dtsch Dermatol Ges* 2013;11(Suppl. 3):29–36, 31–38.
- [2] Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, et al. 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* 2010;63(5):751–61.
- [3] Van Keymeulen A, Mascré G, Youseff KK, Harel I, Michaux C, De Geest N, et al. Epidermal progenitors give rise to Merkel cells during embryonic development and adult homeostasis. *J Cell Biol* 2009;187(1):91–100.
- [4] Hussain SK, Sundquist J, Hemminki K. Incidence trends of squamous cell and rare skin cancers in the Swedish national cancer registry point to calendar year and age-dependent increases. *J Invest Dermatol* 2010;130(5):1323–8.
- [5] Reichgelt BA, Visser O. Epidemiology and survival of Merkel cell carcinoma in the Netherlands. A population-based study of 808 cases in 1993–2007. *Eur J Cancer* 2011;47(4):579–85.
- [6] Girschik J, Thorn K, Beer TW, Heenan PJ, Fritschl L. Merkel cell carcinoma in Western Australia: a population-based study of incidence and survival. *Br J Dermatol* 2011;165(5):1051–7.
- [7] Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. *J Cutan Pathol* 2010;37(1):20–7.
- [8] Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol* 2003;49(5):832–41.
- [9] Lanoy E, Costagliola D, Engels EA. Skin cancers associated with HIV infection and solid-organ transplantation among elderly adults. *Int J Cancer* 2010;126(7):1724–31.
- [10] Lanoy E, Dores GM, Madeleine MM, Toro JR, Fraumeni Jr JF, Engels EA. Epidemiology of nonkeratinocytic skin cancers among persons with AIDS in the United States. *AIDS* 2009;23(3):385–93.
- [11] Koljonen V, Kukko H, Tukiainen E, Bohling T, Sankila R, Pukkala E, et al. Incidence of Merkel cell carcinoma in renal transplant recipients. *Nephrol Dial Transplant* 2009;24(10):3231–5.
- [12] Sihto H, Kukko H, Koljonen V, Sankila R, Bohling T, Joensuu H. Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. *J Natl Cancer Inst* 2009;101(13):938–45.
- [13] Sihto H, Bohling T, Kavola H, Koljonen V, Salmi M, Jalkanen S, et al. Tumor infiltrating immune cells and outcome of Merkel cell carcinoma: a population-based study. *Clin Cancer Res* 2012;18(10):2872–81.
- [14] Kassem A, Technau K, Kurz AK, Pantulu D, Loning M, Kayser G, et al. Merkel cell polyomavirus sequences are frequently detected in nonmelanoma skin cancer of immunosuppressed patients. *Int J Cancer* 2009;125(2):356–61.
- [15] Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008;319(5866):1096–100.
- [16] Becker JC, Houben R, Ugurel S, Trefzer U, Pfohler C, Schrama D. MC polyomavirus is frequently present in Merkel cell carcinoma of European patients. *J Invest Dermatol* 2009;129(1):248–50.

- [17] Paik JY, Hall G, Clarkson A, Lee L, Toon C, Colebatch A, et al. Immunohistochemistry for Merkel cell polyomavirus is highly specific but not sensitive for the diagnosis of Merkel cell carcinoma in the Australian population. *Hum Pathol* 2011;42(10):1385–90.
- [18] Rodig SJ, Cheng J, Wardzala J, DoRosario A, Scanlon JJ, Laga AC, et al. Improved detection suggests all Merkel cell carcinomas harbor Merkel polyomavirus. *J Clin Invest* 2012;122(12):4645–53.
- [19] Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol* 2008;58(3):375–81.
- [20] Kuwamoto S. Recent advances in the biology of Merkel cell carcinoma. *Hum Pathol* 2011;42(8):1063–77.
- [21] Brewer JD, Shanafelt TD, Otley CC, Roenigk RK, Cerhan JR, Kay NE, et al. Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and Merkel cell carcinoma in a SEER population-based study. *J Clin Oncol* 2012;30(8):843–9.
