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Review

Diagnosis and treatment of Merkel cell carcinoma: European consensus-based interdisciplinary guideline – Update 2022

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Abstract Merkel cell carcinoma (MCC) is a rare skin cancer, accounting for less than 1% of all cutaneous malignancies. It is found predominantly in white populations and risk factors include advanced age, ultraviolet exposure, male sex, immunosuppression, such as AIDS/HIV infection, haematological malignancies or solid organ transplantation, and Merkel cell polyomavirus infection.

MCC is an aggressive tumour with 26% of cases presenting lymph node involvement at diagnosis and 8% with distant metastases. Five-year overall survival rates range between 48% and 63%. Two subsets of MCC have been characterised with distinct molecular pathogenetic pathways: ultraviolet-induced MCC versus virus-positive MCC, which carries a better prognosis. In both subtypes, there are alterations in the retinoblastoma protein and p53 gene structure and function. MCC typically manifests as a red nodule or plaque with fast growth, most commonly on sun exposed areas. Histopathology (small-cell neuroendocrine appearance) and immunohistochemistry (CK20 positivity and TTF-1 negativity) confirm the diagnosis. The current staging systems are the American Joint Committee on Cancer/Union for international Cancer control 8th edition. Baseline whole body imaging is encouraged to rule out regional and distant metastasis.

For localised MCC, first-line treatment is surgical excision with postoperative margin assessment followed by adjuvant radiation therapy (RT). Sentinel lymph node biopsy is recommended in all patients with MCC without clinically detectable lymph nodes or distant metastasis. Adjuvant RT alone, eventually combined with complete lymph nodes dissection is proposed in case of micrometastatic nodal involvement. In case of macroscopic nodal involvement, the standard of care is complete lymph nodes dissection potentially followed by post-operative RT. Immunotherapy with anti-PD-(L)1 antibodies should be offered as first-line systemic treatment in advanced MCC. Chemotherapy can be used when patients fail to respond or are intolerant for anti-PD-(L)1 immunotherapy or clinical trials.

Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer, accounting for less than 1% of all cutaneous malignancies which particularly touches old and/or immunosuppressed patients. Two subsets of MCC have been characterized with distinct molecular pathogenetic pathways based on mutational burden due to ultraviolet (UV) exposure and Merkel cell polyomavirus (MCPyV) infection. Five-year overall survival (OS) rates range between 48% and 63%. A collaboration of multidisciplinary experts from the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organisation of Research and Treatment of Cancer (EORTC) was formed to update the information and recommendations

on MCC European guidelines based on scientific evidence and to provide an expert consensus.

The current staging systems are the American Joint Committee on Cancer (AJCC)/Union for international Cancer control (UICC) 8th edition. Whole body baseline imaging is encouraged to rule out regional and distant metastasis.

For localised MCC, first-line treatment is surgical excision with postoperative margin assessment followed by adjuvant radiation therapy (RT). Sentinel lymph node biopsy (SLNB) is recommended in all patients with MCC and without clinically detectable lymph nodes or distant metastasis. Adjuvant RT alone, eventually combined with complete lymph nodes dissection (CLNDs), is proposed in case of micrometastatic nodal involvement. In case of macroscopic nodal involvement, the standard of care is CLND, potentially followed by post-operative RT. Anti-PD-(L)1 antibodies should be offered as first-line systemic treatment in advanced MCC. Several clinical trials are ongoing with new therapies or new combinations of therapies for advanced MCC, and immunotherapy is also currently under evaluation in the adjuvant and neoadjuvant setting. Patients should be involved in shared decision-making regarding their management and should be provided with best supportive care in optimising symptoms' management and improving quality of life. The frequency of follow-up visits and investigations are based on disease stage, treatment given and individual patient needs.

1. Propose

1.1. Societies in charge

These guidelines were developed on behalf of the EDF. The EADO coordinated the authors' contributions under the leadership of Céleste Lebbé. Paul Lorigan was responsible for the collaboration with the EORTC to ensure the interdisciplinary quality of the guideline. Twenty-six experts from 13 countries, all of whom were delegates of national and/or international medical societies, collaborated in the development of these guidelines.

1.2. Financing of these guidelines

The authors did this work on a voluntary basis and did not receive any honorarium or reimbursements. Guideline task-force group members stated their conflicts of interest in the relevant section.

1.3. Disclaimer

The field of medicine is subject to a continuous evolutionary process. This entails that all statements, especially with regard to diagnostic and therapeutic procedures, can only reflect scientific knowledge at the time of printing these guidelines. The attending physician invoking these guidelines recommendations must take into account scientific progress since the publication of the guidelines. In the selection and dosage of the drugs, attention was paid to compliance with the therapeutic recommendations given. Nevertheless, users are requested to use package inserts and technical information from the manufacturers as a backup, and in case of doubt, consult a specialist. The user remains responsible for all diagnostic and therapeutic applications, drugs and doses.

1.4. Scope

These guidelines were written in order to assist clinicians in the diagnosis, treatment and follow-up of MCC. This update was initiated mainly due to advances in systemic treatments and a new AJCC staging system for patients with MCC, which justify a newer approach to definitions, risk classification and multidisciplinary therapeutic strategies. The use of these guidelines in clinical routine should improve patient care.

1.5. Target population

These guidelines give recommendations for the diagnosis, treatment and follow-up of patients with MCC. They are aimed at attending physicians and the medical nursing staff.

1.6. Objectives and formulation of questions

The guidelines are produced for all clinicians who care for patients with all stages of MCC. Particular emphasis is given to the definition, epidemiology, molecular pathogenesis, clinical and histopathological diagnosis, staging, management, and include a specific section on immunosuppressed patients, supportive care and follow-up. The formulation of clear sections has been made to support clinicians in their practice.

1.7. Audience and period of validity

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 the accepted national guidelines. The

Table 1
Oxford centre for evidence-based medicine 2011: Levels of evidence [5].

Question	Step 1 (Level 1[a])	Step 2 (Level 2[a])	Step 3 (Level 3[a])	Step 4 (Level 4[a])	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances[b]	Local non-random sample[b]	Case-series[b]	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Individual cross-sectional studies with consistently applied reference standard and blinding	Non-consecutive studies or studies without consistently applied reference standards[b]	Case-control studies, or poor or non-independent reference standard[b]	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomised trial[a]	Case-series or case-control studies, or poor quality prognostic cohort study[b]	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomised trials or n-of-1 trials	Randomised trial or observational study with dramatic effect	Non-randomised controlled cohort/ follow-up study[b]	Case-series, case-control studies or historically controlled studies[b]	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomised trials, systematic review of nested case–control studies, nof-1 trial with the patient you are raising the question about or observational study with dramatic effect	Individual randomised trial or (exceptionally) observational study with dramatic effect	Non-randomised controlled cohort/ follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms, the duration of follow-up must be sufficient.)[b]	Case-series, case-control or historically controlled studies[b]	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomised trials or n-of-1 trial	Randomised trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomised trials	Randomised trial	Non -randomised controlled cohort/ follow-up study[b]	Case-series, case-control or historically controlled studies[b]	Mechanism-based reasoning

[a] Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO) because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.
[b] As always, a systematic review is generally better than an individual study.

guidelines published here 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 (malpractice), deviation from them should not necessarily be deemed negligent. These guidelines will require updating approximately every 2 years (expiration date: May 2023) but advances in medical sciences may demand an earlier update.

2. Methods

The European Interdisciplinary Guidelines on MCC are written as a uniform text.

The guidelines published here are an update of the existing European consensus-based (EDF/EADO/EORTC) interdisciplinary guidelines for the management of MCC (former version 2015) [1] and based on other up-to-date guidelines, including the German S2k guidelines (2019) [2] and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for MCC (version 1.2021) [3]. *De novo* literature search was conducted by the authors with Medline search in English language publications with last search date on 23rd April 2021. Search terms included: 'MCC' combined with 'epidemiology, incidence, mortality, survival', 'diagnosis, prognosis, staging, imaging, guidelines, treatment, surgical excision, SLNB, lymph node dissection, radiotherapy, neoadjuvant, adjuvant, systemic, anti-PD-(L)1 antibody, avelumab, pembrolizumab, nivolumab, chemotherapy, clinical trials, immunosuppression, solid organ transplant, haematological malignancy, human immunodeficiency virus, acquired immunodeficiency syndrome, follow-up. The references cited in selected papers were also searched for further relevant

publications. The methodology of these updated guidelines was based on the standards of the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument [4].

Recommendations are based on the level of best quality available evidence and good clinical practice.

The levels of evidence were graded according to the Oxford classification (Table 1) [5].

The grades of recommendation were classified as follows:

A: Strong recommendation. Syntax: 'shall'.
B: Recommendation. Syntax: 'should'.
C: Weak recommendation. Syntax: 'may/can'.
X: Should not be recommended.
0: Recommendation pending. Currently not available or not sufficient evidence to make a recommendation in favour or against.

Expert consensus was provided wherever adequate evidence was not available.

2.1. Consensus building process

The consensus building process was conducted as follows:

In the first round, medical experts who participated in their national guideline development processes were involved in producing an initial draft. The EORTC selected experts from different specialties to contribute to these first drafts.

In a second round, a consensus meeting was held on 13th July 2021 with final outcomes: (1) the approval of the text and (2) a consensus rate of agreement of at least 80% for recommendations provided in structured boxes. Voting for the recommendations included the selection of 'Agree', 'Disagree' or 'Abstain' vote and the possibility of providing comments in case of disagree/abstain. Consensus voting on recommendations and finalisation of the draft was conducted among coauthors through emailing between August 15 th September 2021 and the 18th January 2022. There were 3 recommendations that had a lower than 80% consensus rate: the recommendation for 14, 15 and 16. Comments were received from coauthors, the recommendations were revised, and a second round of voting was conducted for these tree recommendations.

3. Definition (inclusion – exclusion)

MCC is a highly aggressive primary cutaneous carcinoma with epithelial and endocrine features. Its origin is still disputed: Merkel cell precursors (potentially derived from epidermal stem cells or hair follicle stem cells), pre-B cells, pro-B cells or dermal fibroblasts have been suggested [6].

