# Merkel cell carcinoma

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Abstract | Merkel cell carcinoma (MCC) is a rare but highly aggressive skin cancer with neuroendocrine features. MCC pathogenesis is associated with either the presence of Merkel cell polyomavirus or chronic exposure to ultraviolet light (UV), which can cause a characteristic pattern of multiple DNA mutations. Notably, in the Northern hemisphere, the majority of MCC cases are of viral aetiology; by contrast, in areas with high UV exposure, UV-mediated carcinogenesis is predominant. The two aetiologies share similar clinical, histopathological and prognostic characteristics. MCC presents with a solitary cutaneous or subcutaneous nodule, most frequently in sun-exposed areas. In fact, UV exposure is probably involved in both viral-mediated and non-viral-mediated carcinogenesis, by contributing to immunosuppression or DNA damage, respectively. Confirmation of diagnosis relies on analyses of histological features and immunological marker expression profiles of the lesion. At primary diagnosis, loco-regional metastases are already present in ~30% of patients. Excision of the tumour is the first-line therapy; if not feasible, radiotherapy can often effectively control the disease. Chemotherapy was the only alternative in advanced-stage or refractory MCC until several clinical trials demonstrated the efficacy of immune-checkpoint inhibitors.

Merkel cell carcinoma (MCC) is a rare, neuroendocrine, cutaneous malignancy that was first described in 1972 by Cyril Toker as "trabecular carcinoma of the skin" (REF. 1). The name was changed to Merkel cell carcinoma because the tumour cells resemble Merkel cells, which are present in the basal layer of the epidermis, in particular around hair follicles. Merkel cells serve as mechanoreceptors for gentle touch stimulation, are associated with afferent sensory nerves and have neuroendocrine features; these cells express neuroendocrine markers such as chromogranin-A, synaptophysin and cytokeratin 20 (CK20; also known as keratin, type I cytoskeletal 20)[2] (FIG. 1). MCC cells also typically express these markers. MCC is highly aggressive, and more than one-third of patients die of the disease; thus, MCC has a case-fatality rate higher than that currently observed with melanoma. Almost one-third of patients present at primary diagnosis with loco-regional metastases, for example, in-transit metastases (a tumour distinct from the primary lesion and located either between the primary lesion and the draining regional lymph nodes or distal to the primary lesion) or lymph node metastases[3–5]. The at-risk population includes elderly people, immunocompromised individuals, patients with haematological neoplasms (who generally are also immunocompromised) and individuals with a history of other cutaneous tumours.

MCC carcinogenesis is associated either with the presence of clonally integrated Merkel cell polyomavirus (MCPyV; also known as human polyomavirus 5 (HPyV5)) or chronic ultraviolet light (UV) exposure (BOX 1); UV exposure could also partially explain the observation that patients with MCC frequently have a history of other UV-associated skin cancers, such as basal cell carcinoma or cutaneous squamous cell carcinoma[6,7]. Until the advent in 2016 of immune-modulating therapies for MCC using immune-checkpoint inhibitors, there was no effective therapeutic approach that resulted in a confirmed survival benefit for metastatic MCC not amenable to surgery and/or radiotherapy.

In this Primer, we summarize the major facets of current MCC research, from epidemiology, carcinogenesis and immunology to clinical care, including surgical, radiation and medical management, in particular the use of immune-checkpoint inhibitors.

## Epidemiology

### *Incidence*

Little is known about the epidemiology of MCC. A comparison of MCC incidence over time in the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), the Netherlands and the United States revealed that rates in the Nordic countries (with the exception of Sweden) have been stable since 1995, whereas rates continued to increase within the observation period (2005–2008) in Sweden, the Netherlands and the United States[8]. The increase of the incidence of MCC over time might reflect improvements in cancer registration and immunohistochemical characterization (in particular,

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the widespread use of CK20 immunostaining), the discovery of viral carcinogenesis in the majority of MCCs and increased awareness of and familiarity with this cancer by physicians[6,8–12]. However, despite these improvements, the incidence in the Nordic countries has not increased further since the mid-1990s[8,12]. Moreover, earlier increases in incidence in the Nordic countries have been attributed to unreliable detection of MCC[12]. Comparisons of incidence across countries are complicated because different studies use different measures (for example, crude rates or age-standardized rates with different age standards) and calendar periods. In addition, studies differ in relation to topographic localizations of MCC, for example MCC with unknown primary, that are excluded from their analyses[9,13].