- [22] Tarantola TI, Vallow LA, Halyard MY, Weenig RH, Warschaw KE, Grotz TE, et al. Prognostic factors in Merkel cell carcinoma: analysis of 240 cases. *J Am Acad Dermatol* 2013;68(3):425–32.
- [23] Andea AA, Coit DG, Amin B, Busam KJ. Merkel cell carcinoma: histologic features and prognosis. *Cancer* 2008;113(9):2549–58.
- [24] Sihto H, Joensuu H. Tumor-infiltrating lymphocytes and outcome in Merkel cell carcinoma, a virus-associated cancer. *Oncoimmunology* 2012;1(8):1420–1.
- [25] Izikson L, Helm T, Sroa N, Zeitouni NC. Clinical stage of Merkel cell carcinoma and survival are not associated with Breslow thickness of biopsied tumor. *Dermatol Surg* 2012;38(8):1351–6.
- [26] Bichakjian CK, Lowe L, Lao CD, Sandler HM, Bradford CR, Johnson TM, et al. Merkel cell carcinoma: critical review with guidelines for multidisciplinary management. *Cancer* 2007;110(1):1–12.
- [27] Gupta SG, Wang LC, Penas PF, Gellenthin M, Lee SJ, Nghiem P. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: the Dana–Farber experience and meta-analysis of the literature. *Arch Dermatol* 2006;142(6):685–90.
- [28] Righi A, Asioli S, Caliendo V, Macripo G, Picciotto F, Risio M, et al. An ultrasonography-cytology protocol for the diagnostic management of regional nodes in a subset of patients with Merkel cell carcinoma of the skin. *Br J Dermatol* 2013;168(3):563–70.
- [29] Veness MJ, Perera L, McCourt J, Shannon J, Hughes TM, Morgan GJ, et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. *ANZ J Surg* 2005;75(5):275–81.
- [30] Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol* 2006;142(6):693–700.
- [31] Maubec E. Sentinel node biopsy in the initial evaluation of 87 patients with Merkel cell carcinoma. ASCO; Chicago: 2014
- [32] Bhatia S. Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: Survival analysis of 6,908 cases from the National Cancer Data Base. ASCO; 2014
- [33] Jouary T, Leyral C, Dreno B, Doussau A, Sassolas B, Beylot-Barry M, et al. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. *Ann Oncol* 2012;23(4):1074–80.
- [34] Scelsi D, Mevio N, Bertino G, Occhini A, Brazzelli V, Morbini P, et al. Electrochemotherapy as a new therapeutic strategy in advanced Merkel cell carcinoma of head and neck region. *Radiol Oncol* 2013;47(4):366–9.
- [35] Grandpeix C, Bonvalot S, Petrow P, Fraitag S, Gounod N, Avril MF. Continued complete remission of Merkel cell carcinoma with in-transit metastasis after treatment with isolated limb perfusion regional chemotherapy. *Ann Dermatol Venereol* 2006;133(8–9 Pt 1):700–3.
- [36] Zeitouni NC, Giordano CN, Kane 3rd 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.
- [37] Asgari MM, Sokil MM, Warton EM, Iyer J, Paulson KG, Nghiem P. Effect of host, tumor, diagnostic, and treatment variables on outcomes in a large cohort with Merkel cell carcinoma. *JAMA Dermatol* 2014;150(7):716–23.
- [38] Desch L, Kunstfeld R. Merkel cell carcinoma: chemotherapy and emerging new therapeutic options. *J Skin Cancer* 2013;2013:327150.
- [39] Voog E, Biron P, Martin JP, Blay JY. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. *Cancer* 1999;85(12):2589–95.
- [40] Tai P, Yu E, Assouline A, Lian JD, Joseph K, Miale T, et al. Multimodality management for 145 cases of Merkel cell carcinoma. *Med Oncol* 2010;27(4):1260–6.
- [41] Tai PT, Yu E, Winkquist E, Hammond A, Stitt L, Tonita J, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. *J Clin Oncol* 2000;18(12):2493–9.