4. Epidemiology – risk factors

MCC is a rare skin cancer, accounting for less than 1% of all cutaneous malignancies [7, 8]. The highest incidence of MCC has been reported in Australia (annual age-standardised incidence rate ranging from 0.82 to 2.5 per 100 000 population) [9–11], followed by New Zealand (0.88–0.96) [12, 13] and the United States (0.66–0.79) [14–16]. Among European countries, incidence rates are fairly similar across the continent: 0.25/100 000 person-years in France [17], 0.31 in Spain [18], 0.3 in Scotland [19] and 0.35 in the Netherlands [20]. However, the incidence rate appears slightly lower in Scandinavian countries: 0.19 in Sweden [21] and 0.12 in Finland [22].

More importantly, the incidence appears to be rising significantly over time in most areas, by as much as a factor 3 to 5 from 1985 to 2013 and could be due to the aging population [23–25], particularly in individuals over 70 years old and non-Hispanic whites [15,26]. This could be due to a true increased incidence related to an increase in risk factors, as well as to upgraded diagnostic immunohistochemical tools and improved registration.

Known risk factors for MCC are the following:

- **Old age**: The median age at diagnosis is reported to be 77 years [14, 27] and the incidence rates increase sharply with age [13,26] with the highest incidence reported in over 85-year-old individuals [14].
- **UV exposure**: The incidence of MCC is strongly associated with lower latitudes and high UV radiation indexes [28, 29] and the tumour occurs preferentially on sun-exposed skin. Moreover, there is a 100-fold increased risk of developing MCC in patients treated with psoralen + UVA [30].
- **White skin type**: MCC is very rare in dark-skinned patients, whether they be Black, Hispanic or Asian [13,15,31]. Incidence is about 8 times higher in white than in non-Hispanic Blacks [26].
- **Male sex**: The incidence is over 2.5 times higher in men than women in virtually all reported studies.
- **Immunosuppression**: Approximately 6–12% of all patients with MCC are immunosuppressed [32]. There is a significant excess risk of MCC from 3 to 90 fold in patients with haematological malignancies [33], in particular chronic lymphocytic leukemia (CLL, [34,35], patients with HIV/AIDS [36,37]) and in solid organ transplant recipients (SOTRs) [38,39]. There is some evidence that there is a stronger association with MCPyV in non-immunosuppressed patients [40]. Epidemiology and outcome of immunosuppression-related MCC are discussed in a dedicated section below.
- **MCPyV infection**: The MCPyV is a ubiquitous virus. It is clonally integrated and is the etiological agent responsible for up to 80% of MCC in Europe [41]. Virus-positive MCC may carry a better prognosis than UV-induced MCC [42,43]. More details on MCC molecular pathogenesis and MCPyV infection are described in the section below.

MCC is an aggressive tumour [20,23]. Five-year relative survival rates range between 48% and 63%.

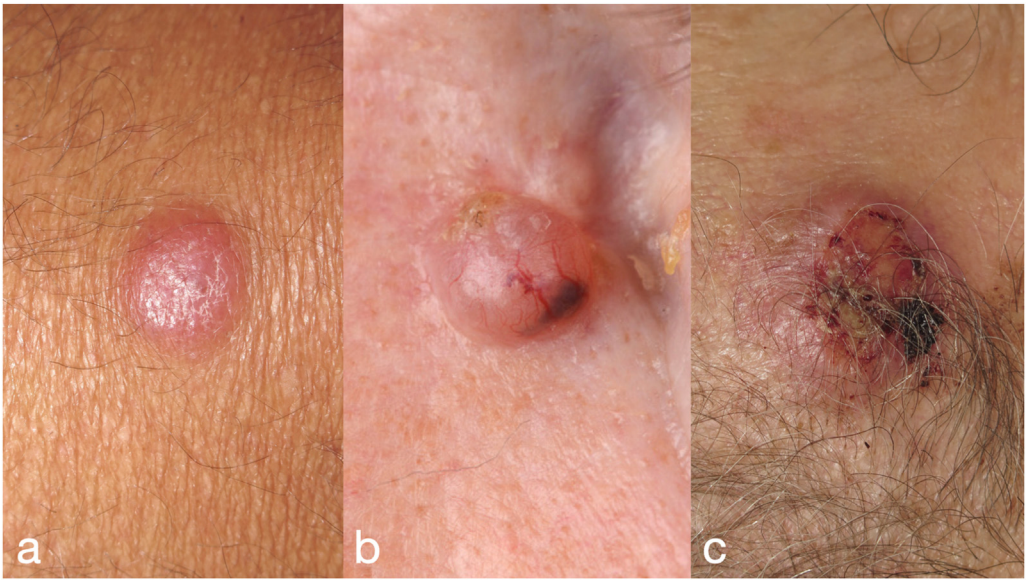

Fig. 1. Clinical manifestations of MCC: (a) a slightly elevated red plaque on the thigh of a 68 year-old man. (b) A well-demarcated nodule on the nose of a 70 year-old woman mimicking a basal cell carcinoma, with clinically visible linear branching vessels and an area of pigmentation. (c) A poorly demarcated amelanotic nodule with central ulceration on the temporal area of a 75 year-old man. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article). MCC, Merkel cell carcinoma.

Better prognosis has been reported for women and in younger ages [9,23,44].

5. Molecular pathogenesis

The main risk factors for developing MCC – chronic UV-exposure and immunosuppression – point to its molecular pathogenesis. Indeed, one subset of MCCs (virus negative) – prevailing in white patients living in areas with high UV exposure – is characterised by a high tumour mutational burden with a strong UV-signature. Retinoblastoma protein (RB) and p53 are among the most significantly mutated genes. However, the other major MCC subgroup – more common in the Northern hemisphere – has a very low tumour mutational burden and instead harbours clonal integration of the MCPyV (virus positive) [40]. Notably, MCPyV-encoded early transforming genes also interfere with RB and p53. Indeed, viral integration leads to the expression of a truncated MCPyV large T (LT) antigen that contains the LXCXE motif, capable of binding to RB protein and inactivating its tumour suppression function [45]. LT plays a major role in tumour maintenance and cell growth. Virus-positive MCC tumours also express MCPyV small T antigen (sT) which, upon binding Fbxw7 (F-Box And WD Repeat Domain Containing 7, a critical tumour suppressor and one of the most commonly deregulated ubiquitin-proteasome system proteins in human cancer), leads to the accumulation of oncogenic proteins such as cyclin-E, c-Jun, mTOR and truncated LT-Ag [46]. sT is considered the main transforming driver gene with a major role in metastasis [6,47,48].

Because of the presence of either multiple neoepitopes or viral proteins, both UV-associated and viral carcinogenesis result in highly immunogenic tumours, which only become clinically evident when they either acquire immune escape mechanisms or cannot be controlled in immunocompromised patients. While there are several phenotypic similarities between both forms of MCC, there are increasing reports indicating histopathologic differences [49]. The cell of origin of MCC remains unknown; suggested candidates include pro/pre-B cells and epidermal stem cells. However, there are increasing lines of evidence pointing towards interfollicular and hair bulge basal keratinocytes for UV- and viral-associated MCC, respectively [6].

6. Diagnostic approach

6.1. Clinical diagnosis

6.1.1. Clinical presentation and dermatoscopic features

MCC typically manifests as a firm, asymptomatic, non-tender flesh-coloured or red nodule or plaque (Fig. 1). The lesion often rapidly increases in size over a period of weeks or months. Ulceration and bleeding are infrequent at first presentation but they might occur at an advanced stage [1,31,50]. The most frequent anatomic sites of MCC are the sun-exposed areas of head and neck (29–43.9%) and the extremities (36.9–45%), whereas less than 5–10% of MCCs develop on partially sun-protected areas (abdomen, thighs and hair-bearing scalp) or highly sun-protected areas (buttocks). Extracutaneous sites such as vulva, vagina, oral mucosa

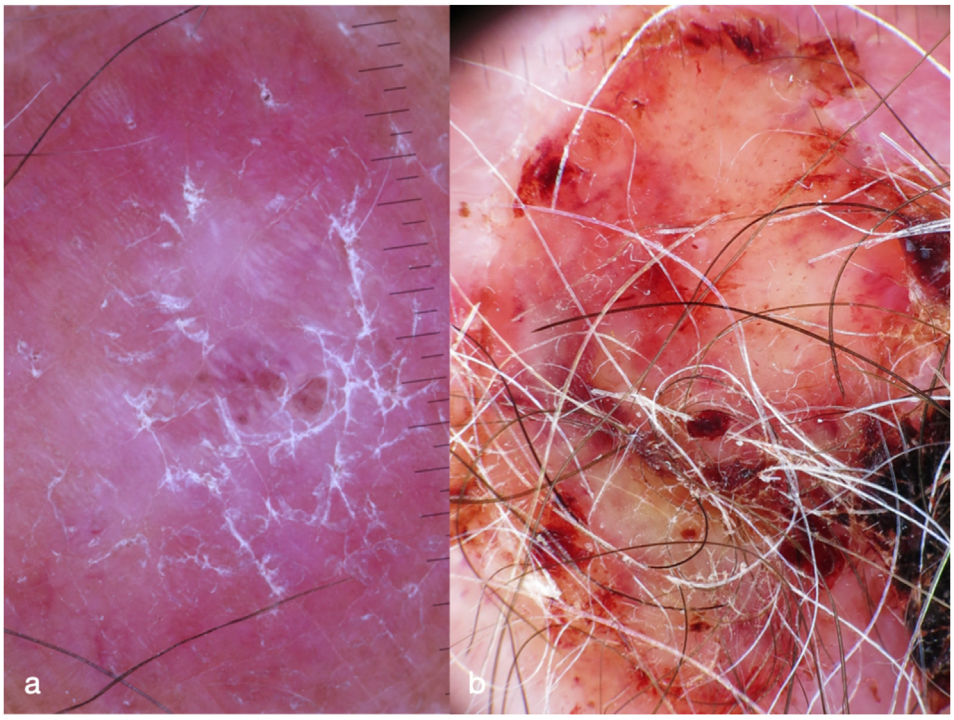

Fig. 2. Dermatoscopic images of MCC: (a) pink structureless colour combined with white structureless areas and white shiny lines. (b) Red and white structureless areas, multiple ulcerations, dotted and short linear vessels. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article). MCC, Merkel cell carcinoma.