The incidence of MCC was 0.6 per 100,000 people per year in the United States in 2009 (REF. 14), 1.6 per 100,000 people per year in Queensland, Australia, in 2006–2010 (REF. 13) and 0.3 per 100,000 people per year in Sweden in 2012 (REF. 12) (all rates were adjusted using the 2000 US Standard Population to enable comparison). Thus, melanoma is about 50-fold more frequent than MCC. The median age at diagnosis is 75–80 years[12,13]. An analysis of data from >9,000 patients for the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging System documented a median age of 76 years, with only 12% of patients being <60 years of age[15]. Although the 5-year relative survival of patients with MCC in single-institution studies was as high as 75%[16], in larger national databases, it was ~60% in the United States (1973–1999) and ~40% in Queensland, Australia (2006–2010)[13]. Notably, the disease-specific survival was associated with the stage at diagnosis and localization[9].

### *Risk factors*

The correlation between MCC and UV radiation is well documented: the solar UV index was positively associated with the incidence of MCC in the United States in 1986–1994 and 1986–1999 (REFS 9,17). Notably, skin pigmentation seems to protect against MCC, as black, Asian and Hispanic individuals have considerably lower risk of MCC than white populations. Additional evidence arises from the frequent occurrence of MCC in elderly patients on chronically sun-exposed skin, the increased MCC incidence in individuals treated with UVA photochemotherapy and the observation that many patients with MCC have a history of other skin cancers associated with sun exposure[17,18]; a history of melanoma is also linked with a threefold greater risk of MCC[18]. However, a molecular UV signature (DNA mutations that are typically caused by UV damage, such as C to T transitions that occur in the context of di-pyrimidines: C[C>T]N and N[C>T]C) has been demonstrated only in a subset of cases of MCPyV$^-$ MCCs[19,20]; thus, the association with UV exposure in MCPyV$^+$ MCC might be related to other factors, such as UV-induced immune suppression. In fact, immune deficiencies have a crucial aetiological role: MCC is more-frequent in patients with leukaemia, lymphoma (particularly B cell chronic lymphocytic leukaemia[21,22]) or HIV infection[23,24] and in those who are immunosuppressed as a result of organ transplantation or other causes[25–27]. Notably, the age of onset of MCC is lower and the mortality is higher in immunosuppressed individuals than in immune-competent patients[28]; these findings emphasize the crucial role of efficient immune surveillance in the control of tumour growth and progression. Chronic inflammatory disorders such as rheumatoid arthritis are also associated with higher incidence of MCC[29]. An association between MCC and chronic arsenic exposure has also been noted[30].

## Mechanisms/pathophysiology

MCC carcinogenesis can be initiated by the clonal integration of the MCPyV genome or UV-mediated DNA damage caused by chronic exposure to sunlight. Of note, UV exposure could also play a part in viral carcinogenesis by causing local immunosuppression[31]. UV radiation induces the expression of inflammatory mediators and functional alterations in the antigen-presenting dendritic cells, which result in a cascade of events that modulate immune sensitivity[32]. Despite major advances in understanding MCC carcinogenesis, the cellular origin of MCC remains obscure. On the basis of histomorphology, gene expression profiling and molecular analyses, MCC has been hypothesized to originate from Merkel cell precursors (potentially derived from epidermal stem cells or hair follicle stem cells), pre-B cells, pro-B cells[33] or dermal fibroblasts[34]. Because normal Merkel cells are terminally differentiated and do not undergo cell division, they are unlikely to be the cell of origin for MCC.