[51], parotid gland, submandibular gland or nasal cavity are very rarely involved (around 0.5%) [31,50,52,53]. In some cases, the primary tumour (pT) site is unknown and the disease presents metastatic disease to lymph nodes or distant organs (0.8–14%) [31]. A few cases of intraepidermal MCC manifesting a slightly scaly erythematous patch or violaceous nodule have also been described in the literature [54,55]. The pT can vary in size. One series reported that 21.2% measured less than 1 cm in the largest diameter, 43.3% between 1 and 2 cm and 35.3% more than 2 cm [50].

MCC is frequently misdiagnosed initially, contributing to diagnostic delay; MCC may be confused with an inflammatory lesion such as acne or other folliculitis or with a benign tumour such as epidermal cyst, lipoma, dermatofibroma, fibroma and angioma. In many other cases, MCC is misinterpreted as another malignant tumour, mainly basal or squamous cell carcinoma and less frequently lymphoma, metastatic carcinoma, nodular or amelanotic melanoma or sarcoma, with low impact on prognosis since these tumours are usually rapidly biopsied or removed and the correct diagnosis is established. A clinically useful recommendation is that any nodule with non-specific morphology, lack of tenderness and fast growing should be biopsied rather than monitored.

The dermatoscopy of MCC reveals a predominant red colour corresponding either to numerous vessels or generalised erythema (Fig. 2). Milky-red or pink structureless colour is an additional dermatoscopic characteristic of MCC [56,57]. It might be seen either as a pink background or as smaller roundish areas (milky red areas or globules or clods). Several morphologic types of vessels may be present, including dotted, glomerular, arborising and linear irregular vessels [56,57]. Usually, more than one morphologic type of vessel co-exist, resulting in the so-called polymorphous vascular pattern, although lesions with monomorphous vessels have also been described. White areas are also frequently described (Fig. 2) [58].

Overall, the dermatoscopic pattern of MCC cannot be considered as specific since it overlaps with other non-pigmented cutaneous tumours such as poorly differentiated squamous cell carcinoma and amelanotic melanoma. However, the detection of polymorphous vessels and/or milky red colour raises the suspicion of malignancy since both are exceedingly rare in benign tumours. This justifies the diagnostic value of dermatoscopy from a clinical perspective.

6.2. Histological diagnosis: characteristics and differential diagnosis, pathology report

6.2.1. Characteristics and differential diagnosis

Though histopathologic assessment is essential to diagnose and further differentiate this clinically non-specific tumour. Depending on size and location, tissue sampling in suspicious lesions should be accomplished by punch, incisional or excisional biopsy [59,60]. MCC generally consists of a solid nodular lesion in the dermis

Table 2
Immunohistochemistry profile of MCC (adapted from Becker *et al.* [2]).

	MCC	Lymphoma	Melanoma	SCLC[a]
CK 20	+	−	−	−
Neuron-specific-enolase	+[#]	−	−	+/−
Chromogranin A (CgA)	+/−	−	−	+/−
Huntingtin interacting protein 1 (HIP1)	+	+/−	−	−
Vimentin	−	+	+	−
Melan-A/MART-1	−	−	+	−
Leukocyte common Antigen (LCA)	−	+	−	−
Thyroid transcription factor-1 (TTF-1)	−	−	−	+

[a] SCLC small cell lung cancer.

and subcutis. On haematoxylin eosin stains, the tumour typically exhibits sheets and nests of uniform small round blue undifferentiated cells with scant cytoplasm, a 'salt and pepper' chromatin pattern, large lobulated nucleoli, high mitotic rate and occasional necrotic cells. A small cell variant displays overlapping features with cutaneous lymphoma. Important differential diagnoses include melanoma, Ewing sarcoma, neuroblastoma, leukaemia cutis or poorly differentiated carcinoma metastatic to the skin (e.g. small cell lung cancer). Superficial or in-situ types may be mistaken for other intraepithelial malignancies.

Given the broad differential diagnosis, immunohistochemistry is mandatory to confirm the diagnosis and to distinguish MCC from potential histopathologic imitators (Table 2). MCC is characterised by the expression of both epithelial markers such as cytokeratin 20 with a characteristic paranuclear dot-like staining AE1/AE3 and CAM5.2, and neuro-endocrine markers such as neuron-specific enolase (very sensitive but expressed by other neuroendocrine tumours), synaptophysin, CD56 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: thyroid transcription factor1 (TTF-1) important for differential diagnosis with small-cell lung cancer particularly when the primary is unknown, S-100 and HMB-45 expressed by melanoma, leukocyte common antigen and other lymphocyte markers expressed by lymphomas, CK7 and carcinoembryonic antigen expressed by sweat gland carcinomas (see Table 2). However, an aberrant profile with positive CK7 and TTF-1 expression can occur in CK20- and MCPyV-negative cases [61]; in these cases, a lower expression of neurofilament and AT-rich sequence-binding protein SATB2 can also be observed [62].

6.2.2. Pathology report

In clinical practice, a typical histology complemented with positive CK-20 and negative TTF-1 immunostaining is usually considered sufficient for the diagnosis of MCC. Depending on the individual histomorphological features and in special variants (e.g. CK-20 negative tumours), further immunohistochemical analysis should be performed to confirm diagnosis and differentiate MCC from potential mimics. Apart from tumour-thickness, infiltrative growth pattern and lymphovascular invasion can also be documented as potential features of more aggressive tumour behaviour.

7. Tumour staging – prognosis and risk classification – staging work up

7.1. Prognostic classification (Table S1)

7.1.1. AJCC/UICC 8 staging [63]

AJCC/UICC 8 classification are recommended for staging. It is based on an updated analysis of 9387 cases of MCC from the National Cancer Data Base. In these classifications, there are no differences between the pathological pT assessment and clinical pT assessment (Table 3).

For the N categories, the clinical stage where lymph node involvement is identified by clinical **or** radiological evaluation, and the pathological stage where lymph node involvement is histologically proven either by SLNB or lymphadenectomy or fine biopsy are distinguished (see Table 3).

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 clinical/radiological and pathological assessment of metastasis are also distinguished (Table 3).

The stage groups with corresponding prognostic values are summarised in Table 4.

7.1.2. Clinical features (demography, pT)

MCC has a high rate of local recurrence, regional recurrence and distant metastasis. Clinical factors related to an adverse outcome are older age, male sex, location in head and neck or trunk compared to upper limbs, size of the pT and the presence of immunosuppression, which is described in a dedicated section below [64–67]. The maximum tumour diameter, which is included in AJCC8 staging, is also an important clinical predictor. In the 2021 NCCN guidelines 2021, unfavourable prognostic factors include tumour size >2 cm, chronic immunosuppression and head/neck primary site (Table 5) [3].

Tumour size is strongly correlated with lymph node metastasis which is, in turn, a very strong prognostic indicator. The risk of regional nodal involvement (micro or macroscopic) increased from 14% for 0.5-cm diameter tumours to 25% for 1.7-cm (median-sized) tumours and to more than 36% for tumours 6 cm or larger [68].

Table 3
TNM classification and staging (8th edition) for Merkel cell carcinoma of the skin *(Union for International Cancer Control (UICC). TNM Classification of malignant tumours, Eighth edition. Merkel cell carcinoma*. Oxford: WILEY Blackwell; 2017.)/AJCC 8th edition 2017 (AJCC Cancer Staging Manual. Eighth Edition. In: Amin MB *et al*., 2017).

Clinical stage groups (cTNM)[a]				Pathological stage groups (pTNM)[b]			
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
I	T1	N0	M0	I	T1	N0	M0
IIA	T2, T3	N0	M0	IIA	T2, T3	N0	M0
IIB	T4	N0	M0	IIB	T4	N0	M0
III	Any T	N1-3	M0	IIIA	T0	N1b	M0
					T1-T4	N1a, N1a (sn)	M0
				IIIB	T1-T4	N1b, N2, N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

c/pT – Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	2 cm or less in greatest dimension
T2	More than 2 cm but not more than 5 cm in greatest dimension
T3	More than 5 cm in greatest dimension
T4	Tumour invades deep extra dermal structures, i.e. cartilage, skeletal muscle, fascia or bone
cN- Regional lymph nodes	
NX	Regional lymph nodes cannot clinically be assessed
N0	No clinically or radiologically detected regional lymph node metastasis
N1	Clinically or radiologically detected regional lymph node metastasis
N2	In-transit metastasis[c] without lymph node metastasis
N3	In-transit metastasis[c] with lymph node metastasis
pN – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a (sn)	Clinically occult (microscopic) metastasis detected on sentinel node biopsy
N1a	Clinically occult (microscopic) metastasis detected on node dissection
N1b	Clinically and/or radiologically detected (macroscopic) regional lymph node metastasis, microscopically confirmed
N2	In-transit metastasis[c] without lymph node metastasis
N3	In-transit metastasis[c] with lymph node metastasis
cM – Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Skin, subcutaneous tissues or non-regional lymph node(s)
M1b	Lung
M1c	Other site(s)
pM- Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis microscopically confirmed
M1a	Skin, subcutaneous tissues or non-regional lymph node(s), microscopically confirmed
M1b	Lung, microscopically confirmed
M1c	Other site(s), microscopically confirmed

c: clinical, p: pathological.
[a] Clinical staging is defined by microstaging the primary Merkel cell carcinoma (MCC) with clinical and/or radiological evaluation for metastasis.
[b] Pathological staging is defined by microstaging the primary MCC and pathological nodal evaluation of the regional lymph node basin with sentinel lymph node biopsy or complete lymphadenectomy or pathologic confirmation of distant metastasis.
[c] In transit metastasis: a discontinuous tumour distinct from the primary lesion and located between the primary lesion and the draining regional lymph nodes or distal to the primary lesion.

7.1.3. Histological prognostic markers of the pTs

Although several prognostic markers have been studied in MCC, to date there is no convincing demonstration of any histological or immunohistochemical prognostic marker. However, several prognostic markers have been studied and some deserve further evaluation:

Increasing pT thickness was significantly associated with poorer disease-free survival (69% 5-year disease-free survival in tumours $\leq$10 mm thick compared to 18% for patients with tumours >10 mm thick, $p = 0.002$) and disease-specific survival (97% 5-year survival in tumours $\leq$10 mm thick compared to 74%

Table 4
AJCC 8th edition, 2017 clinical and pathological staging for Merkel cell carcinoma [63] with the prognosis of stage groups (adapted from Harms *et al.*, 2016 [27]).

Stage	TNM	5-year OS (%)
0	Tis N0 M0	
cI	T1 N0 M0	45
pI	T1 N0 M0	62.8
cIIA	T2/T3 N0 M0	30.9
pIIA	T2/T3 N0 M0	54.6
cIIB	T4 N0 M0	27.3
pIIB	T4 N0 M0	34.8
cIII	AnyT N1-3 M0	26.8
pIII		39.7
IIIA	AnyT N1a (sn) or N1a M0	40.3
	T0 N1b M0	26.8
IIIB	T1-4 N1b-3 M0	
cIV	AnyT AnyN M1	
pIV	AnyT AnyN M1	13.5

c: clinical, p: pathological, T0: no primary tumour, Tis: in situ, OS: overall survival.
Other abbreviations are detailed in the text.

for patients with tumours ≥10 mm thick, p = 0.006) [69,70]. However, it is well known from clinical practice that even a superficial MCC can metastasize, and in the AJCC classification, tumour depth is not regarded as a high-risk feature [27].

- Lymphovascular invasion is also a prognostic factor for poor outcome [71]. Although it is not included in the AJCC staging system, it is included in the 2021 NCCN guidelines as a baseline risk factor [3].
- Tumour infiltrating immune cells have been suggested as having a positive prognostic value although their presence deserves further evaluation [70,72,73].
- Deep tumour invasion of fascia, muscle, cartilage or bone defines T4 in AJCC8 [63].
- The prognostic value of MCPyV status has been debated in the past years. Several small studies have shown that MCPyV-negative tumours have a worse prognosis and two recent studies showed that MCPyV-positive tumours are associated with a more favourable prognosis. A Swedish study found an increased risk of death for men with a virus-negative MCC (HR 3.6 [64]). A second study showed that MCPyV-positive tumours display longer disease-specific and recurrence-free survival in both univariate and multivariate analysis [74]. Therefore, the diagnostic value of MCPyV detection using either molecular or immunohistochemical techniques is currently under investigation. However, there is as yet no routine method available to accurately distinguish between both types. In particular, immune-staining for MCPyV large T antigen cannot reliably discriminate virus-positive from the more aggressive virus-negative MCC [40,53,59].

Table 5
Clinical and histological features associated with high-risk MCC versus low-risk MCC.

Risk of recurrence	Clinical features
High-risk MCC: any of the criteria is sufficient to classify as high-risk tumour	- Tumour size ≥2 cm, - Chronic immunosuppression - Head/neck primary site - Pathologically positive lymph nodes or no correct assessment of the lymph node status - Lymphovascular invasion

The favourable prognostic values of lower mast cell counts, reduced vascular density, absence of p53 and p63 and phosphorylated CRE-binding protein P-CREB deserve also further evaluation [70,72,73,75].

7.1.4. Regional and distant involvement

The main prognostic factors are related to regional and distant involvement. The localised MCC tumours carry the best prognosis (50.6% 5-year OS rate) [27]. In regional and distant disease, 5-year OS was estimated to be 35.4% and 13.5%, respectively, from a National Cancer Database study of 2856 cases [27]. Nodal MCC with unknown pT have a higher 5-year OS of 42.2% [27]. Remarkably, a recent study showed substantially higher OS rates than predicted in the AJCC8 study: 5-year OS of 72.6% for local disease and 62.7% for nodal disease [76].

Lymph node status is the most important independent prognostic predictor including occult microscopic nodal involvement which occurs in around one-third of patients [77–79]. SLNB is therefore considered as an important procedure in MCC management as it allows the detection of nodal micro-metastasis (metastatic involvement of clinically or radiologically negative nodes) [59]. Tumour burden in the regional nodal basin was predictive of survival, with 40% and 27% 5-year OS for clinically occult and clinically detected nodal disease, respectively [27]. Moreover, the number of involved nodes proved to be strongly predictive of 5-year relative survival: 0 nodes, 76%; 1 node, 50%; 2 nodes, 47%; 3–5 nodes, 42% and ≥6 nodes, 24% [68]. This was also confirmed in a recently published large study showing that each additional metastatic node conferred an increased risk of death, even after adjusting for a variety of tumour- and patient-associated factors [80]. This effect was found to be most pronounced for the first 3 metastatic LNs, with an added 17% risk of death for each metastasis-positive LN. Beyond 3 LNs, the risk of death continued to increase at a reduced rate of 3% per each additional LN [80].

Patterns for first-site metastasis have reported regional lymph nodes in 87% and distant metastasis in 13% of patients (most commonly abdominal viscera and distant lymph nodes) [81]. In a study among elderly patients with MCC, liver metastasis proved to be an independent unfavourable prognostic factor [82].

Clinical and histological features associated with high-risk MCC (versus low risk MCC) are summarised in Table 5 below.

7.2. Preoperative/baseline staging work up

Initial staging includes full body skin examination with a clinical examination of all main nodal basins with particular consideration to the locoregional nodes.

MCC is clinically localised in 65% of cases and presents with nodal and distant metastasis in 26% and 8% of patients, respectively [27,31]. Imaging is encouraged to rule out regional and distant metastasis. Baseline cross-sectional imaging such as CT, PET-CT or magnetic resonance imaging (MRI)) including at least the chest-abdomen-pelvis and draining node bed upstaged 13.2% of patients with MCC and with non-palpable regional lymph nodes (8.9% to radiographic nodal involvement and 4.3% to distant metastatic involvement). PET-CT appears more sensitive than CT alone. In a recent study, 16.8% of patients who underwent PET-CT imaging had their disease up-staged compared to 6.9% of those who received CT scans only ($p = 0.0006$) [83].

The value of somatostatin receptor (SSTR) PET in the diagnosis of MCC metastatic spread cannot be definitively assessed yet. A clear advantage over 18 F FDG PET has not yet been demonstrated [84]. However, a potential additional benefit of SSTR PET lies in a better detection of brain metastases as well as the assessment of the possibility of radionuclide therapy with SSTR-specific radiotherapeutics (i.e. peptide receptor radionuclide therapy, yPRRT) [85,86].

Brain metastases occur only in 5% of patients with initial metastatic disease [87]. Therefore, brain MRI is not indicated in asymptomatic stage I-II patients.

Recommendation 1	
Preoperative staging procedure	Evidence-based recommendation
Level of recommendation B	Clinical examination: Full body skin examination with the clinical examination of all main lymph node basins Imaging: - 8–14 megaherz Ultrasound of regional nodal basin should be performed - Whole body imaging should be performed. If available, FDG PET/CT whole-body is preferable over contrast-enhanced CT-scan of neck/thorax/abdomen/pelvis [83] - Routine brain imaging is not recommended in asymptomatic stage I-II patients
Level of evidence: 3-4	Guidelines adaptation [3] Retrospective small sample study [83]
Strength of consensus: 93%	

The most reliable staging tool to identify subclinical nodal disease is SLNB. Thus, SLNB is recommended in all patients with MCC without clinically detectable lymph nodes, when feasible, if baseline imaging is negative [3,83]. Before SLNB, regional lymph node ultrasonography (US) is recommended. In case of clinical/radiological suspicion of regional lymph nodes involvement, fine-needle aspiration or core biopsy is recommended.

Patients seronegative for MCPyV oncoprotein (ST-antigen) antibodies may have a higher risk of recurrence, while in seropositive patients, recurrence may be associated with a rising titre [3,59,88–90]. However, MCPyV oncoprotein antibody detection by ELISA (coated with GST-TAg) at diagnosis and during follow-up) is not a standard of care but should be further evaluated in prospective validation studies.

8. Management

8.1. Surgical therapy of the pT (Table S2)

Surgical excision is the first-line treatment for MCC; the goal is to achieve the removal of the primary lesion with histologically clear margins. This outcome, however, should be balanced with the morbidity of the surgical procedure and with a possible delay in adjuvant RT to the pT site, if a skin graft or a flap is needed for surgical closure. The optimal surgical margins have not been well defined yet since no randomised clinical trial has attempted to address this issue and most studies do not separately consider whether patients subsequently received adjuvant RT. Also, studies frequently include node negative and loco-regional disease in the same data analysis.

Two large retrospective studies (>6000 patients) reported significant differences in survival outcome measures between patients treated with narrow margins and those treated with wide surgical margins [91,92]. Andruska *et al.* [92] recently showed that clinical margins >1.0 cm improve OS (HR, 0.88; 95% CI, 0.81–0.95; $P < .001$) compared with margins of 1.0 cm or smaller, regardless of tumour subsite, whereas no difference in OS was observed between margins of 1.1 cm–2.0 cm and margins larger than 2.0 cm (HR, 0.99; 95% CI, 0.83–1.19; P = .79). This study was underpowered to evaluate the benefit of margins larger than 1.0 cm in the subgroup of patients with negative SNLB. Receiving adjuvant RT improved OS in patients in all excision margin groups [92]. According to Yan *et al.* [91], large excision margins do not significantly impact on survival rates in patients aged >75 years or with stage III MCC.

These results above, albeit based on a moderate level of evidence, support complete excision with clinical safety margins of 1 cm followed by adjuvant

Recommendation 2	
Treatment of primary MCC tumour	Evidence-based recommendation
Grade of recommendation B	• Complete excision of the tumour with clinical safety margins of 1 cm followed by post-operative adjuvant RT on the tumour bed is the preferred treatment
Level of evidence: 3	*Retrospective large sample studies* [91,92,98–103]
Strength of consensus: 92%	

Recommendation 3	
Sentinel lymph node biopsy	Evidence-based recommendation
Grade of recommendation B	Sentinel lymph node biopsy should be offered in the absence of clinical or imaging evidence for nodal or distant metastases.
Level of evidence: 2-3	Prospective large simple study [104] Retrospective large sample studies [105,106,109] Systemic review [110] Strength of consensus: 96%

RT as the preferred treatment. If no adjuvant RT is possible, safety margins of up to 2 cm should be performed. Excision of the tumour with clinical margins <1 cm followed by adjuvant RT can be acceptable in situations when obtaining wide surgical resection margins may be difficult or impossible due to patient or tumour-related factors or would postpone RT.