### *Merkel cell polyomavirus*

Given the increased risk of MCC in patients with immune deficiencies or treated with immunosuppressive therapies, the presence of pathogens was assessed through whole-transcriptome sequencing[35]. This study identified a new human polyomavirus, MCPyV, and determined that the viral DNA was clonally integrated into the genome of MCC cells. MCPyV was detected in eight out of ten tested MCCs. Furthermore, the Southern blot

patterns of the primary tumour and a metastatic lymph node isolated from the same patient were identical, indicating that the viral integration event was clonal and probably occurred early in the tumorigenic process.

MCPyV belongs to the family *Polyomaviridae*[36] (BOX 2; FIG. 2a). Primary infection with MCPyV does not cause any discernible signs or symptoms[37]. MCPyV is usually acquired during childhood and can be detected in the skin of most healthy individuals. Seropositivity (the presence of antibodies against the capsid protein VP1 in the blood) indicates chronic infection with MCPyV and is common in the general population[38]. Substantial titres of antibodies against MCPyV can be detected in newborn babies, but these titres gradually decrease to undetectable levels by 16 months of age[39,40]. Maternally derived antibodies might account for the seropositivity in newborn babies and are probably effective in preventing primary infection. By 18 months of age, when the maternal antibodies are no longer present, children are susceptible to *de novo* infection and capable of mounting an antibody response of their own. Thus, increasing proportions of children >18 months of age become seropositive, and ~80% test positive by 5 years of age[39]. These observations suggest that MCPyV is part of the normal skin microbial flora[41]. Despite the widespread and lifelong infection with MCPyV in most people, very few will develop MCC. Interestingly, MCPyV is not found in cases of MCC associated with cutaneous squamous cell carcinoma[42], indicating that it does not play a part in these combined tumours.

***Viral transforming genes.*** An important feature of MCPyV$^+$ MCC is that the tumour maintains the expression of the early transforming genes, namely, large T antigen (LT) and small T antigen (ST)[35]. Silencing of these viral genes in MCPyV$^+$ MCC cell lines caused cell death[43]; thus, LT and ST have also been referred to as viral oncoproteins. In all cases reported to date, LT is truncated such that the N-terminal J domain and LXCXE (also known as retinoblastoma-associated protein (RB1)-binding) motif are preserved but the DNA binding, helicase and cell growth-inhibitory domains are lost[44,45]. Moreover, these