Comparison of wide local excision and Mohs micrographic surgery yielded similar OS and cancer-specific survival rates for the treatment of pTs [93–97]. Mohs micrographic surgery can be considered a safe and effective alternative to standard wide local excision, especially for cosmetically and functionally sensitive areas as the head and neck, allowing a tissue sparing approach.

8.2. Sentinel lymph node biopsy, clinically-identified lymph node metastases and indication to subsequent complete lymph node dissection

In patients with MCC, SLNB has shown a rate of microscopic metastases between 24% and 48% in the different available studies (Table S3). This supports the recommendation to use SLNB as routine staging in patients with primary clinical stage I/II MCC.

Results from the SEER Database show a better disease-specific survival in patients with a negative SLNB versus a positive SLNB (84.5% versus 64.6%) [105]. Undergoing a SLNB was also borderline significantly associated with an improved survival [105]; however, selection bias of younger, less frail patients is a likely cause for this observation due to the retrospective design of the study and lack of therapeutic effect of SLNB for other cancers [105].

Furthermore, when considering the potential therapeutic advantage of having a SLNB, it's likely, that patients who had a positive SLNB were selected for further adjuvant RT and that this might confer a benefit [104,105].

In summary, positive SLNB has been associated with decreased overall and disease-specific survival in large database analyses and is thus recognised as a prognostic factor for poor outcome [102–105]. These findings were also observed in shorter cases series, whilst other reports failed to find a significant relationship between SLNB status and recurrence or survival [106,107] (Table S3).

In view of these results, SLNB should be offered as a staging procedure for patients with MCC without evidence of nodal metastases clinically or by imaging (stage I-II). Patient's age, performance status and anatomic location of the pT must be considered carefully by the tumour board (Table S3, recommendation 3).

8.3. CLND

No prospective studies have analysed the outcome of completion lymph node dissection in patients with MCC and nodal involvement, either microscopically or clinically detected. In a monocentric prospective study enrolling 163 patients, there was no significant difference in 5-year disease specific survival, disease-free survival and nodal recurrence-free survival between patients with microscopic nodal disease detected by SLNB undergoing CLND versus RT [111] (Table S4). However, patients with non-sentinel lymph node (SLN) involvement showed a significantly worse disease-specific and disease-free survival compared to patients without non-SLN metastases after CLND [111].

A retrospective analysis of the National Cancer Database on 447 MCC with positive SNLB did not find a significant improved OS after CLND compared to observation (HR 0.62, CI 0.33–1.16), but the study was clearly underpowered. In the same study, adjuvant RT increased significantly survival (HR 0.48, CI 0.28–0.82). Moreover, both observation (HR 3.54, CI 1.36–9.18) and CLND alone (HR 2.54, CI 1.03–6.27) were associated with worse OS compared to CLND and adjuvant RT [112]. A retrospective case series based on only 71 SLNB-positive MCC did not find significant improvement of recurrence-free survival, overall and disease-

specific survival with respect to CLND and RT alone [113] (Table S4). These results, albeit based on a moderate-to-low level of evidence, along with the high risk of lymphatic spread of MCC support the recommendation of RT alone or eventually combined with CLND in patients with microscopic metastasis to the sentinel node (recommendation 4a).

Recommendation 4a	
Management of microscopic nodal metastases	Consensus-based recommendation
GCP	In patients with microscopic nodal disease (positive SLNB), adjuvant RT alone (50–55 Gy see RT section) or eventually combined with CLND is preferred over CLND alone, which could constitute an option in case adjuvant RT is not possible
Strength of consensus: 81%	

Recommendation 4 b	
Management of nodal metastases identified clinically or by imaging	Consensus-based recommendation
GCP	Therapeutic lymph node dissection should be performed in patients with nodal metastases identified clinically or by imaging. Strength of consensus: 92%

No studies specifically analysed the outcomes of CLND in patients with MCC and with nodal disease detected either clinically or by imaging tests. However, the recommendation of offering CLND to any patient with macroscopic nodal metastasis is supported by a broad consensus (Table S4, recommendation 4 b).

8.4. Radiotherapy: primary and regional disease (Table S5, S6)

As MCC cells are highly sensitive to radiation [114], RT is a major therapeutic tool at diverse disease stages.

Since MCC is a rare disease, no data are available from randomised controlled studies. Several large registry studies and retrospective case series strongly suggest that, after surgical excision, **adjuvant RT to the pT bed** improves local and regional relapse-free survival [98,115], disease-free survival [22,109,116,117], distant metastasis-free survival and OS [109,118] when compared to surgery alone without adjuvant **RT**. RT effects could particularly impact on large tumours [119] and MCC of the head and neck [120]. Adjuvant RT should be performed within the first 8 weeks following surgery [98].

Omitting adjuvant RT was recently suggested for small (<2 cm, stage I), margin-free tumours in patients with the following features: pathologically negative lymph nodes and no risk factors, such as lymphatic-vascular invasion, pT in the head and neck area [121], absence of a correct pathological assessment of the lymph node status, immunosuppression and lymphoproliferative diseases. As the study is small sized and all the unfavourable factors were not precisely defined, decision-making on this option needs to be shared by the multidisciplinary team [122] (Table S5).

Due to the introduction of SLNB as the standard approach in clinically node-negative patients, an underpowered randomised trial was prematurely closed. It did, however, demonstrate that **prophylactic RT to the regional nodes** was associated with increased regional relapse-free survival but not an improved OS [123]. As stated in Recommendation 4a, in patients with microscopic nodal disease (positive SLNB), 50–55 Gy adjuvant RT is the preferred choice.

No differences in OS emerged whether patients with nodal metastases (stage III) received adjuvant RT or not [118]. In some series, adjuvant RT significantly improved regional control [124,125] and disease-free or -specific survival [106,116]. Definitive conclusions are hard to reach as data on the irradiated volumes were sometimes lacking and patients were enrolled at different stages of disease and with clinical and pathological nodal involvement.

In patients not eligible to SLNB in the head and neck region, radical RT can be suggested (SLNB is not performed and the only treatment is RT with a radical and curative intent.) [3].

In macroscopic stage III disease, adjuvant RT is generally recommended after regional CLND, particularly in cases of multiple node involvement and/or extracapsular extension. In a retrospective study of stage III patients, **lymph node irradiation alone to positive regional lymph nodes** conferred an excellent regional control rate that was comparable to CLND for both microscopic and palpable lymph node disease, without improving OS [126] (Table S6).

Data from a large registry study suggested doses from 40 to fewer than 50 Gy adjuvant RT are adequate in stage I–III MCC of the trunk or extremities. Compared with the group who received 50–55 Gy, OS was equivalent in groups receiving 40 to <50 Gy or >55–70 Gy. It was worse in the group that received >30 to <40 Gy [127]. Data also showed that optimal adjuvant RT doses are 50–55 Gy in head and neck MCC [128]. Regardless of the tumour site, higher doses are required when margins are positive, up to 60 and 66 Gy for microscopically and macroscopically positive margins, respectively [3]. Fractionation is conventional, with 2 Gy

Recommendations 5	
Adjuvant radiotherapy on the primary tumour bed	Evidence-based recommendation
Grade of recommendation B	Adjuvant RT (doses: see text) to the primary tumour bed should be performed within 8 weeks of surgical excision.
Level of evidence 3	Retrospective large sample studies [109,115–118] [22] Strength of consensus: 93%

Recommendation 6	
Adjuvant radiotherapy after lymphadenectomy for clinically involved nodal basin	Consensus-based recommendation
GCP	Adjuvant RT (doses: see text) should be discussed in a multidisciplinary board after complete lymph node dissection for clinical or radiological nodal disease Strength of consensus: 93%

Recommendation 7	
Palliative radiation therapy for primary tumours or clinically involved lymph node basin disease	Evidence-based recommendation
Grade of recommendation C	Palliative radiotherapy alone can be suggested in frail patients to treat primary tumours and/or nodal involvement when surgery is not feasible
Level of evidence 3-4	Retrospective small sample studies [129,130] Strength of consensus: 85%

single dose. A bolus should be considered to ensure an adequate skin dose [3].

For frail patients and/or tumours in difficult areas where surgery is not feasible, RT to the pT ± lymph nodes seems to be a valid option which, however, should be discussed in a multidisciplinary team. When performance status is good, RT total dose should be 60–66 Gy, with 2Gy single dose [3]. Moderate hypofractionated schedules may be taken into account, mainly in elderly patients, as they reduce their hospital attendances for RT [129,130].

- Treatment of locally advanced and metastatic disease & Adjuvant, neoadjuvant systemic therapy (state of the art, trials)

8.5. Treatment of locally advanced and metastatic MCC

In metastatic disease, the historical 5-year survival is at 13.5% [27]. Until 2017, recommendations for systemic therapy of advanced MCC were based on data usually obtained by single-centre and oligo-centre, mostly retrospective analyses as well as on data inferred from other tumour entities such as small-cell lung carcinomas and personal experience.

Based on an increased understanding of the biology of MCC in recent years and the development of immunotherapy with check-point inhibitors in other tumour types, prospective phase I/II immunotherapy trials have demonstrated encouraging results. While there are no randomised clinical trials available to guide the recommendations for advanced MCC treatment on a high level of evidence, the superiority in the mid-term outcomes of these immunotherapy phase I/II trials compared to historic data on cytotoxic therapies makes such a study design ethically difficult and out of date. However, as combination therapies will likely enter the field of MCC, participation in clinical trials, if available, should be encouraged.

Multidisciplinary tumour board consultations (dermatologist, surgeon and radiotherapist) for patients with advanced MCC are needed to consider all options for the management of advanced MCC cases.

8.5.1. Immunotherapy

8.5.1.1. Rationale. There are clinical and scientific data available implying that MCC is an immunosensitive solid malignancy. MCC often develops in immunodeficient patients, and spontaneous regression of pTs has been observed occasionally. Both MCPyV-negative MCC, which is known to harbour a high burden of UV-induced somatic tumour mutations which can serve as neo-antigens and MCPyV-positive MCC, which expresses viral oncogenes, can provide a basis for the immune recognition of MCC [131]. Approximately 50% of MCC cells express PD-L1 on their surface, while tumour-infiltrating lymphocytes and circulating MCPyV-specific T cells express PD-1 [132]. This PD-1/PD-L1 pathway is known to contribute to local immune evasion by inhibiting T-cell activation and impairing the CD8/Treg ratio. In MCC, like in many other tumours, PD-1 and PD-L1 inhibitors are thus expected to restore T-cell-dependent antitumour response. Anti-PD-L1 antibodies could also play a role through NK-cell-dependent ADCC [133] against PD-L1 positive malignant cells and cells of the tumour microenvironment [133,134].

8.5.1.2. Anti-PD-1/PD-L1 agents in MCC. PD-1/PD-L1 inhibition has been investigated in advanced MCC in phase-1/2 trials. The results of three phase −2 [135])

Table 6
Summary of 4 Phase II anti PD-1/PD-L1 trials.

Trial	Pembrolizumab [136]	Avelumab [135] *updated in SITC2019*	Nivolumab [138]	Avelumab [134] *Updated in ASCO2021*
N	50	116	25	88
Line	1st	1st	1st, 2nd and 3rd	>2nd
ORR (CR)	56% (24%)	39.7 (16.4%)	68% (14%)	33.0% (11.4%)
Median PFS (months) (95%CI)	16.8 (4.6 – NR)	4.1 (1.4–6.1)	NA	2.7 (1.4,6.9)
Median OS (months) (95%CI)	NR (26-NR)	20 (12.4-NR)	NA	12.6 (7.5–17.1)
1-year OS %, (95%CI)	~73 (NA)	60 (50–68)	NA	50 (39–60)
2-year OS %, (95%CI)	68.7% (NA)	NA	NA	36 (26–46)
3-year OS %, (95%CI	NA	NA	NA	32 (23–42)
5-year OS % (95%CI)	NA	NA	NA	26 (17–36)
Follow-up (months) (range)	14.9 (0.4–36.4+)	21.2 (14.9–36.6)	6.5 (1.3–8.8)	65.1 (60.8–74.1)

[136,137], and 1 phase I trial [138] have been published and are summarised in Table 6.

8.5.1.2.1. Avelumab. Avelumab is a fully human anti-PD-L1 antibody [133], which was first evaluated in a phase II trial on 88 previously treated patients (JAVELIN Merkel 200 trial) [134,139,140] at 10 mg/kg every 2 weeks with a median follow-up of 65.1 months (range 60.8–74.1 months). The overall response rate (ORR) was 33.0% (95% CI 23.3%–43.8%), including a complete response (CR) of 11.4% (10 patients) [134]. The median progression-free survival (PFS) was 2.7 months (95% CI, 1.4–6.9). However [140], the median duration of responses was 40.5 months (95% CI 18.0 months not estimable), showing that responding patients benefit in the long-term, which was not seen with conventional chemotherapies. The median OS was 12.6 months (95% CI 7.5–17.1 months), the 3-year OS rate was 32% (95% CI 23%–42%,) and the most recent update at ASCO2021 showed a 5-year OS rate of 26% (95%CI 17%–36%), thus confirming durable responses and a potential survival benefit in an indirect comparison to chemotherapies (Abstract No. 9517 ASCO 2021). Of long-term survivors (OS > 36 months) evaluable for PD-L1 expression status (n = 22), 81.8% had PD-L1+ tumours [134]. Moreover, longer median OS (12.9 months [95% CI, 8.7–29.6 months] versus 7.3 months [95% CI, 3.4–14.0 months], respectively) and a higher 5-year OS rate (28% [95% CI, 17%–40%] versus 19% [95% CI, 5%–40%]) were observed in patients with PD-L1+ versus PD-L1− tumours. Patients who experienced irAEs seem to have better outcome (HR 0.71, 95% CI, 0.59 to 0.85) using the time-dependent Cox model. The JAVELIN Merkel 200 part B was recently updated at the Society for Immunotherapy of Cancer congress 2019 and focused on 116 treatment-naïve patients, also using avelumab 10 mg/kg every two weeks. After a median follow-up of only 21.2 months (range: 14.9–36.6), response was higher than in the second-line cohort with an ORR of 39.7% (95% CI, 30.7%–49.2%). The median PFS was 4.1 months (95% CI, 1.4–6.1), higher than previous retrospective reports for chemotherapy in the same population for which median PFS ranged from 3 to 5 months. The median OS reached 20 months (95% CI, 12.4-NR). The avelumab flat dose of 800 mg IV every 2 weeks is currently recommended for all cancer entities.

After approval, a real-world experience with avelumab in patients with mMCC from an expanded access program was published [141] and confirmed efficacy and safety data of the registrational study, 494 patients received avelumab in the expanded access program . Among 240 evaluable patients, the objective response rate was 46.7%. The median duration of treatment in evaluable patients with response was 7.9 months (range,

Table 7
Recommended follow-up for patients with MCC.

Stage	Clin			Nodal sonography			Contrast-enhanced neck/thorax/ abdomen/pelvis CT or FDG PET/CT whole-body, Brain MRI		
Year	1–3	4–5	6–10	1–3	4–5	6–10	1–3	4–5	6–10
Baseline	Full body clinical examination 8-14 megaherz ultrasound of regional nodal basin Whole body imaging FDG PET/CT (preferred)/contrast-enhanced neck/thorax/abdomen/pelvis CT Brain MRI for stage ≥ III or symptomatic patients								
stage Tis-II	3–6 mo	12 mo	X	3–6 mo	x	x	x	x	x
≥III	3mo	6 mo	12 mo	3mo	6 mo	x	3–6 mo	6–12 mo	x
IV**	Adapt clinical visits, laboratory examinations and imaging according to treatment and symptoms								

1.0–41.7) overall and 5.2 months (range, 3.0–13.9) in immunocompromised patients. No new safety signals were identified.

8.5.1.2.2. Pembrolizumab. Pembrolizumab is a humanised IgG4 antibody directed against PD-1. A multicentre phase-2 trial (Keynote-017) evaluated pembrolizumab 2 mg/kg every 3 weeks for up to 2 years in 50 patients with treatment-naïve advanced MCC. The median follow-up time was 14.9 months (range, 0.4 to 36.4+ months). ORR was 56% (95% CI, 41.3%–70.0%) with CR and PR rates of 24% and 32%, respectively. The median duration of response was not reached and median PFS was 16.8 months (95% CI, 4.6 months to not estimable). The 2-year OS was 68.7% and median OS was not reached [136]. These data confirm the high efficacy of anti-PD-1/PD-L1 blockade in treatment-naïve patients.

8.5.1.2.3. Nivolumab. Nivolumab, a fully human IgG4 antibody against PD-1 was evaluated in patients with previously untreated advanced MCC (60%) or in previously treated patients (1–2 previous systemic therapies; 40%) in the Checkmate 358 trial, that includes patients with virus-associated malignancies. Nivolumab was given at 240 mg every 2 weeks with a median follow-up of 26 weeks (range, 5–35 weeks). Twenty-five patients were enrolled. ORR was 68% for the overall population: 71% for treatment-naïve patients and 63% for pre-treated patients. With a very short follow-up, at 3 months, PFS and OS rates were 82% and 92%, respectively [138].

8.5.1.3. Safety profile of anti-PD-(L)1 agent. The safety profile of anti PD-(L)1 immune check point inhibitors in MCC showed that these drugs were generally well-tolerated and that their side-effects were comparable to known side-effects in other indications for solid tumours. Grade 3-4 adverse events did occur in 11.4–28% of treated patients and treatment-related adverse event leading to treatment discontinuation in 9.1–15.4%. Only one treatment-related death occurred during these trials [134–136,138].

8.5.1.4. Biomarkers associated with response. Clinical benefit was not consistently predicted by any single biomarker [134].

8.5.1.4.1. PD-L1 status. Although statistical significance was not reached [136], PD-L1 positive tumours were more likely MCPyV-positive [136]. A trend for higher OS rates was observed in patients with PD-L1 positive versus PD-L1 negative tumours but did not reach statistical significance [134,136]. PD-L1 was also positive in most long-term survivors suggesting that patients with PD-L1 positive tumours may have a higher probability of long-term survival [134].

8.5.1.4.2. Tumour mutational burden. High tumour mutational burden was generally associated with MCPyV negativity. There was a trend for increasing efficacy (PFS and OS) in patient with high mutational burden tumours.

8.5.1.4.3. Tumour MCPyV status. Virus-positive or virus-negative status was evaluated in several trials and no strong association with anti-PD(L)1 efficacy was shown [134,136].

The response rate was particularly high in tumours combining 3 factors: high mutational burden, MCPyV negative and high CD8+ T cell density at the invasive margin [134].

Additional work is needed to further investigate these biomarker findings.

8.5.1.5. Immunotherapy discontinuation. Data on ICI discontinuation for other reason than progressive disease from a multicentre retrospective cohort of patients were recently presented at ASCO 2021. ICI responses in metastatic MCC do not appear to be as durable off treatment as in other cancers, including those patients who achieve a complete response since 35% of all patients (n = 40) had progressed within a median time of 5.5 months (range 4–29) after treatment discontinuation including 26% of complete responders although these patients were less likely to progress p = 0.044. A trend for an association between progression and short duration of treatment was observed but not significantly demonstrated. Initial data on response to retreatment were, however, promising: 75% of patients (n = 8; 4CR, 2 PR) did show a response that was ongoing after a median follow-up of 10 months after the restart of treatment. Limitations of the study, however, include a small patient sample, the lack of predefined common treatment duration and that nearly 40% of patients stopped therapy due to toxicity or other reasons than a major response. Further research is therefore needed to define the optimal duration of

Recommendation 8	
First-line treatment for inoperable locally advanced or metastatic MCC	Evidence-based recommendation
Grade of recommendation: A	Immunocompetent patients with locally advanced or metastatic MCC (surgery no feasible) shall receive anti PD-(L)1 -based immunotherapy as first line treatment.
Level of evidence: 2	Phase II study of avelumab* [134,135] Phase II study of pembrolizumab [136] Phase I/II study of nivolumab [138]
Strength of consensus: 100%	

ICI treatment and predictors of long-term ICI responses (Abstract #336113, ASCO 2021).

8.5.2. Chemotherapy

Before immune therapy, there was no standard of care but management relied either on best supportive care or chemotherapy regimen selected on the basis of histological similarity to small-cell lung carcinoma. These regimens include platinum-based drugs, etoposide, taxanes and anthracyclins, either alone or in various combinations, mainly reported in case-reports, case series, retrospective studies or literature reviews. One of the most frequently used regimen for patients with good performance status was a combination of platinum and etoposide (Cisplatin 60–80 mg/m2 IV on day 1 plus etoposide 80–120 mg/m2 IV on days 1–3 every 21-28 d or Carboplatin AUC 5 IV on day 1 plus etoposide 80–100 mg/m2 IV on days 1–3 every 28 d). A recent comprehensive, systematic review of chemotherapy regimens in patients with advanced MCC identified 35 publications [142]: ORR in these publications ranged from 23% to 61%, with higher response rates in the first-line setting (53–61%) than in second-line therapy (23–45%). The median PFS was short: 3.1 months in the first-line setting versus 2 months in the second-line setting [143], suggesting no durable response. The median OS was reported in only two of the five retrospective studies/literature reviews, ranging from 9 to 9.5 months [143,144]. Moreover, chemotherapy is associated with a high-risk of toxicity, particularly in elderly patients who frequently have impaired liver and kidney function as well as a limited bone marrow reserve. The most common adverse effects are those of aggressive chemotherapy: myelosuppression, sepsis, fatigue, alopecia, nausea/vomiting and renal injury [144]. Death from chemotherapy-related toxicities was therefore very high, ranging from 3% to 10% of the reported patients [60]. For all these reasons, chemotherapy can only be considered as a palliative strategy after failure or contraindication to immunotherapy.

Recommendation 9	
Chemotherapy for locally advanced or metastatic MCC	Evidence-based recommendation
Grade of recommendation: C	Chemotherapy can be used when patients fail to respond, are intolerant or present contraindication to anti-PD-(L)1 immunotherapy, or when immunotherapy or clinical trials are not available
Level of evidence: 3-4	Systematic review of 35 studies including retrospective studies and cases series [142]
Strength of consensus: 100%	

8.5.3. Immunotherapy in the adjuvant setting

Adjuvant treatment with ipilimumab versus observation was tested in a randomised DeCOG phase-2 trial ('ADMEC') in Germany, but prematurely closed due to a futility analysis. After the inclusion of just 40 patients, no difference in PFS had been observed and ipilimumab caused significant toxicities [145]. The subsequent randomised phase-2 trial of the DeCOG ("ADMEC-O') compares the efficacy of nivolumab versus observation alone in 180 patients randomised in a 2:1 ratio, but data are not yet available [146]. A few clinical trials are ongoing (NCT04291885, NCT03271372, NCT03712605) and results are awaited.

8.5.4. Immunotherapy in the neoadjuvant setting

In a neo-adjuvant cohort of CheckMate 358, patients with resectable MCC received nivolumab 240 mg intravenously on days 1 and 15. Surgery was planned on day 29.39 patients with AJCC stage IIA-IV resectable MCC received $\geq$1 nivolumab dose. Three patients (7.7%) did not undergo surgery because of tumour progression (n = 1) or adverse events (n = 2). Any-grade treatment-related adverse events occurred in 18 patients (46.2%) and grade 3–4 events in 3 patients (7.7%), with no unexpected toxicities. Among 36 patients who underwent surgery, 17 (47.2%) patients achieved a complete pathologic response (pCR). Among 33 radiographically evaluable patients who underwent surgery, 18 (54.5%) patients had tumour reductions $\geq$30%. Responses were observed regardless of tumour MCPyV, PD-L1 or TMB status. At a median follow-up of 20.3 months, median recurrence-free survival (RFS) and OS were not reached. RFS significantly correlated with pCR and radiographic response at the time of surgery. No patient with a pCR had tumour relapse during observation [147].

8.5.5. Ongoing clinical trials with a novel approach

Despite very encouraging results obtained with PD-1/PD-L1 blockade, approximately 50% of patients with advanced MCC do not have a durable benefit due to the primary and secondary resistances of unknown mechanisms, highlighting the need for further clinical trials.

Because advanced MCC is a rare disease that precludes robust randomised studies, enrolment in clinical trials is encouraged whenever available and appropriate [148]. Many hypotheses are currently being tested in early trials. Main ongoing trials are listed in Table S7.

Recommendation 10	
Clinical trials for locally advanced or metastatic MCC	Consensus-based recommendation
GCP	If available and appropriate, inclusion in clinical trial should be encouraged
Strength of consensus: 100%	

8.5.6. Locoregional control and palliative radiotherapy

The place of isolated hyperthermic limb perfusion with alkeran and actinomycin D or isolated limb perfusion with TNF and alkeran combination therapy remains uncertain despite some favourable results in case reports or small retrospective and prospective cohort studies [149,150].

In advanced patients with MCC, RT is routinely performed with palliative intent for symptomatic lesions either alone or combined to systemic therapies: 8 Gy in one session may be enough to reduce tumour burden providing durable palliation [151]. Other hypofractionated schedules can be used in the palliative treatment setting, such as 20 Gy in five fractions [129]. Stereotactic RT (i.e. a local ablative treatment which delivers over 5 Gy per fraction in 1–5 fractions) is suitable for oligometastatic disease i.e. up to 5 small metastatic lesions in the brain or extracranial organs. RT is indicated for in-transit metastases which cannot be resected surgically. External beam RT or brachytherapy, although not in widespread use, are both valid options [152,153].

9. Quality of life, Palliative, Best supportive care

The mean age of patients diagnosed with MCC is 77 years. Whilst the prognosis for patients with MCC is overall poor, advanced age worsens the prognosis [154]. Older age is associated with increased comorbidity burden and frailty [155]. But chronological age alone provides limited information to physicians. Therefore, incorporating geriatric assessments, such as a comprehensive geriatric assessment allows a better understanding of the patients' functional status, as well as planning interventions to optimise and/or better support vulnerable/frail patients [156]. But beyond that, this provides important information regarding the patient's individual risk and prognosis which supports the shared decision-making process when determining the best treatment plan. However, these assessments are not necessary for all older patients. Therefore, implementing validated screening tools, such as Geriatric 8 (G8), is a strategy to identify those older patients who may benefit the most from more in-depth assessments and support [157].

The impact of the vulnerability of many of these patients with MCC was highlighted in an observational study with 500 patients with MCC and with a median age at diagnosis of 71 years who had been treated at a single centre. It found that half of the patients died during a median follow-up of 3 years. Yet, whilst 25% died due to MCC, the other 24% died of other causes [71].

Health-related quality of life (HRQoL) is another important consideration when determining the best treatment plan. Older patients with cancer often value quality of life more than survival outcomes. Therefore, incorporating this information at decision timepoints is paramount [158]. Furthermore, assessing HRQoL at baseline and monitoring throughout a treatment pathway is a key to intervene time and meet the patients' needs. This is particularly important when a curative-intent treatment is not appropriate, and the prognosis is poor. Several HRQoL tools have been developed and are widely used, such as the EORTC QLQ-C30 [158].

Patients and their carers often suffer from both physical and psychological distress which fluctuates throughout the cancer journey, being at times worsened by the treatments provided. Therefore, similarly to what is advocated in other cancer types, an early integration with palliative and supportive care should be promoted.

Apart from the potential side-effects and toxicity caused by the MCC treatments, which may require targeted interventions, the tumour itself is a frequent cause of symptoms which can have a great impact in the HRQoL and the well-being of patients. The key symptoms related to the pT and local cancer involvement are pain, ulceration, exudate and odour.

Pain should be assessed regularly using validated pain scales [159]. The visual analogue scale, the verbal rating scale and the numerical rating scale (NRS) are most frequently used. When the score exceeds 2, a conversation about pain is required. Analgesics for chronic pain are best taken orally and should be prescribed on a regular basis instead of an 'as required' schedule [159]. The WHO proposes a sequential three-step analgesic ladder strategy, from non-opioids (paracetamol, anti-inflammatory drugs (NSAIDs)) to weak opioids to strong opioids according to pain scores [160]. However, in case a patient already suffers from intermediate (NRS $\geq$4) to severe (NRS $\geq$7) pain, weak opioids (e.g. tramadol, dihydrocodeine and codeine) might be best added to the mild analgesics immediately.

Regarding ulcerating wounds, surgery and RT are effective palliative treatments but this is not always possible. The first step in odor prevention is daily rinsing with tap water or sodium chloride cleaning fluid. In a large review, evidence was found for topical metronidazole (gel or solution of metronidazole in concentrations of 0.75%–0.8% once daily for at least 14 days), sodium chloride dressing, activated carbon dressing and curcumin ointment [161]. Metronidazole is effective

Recommendation 11	
Geriatric assessments	Consensus-based recommendation
GCP	Older patients should undergo frailty screening at decision-making timepoints and further geriatric assessments should be implemented as required
Strength of consensus: 96%	

Recommendation 12	
Quality of life	Consensus-based recommendation
GCP	Health-related QoL (HRQoL) tools and pain scales should be encouraged for patients with MCC before, during and after treatment.
Strength of consensus: 96%	

Recommendation 13	
Palliative and supportive care referrals	Consensus-based recommendation
GCP	Early referral to supportive and palliative care team should be done particularly for patients with symptomatic locally advanced or metastatic disease.
Strength of consensus: 96%	

against anaerobic bacteria and protozoa. It can also be administrated orally (3 times daily 500 mg for 10–14 days). Absorbent dressing made up of viscose or polyester impregnated with sodium chloride acts through the hypertonic effect produced on the lesion [161]. In a randomised study, including 24 patients, 0.2% polyhexamethylene biguanide proved to be equally effective as metronidazole 0.8% solution in treatment of odor; 100% achieved no wound odor by day 8 ($P < .001$) [162]. Furthermore, odor control significantly improved the general HRQoL.

Bleeding can also occur in MCC evolution and impair patients' outcome. Treatments strategies depend on bleeding severity and are based on local modalities, such as haemostatic agents and dressings, RT, endoscopic ligation and coagulation in case of gastrointestinal bleeding and transcutaneous arterial embolization [163].

10. Selected cases: management of patients in immunosuppressed patients

10.1. Epidemiology

As discussed in the epidemiology section, immunosuppression is a significant risk factor for MCC [59,164,165]. And 11.7% of all patients with MCC are immunosuppressed [166].

Among immunosuppressed patients:

- SOTRs have more than 20-fold increased incidence ((SIR) = 24 to 97) of MCC compared with the immunocompetent population and this increases with time post-transplant [167,168]. This higher risk is attributable to reduced immune surveillance resulting from immunosuppressive medication and from direct mutagenic effects of some immunosuppressive drugs, including azathioprine and ciclosporin [167] [38,169,170] [168].
- Haematological malignancies such as non-Hodgkin lymphoma (NHL) and CLL are associated with a 3- to 8-fold increased risk of non melanoma skin cancers including MCC in comparison with the immunocompetent population (SIR = 3.64 in haematological malignancies in general and 6.89 in CLL in particular) [33–35]. Impaired immune function is the main driver, particularly in CLL which is characterised by impaired B cell function, decreased T-helper cell activity and increased regulatory T-cell activity. Anticancer treatments including chemotherapy may also contribute to immune dysregulation [35,171].
- HIV infection/AIDS confers an increased risk of 11- to 13-fold in comparison with the immunocompetent population and this is linked to immunosuppression through depletion of CD4+T cells [36,37,172].
- Immune-mediated inflammatory diseases such as inflammatory bowel disease and rheumatoid arthritis on treatment are also associated with an increased risk of MCC due to immunosuppressive medication or immune system dysregulation [173,174].

Although age at diagnosis and stage of disease are similar in immune-suppressed and immunocompetent individuals overall [166,170], the specific type of immunosuppression is also relevant: for patients with HIV/AIDS and solid organ transplantation age at diagnosis is significantly lower and they present with more advanced disease in comparison to the other immunosuppressed groups such as haematological malignancies [175]. SLN positivity rate is also higher at diagnosis in immunosuppressed patients, although the implication for OS is not conclusive [166,175].

10.2. Outcomes

In immunosuppressed patients with MCC, the disease course is more aggressive [175] [171,176,177], regardless of competing comorbidities [169,175]. MCC-specific survival is decreased in immunocompromised patients in comparison with the immunocompetent population (40% versus 74% at 3-years, respectively: HR 6.11 [1.61–23.26]; $P = .008$) [31,97,170,175] and for each type of immunosuppression, except for NHL [35]. This is particularly significant for HIV/AIDS and OTRs compared with other immunocompromised states although PFS is not decreased [175]. Immunocompromised patients also have a higher risk of recurrence

(HR:3.67 [1.80–7.51]; P < .0001) with a 5-year RFS of 43% [175].

10.3. Management

Because of the potentially aggressive nature of MCC, the inevitable complexity of individual cases and the paucity of evidence to guide management in immune deficiency, a multidisciplinary approach to clinical decision-making is particularly important.

10.3.1. Surgery and radiotherapy

In addition to higher rates of local recurrence after surgery [175], efficacy of RT for MCC at standard doses is also impaired, with higher local recurrence rates after palliative RT and reduced PFS with curative-intent RT [151,177]. The mechanism of this apparent radioresistance is unclear but reduced immune surveillance may allow the unchecked growth of residual microscopic tumour cells after RT, and it has been suggested that the intensification of RT for immunocompromised individuals should be considered [177]. However, this difference is not observed for adjuvant RT, with no differences in OS according to immune status in either stage I/II or III MCC (both P values > 0.05) [65], thus suggesting adjuvant RT should be considered at standard doses not only for immunocompetent but also for immunosuppressed patients with localised MCC.

10.3.2. Immune checkpoint inhibitors

Because immune deficiency has been an exclusion criterion in pivotal clinical trials, data concerning ICI efficacy and adverse effects in immunocompromised patients with advanced MCC are limited. Small cohort studies or systematic literature review of immunocompromised patients with several solid tumours treated with ICI have been reported, which demonstrated encouraging results in global tumour control rates, higher in kidney versus liver OTRs. Allograft function was preserved in two-third of patients and death was most frequently linked to the progression of malignancy [178,179]. Only few cases of MCC in OTRs population receiving ICI have been reported and no data from large retrospective or prospective cohorts are available. Therefore, further studies are needed to investigate MCC outcome with ICI in SOTRs [180].

In haematological malignancies (mainly CLL and NHL), data from a real-world retrospective, multicenter, DeCoG study (MCC n = 16) reported similar OS but lower PFS outcomes than those reported for immunocompetent patients in clinical trials, but no significant differences were observed after comparing with real-world registry-based patient cohorts without haematological malignancies [181]. Published case series and case reports provide support that advanced MCC in patients with HIV/AIDS may also respond favourably to ICIs, despite low CD4 counts [182–185].

10.3.3. Modification of immunosuppressive therapy

Few studies have addressed the optimal modification of immunosuppressive therapy in OTRs and other iatrogenically immunosuppressed patients diagnosed with MCC. However, extrapolating from other skin cancers including cSCC, the risk/benefit ratio of minimising immunosuppressive drugs should be considered and discussed on a case-by case basis. Similarly, although switching to mTOR inhibitors has been demonstrated to reduce subsequent tumours for OTRs after the first cSCC in secondary prevention (cancer recurrence) [186–188], there is currently no objective evidence that this is the case for MCC and for metastatic disease.

In summary, the epidemiology and outcomes for MCC in the context of immune deficiency are well-established. However, there remain major evidence gaps relating to management, particularly of advanced disease, and clinical trials in this area are now a research priority.

11. Follow-up and recurrence

11.1. General concepts

Follow-up of MCC, as for any cancer, aims at 3 main goals:

- First, to detect recurrence at an earlier stage;
- Second, to detect second primary cancers at an early stage;
- Third, to manage potential side-effects of local or systemic treatment.

11.2. Risk for recurrence

MCC has a generally high-risk for recurrence varying between 25% and 50%, and the risk of recurrence increases with tumour stage, location of the pT, age, sex, viral MCPyV status and immunosuppression. The risk for recurrence is highest within the first 2–3 years after initial diagnosis with about 40%–50% of patients developing nodal metastases (not only regional) and about 33% distant metastases [27,108,189,190].

Most common sites of distant metastases are the skin/soft tissue (25%), liver (23%), bone (21%), pancreas (8%), lung (7%) and brain (5%) [81,87,191]. The frequency of specific sites of spread influences the choice of imaging and laboratory investigations during follow-up.

11.3. Risk of secondary cancers

There are lines of evidence suggesting that patients with MCC are also at increased risk of developing secondary cancers, especially skin cancers such as melanoma and other non-melanoma skin cancers. This is supported by common UV-dependent pathogenic mechanisms. Further, MCC may also be associated with haematologic co-morbidities such as CLL [192,193].

11.4. Clinical and imaging visits

As a general rule, follow-up of MCC should include a careful regular full body skin examination coupled with dermoscopy carried out by a trained dermato-oncologist, physical palpation of the scar, the surrounding skin and nodal areas, as well as radiologic imaging such as ultrasound of the lymph nodes, CT scans, MRI and PET-CT which is more sensitive than CT alone [83]. Performing SSTR PET for MCC follow-up is another option whose value is not yet definitively assessed (cf staging paragraph above) [84–86]. Schedule of imaging is not yet standardised.

A recently introduced web-based risk calculator considering relevant factors may be helpful in assessing the risk of recurrence and the appropriate frequency of surveillance studies (https://merkelcell.org/prognosis/recur/).

11.5. Laboratory investigations

While Neuron-Specific Enolase serum levels failed to date to predict outcome for MCC patients [194], recent evidence suggests Neuron-Specific Enolase may be a potential useful biomarker in MCC as increasing levels correlated with progression while decreasing levels during immunotherapy correlated with response to immunotherapy [195]. Further studies are needed to confirm its utility during MCC follow-up. Currently, MCPyV oncoprotein antibody titre (tested at diagnostic and during follow up) is not a standard of care but should be further evaluated in prospective validation study [3,59,88,88–90].

11.6. Time frames for clinical, imaging and laboratory examinations during follow up

MCC, being a rare skin cancer, large prospective and well-designed studies defining the best time intervals between clinical/laboratory/imaging visits during follow-up are lacking.

In the light of missing standardised national and international post-treatment surveillance data for MCC, the

Recommendation 14	
Follow-up	Consensus-based recommendation
GCP	• For primary tumours, without additional high-risk factors (Table 7). Regular clinical visits coupled with ultrasound of the scar of the primary, of the draining area and lymph nodes every 3–6 months for the first 3 years, followed by clinical visits every 12 months until 5 years No further laboratory examinations
Strength of consensus: 85%	

Recommendation 15	
Follow-up	Consensus-based recommendation
GCP	Stage III patients without immunosuppression and in good clinical condition *(Table 7).Clinical visits: - 3 monthly for 3 years, - Then every 6 months for years 4–5, - Then annually [192] Imaging: Ultrasound of the scar of the primary, of the draining area and lymph nodes should be performed every 3 months in the first 3 years and every 6 months for the next 2 years. FDGPET/CT whole-body (more sensitive) (if available) or contrast-enhanced neck/thorax/abdomen/pelvis CT and brain MRI or CT [87] can be performed every 3–6 months in the first 3 years, followed every 6–12 months for the next 2 years. * For frail patients and in stage IV, personalised protocol should be adopted.
Strength of consensus: 88%	

Recommendation 16	
Follow-up for immunosuppressed patients	Consensus-based recommendation
GCP	• Patients with immunosuppression (high-risk for second primary cancers) (Table 7). Clinical visits: - 3 monthly for 3 years, - then every 6 months [192] switch to annual clinical follow-up after 5 years if no subsequent cancers have occurred. Imaging: - Ultrasound of the scar of the primary, of the draining area and lymph nodes should be performed every 3 months in the first 3 years and every 6 months for the next 2 years. - FDG PET/CT whole-body (more sensitive) (if available) or contrast-enhanced neck/thorax/abdomen/pelvis CT and brain MRI or CT [87] can be performed every 3–6 months in the first 3 years, followed every 6–12 months for the next 2 years.
Strength of consensus: 88%	

frequency of visits should be individualised taking into account tumour-related and patient-related risk factors, institutional capacity and potential treatment options.

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