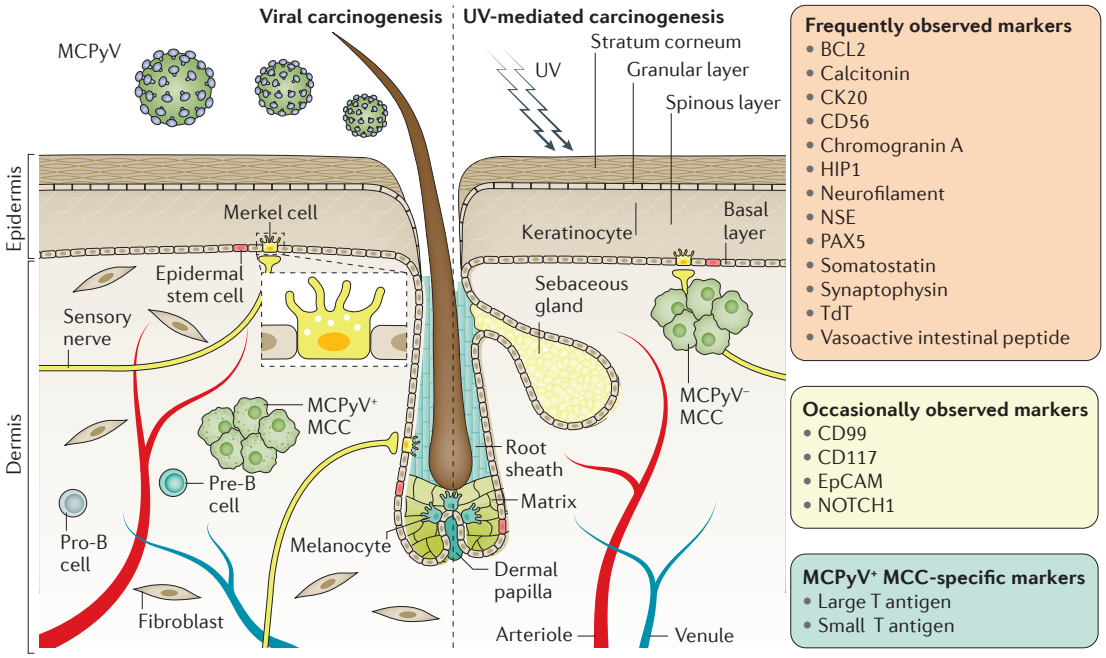


Figure 1 | **Hypothetical cells of origin, causal events and tissue markers for MCC.** The cell of origin of Merkel cell carcinoma (MCC) has not been identified. Possible candidates include epidermal stem cells, keratinocytes (the predominant cells in all the epidermal cell layers), dermal fibroblasts, pro-B cells or pre-B cells. Fibroblasts, pro-B cells and pre-B cells are localized in the dermal compartment, which is not exposed to relevant amounts of ultraviolet light (UV), and, therefore, are probably not cells of origin in UV-mediated carcinogenesis. Merkel cells are postmitotic cells and, therefore, are probably not the cell of origin of MCC. Merkel cells are found in the basal layer of the epidermis and are probably derived from epidermal or hair follicle stem cells. Merkel cells function as mechanoreceptors to detect gentle touch and are associated with sensory nerves. Merkel cell polyomavirus (MCPyV) is a common component of the commensal skin microbiota. However, it is not known what cell type MCPyV preferentially infects. In countries with low UV exposure, the majority of MCCs are positive for MCPyV (MCPyV$^+$ MCC), whereas in countries with high UV exposure, MCPyV is less frequently associated with MCC; these MCPyV$^-$ MCCs are characterized by DNA mutations bearing a UV signature. The two MCC types have similar phenotypes. Tissue markers that can be frequently or occasionally observed in both MCPyV$^+$ MCC and MCPyV$^-$ MCC, as well as MCPyV$^+$ MCC-specific markers, are listed. BCL2, apoptosis regulator BCL2; CK20, cytokeratin 20; CD56, neural cell adhesion molecule 1; CD99, CD99 antigen; CD117, mast/stem cell growth factor receptor Kit; EpCAM, epithelial cell adhesion molecule; HIP1, huntingtin-interacting protein 1; NSE, neuron-specific enolase, also known as γ-enolase; NOTCH1, neurogenic locus notch homologue protein 1; PAX5, paired box protein Pax-5; TdT, DNA nucleotidylexotransferase.

Box 1 | **Characteristics of the different MCC types**

**MCPyV⁺ MCC**

- Clonal integration of MCPyV DNA into tumour genome
- Expression of MCPyV small T antigen (ST) and truncated large T antigen (LT)
- Wild-type *RB1* and *TP53*
- No UV mutational signature
- Predominantly diploid with minimal number of copy number alterations
- Minimal number of somatic nucleotide alterations

**MCPyV⁻ MCC**

- No presence of MCPyV DNA
- No expression of MCPyV LT and ST RNA or protein
- Inactivating mutations in *RB1* and *TP53*
- High frequency of DNA mutations induced by UV damage
- High degree of aneuploidy
- Inactivating mutations in genes involved in various signalling pathways, including DNA damage response and repair genes and chromatin-modifying genes

MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; *RB1*, RB transcriptional corepressor 1 (which encodes retinoblastoma-associated protein); *TP53*, tumour protein p53; UV, ultraviolet light.

truncated mutants are thought to be necessary for a stable integration of the MCPyV genome into the host genome[44] (FIG. 2b), although the mechanism of viral gene integration remains unknown. Some tumours express a truncated LT that retains the nuclear localization signal[46,47]. Expression of full-length LT in MCPyV⁺ MCC cell lines causes a specific DNA damage response, which is probably induced by *in situ* replication of the integrated viral DNA, which in turn is triggered by the binding of LT to the MCPyV origin of replication[44,48]. This DNA damage process is thought to select against any tumour that expresses full-length LT.

MCPyV⁺ MCC tumours also express ST[49] (FIG. 2a). Although its exact molecular functions are not well understood, MCPyV ST has strong oncogenic activity. For example, ST can transform rat-1 fibroblasts *in vitro*[49] and can cooperate with truncated LT to transform human fibroblasts *in vitro*[50]. ST can induce tumour formation when expressed in mice as the sole transgene[51–53]. MCPyV ST binds to regulatory and catalytic subunits of protein phosphatase 2A (FIG. 2b), although no phosphatase substrates that are perturbed by ST binding have been identified. MCPyV ST has an additional domain, the LT stabilizing domain (LSD), which is unique and not conserved in ST from other polyomaviruses. The ST LSD increases the levels of MCPyV LT and might reflect the ability of ST to perturb the function of F-box/WD repeat-containing protein 7 (FBXW7), a component of the cullin-RING ligase family of ubiquitin ligases[54]. However, although several lines of evidence suggest a more-dominant role of ST during transformation, LT is highly relevant to maintaining the oncogenic phenotype. Notably, LT overexpression can rescue MCPyV⁺ MCC cell lines from cell death following knock down of the T antigens[55].

MCPyV ST expression increases the levels of phosphorylated eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), which in turn promotes the translation of 4E-BP1 in a positive-feedback loop[49]. Expression of ST can promote substantial changes in gene expression, including the induction of proglycolytic genes, and can induce aerobic glycolysis in fibroblasts[56]. Malignant, rapidly growing tumour cells typically have glycolytic rates up to 200-fold higher than those of their normal tissues of origin (a phenomenon known as the Warburg effect). Whether the ability of ST to induce the Warburg effect in MCC cells is linked to the LSD, phosphatase binding or 4E-BP1 phosphorylation is not known.

### *Mutational landscape in MCC subtypes*

MCPyV⁺ MCC cells typically contain very few mutations, copy number variations or evidence of UV damage. By contrast, MCPyV⁻ MCCs show a very high frequency of DNA mutations associated with UV damage, which are also typically evident in other skin cancers associated with sun exposure, such as melanoma, basal cell carcinoma and cutaneous squamous cell carcinoma (FIG. 3).

Further support for the two distinct subtypes of MCC has emerged from DNA sequencing studies of MCC samples, which relied on sequencing of cancer-specific genes, whole exomes or whole genomes. These studies observed that MCC samples fell into two categories: one form characterized by numerous mutations reflecting UV damage to the DNA and another that contained integrated MCPyV DNA, few somatic mutations and little evidence of UV damage. UV-damaged MCPyV⁻ MCC had a 25–90-fold increase in the number of mutations compared with MCPyV⁺ MCC[7,19,20,57,58]. In addition, these mutations reflected faulty repair of pyrimidine dimers induced by UV radiation. By contrast, MCPyV⁺ tumours had extremely low numbers of mutations (in the range of 0.4 per megabase).

MCPyV⁻ MCCs almost invariably contain mutations that disrupt *RB1*, which regulates cell cycling, whereas most MCPyV⁺ MCCs contain intact *RB1* (REFS 19,59). RB1 restricts cell cycle progression by binding to and repressing transcription factors of the E2F family that transactivate genes required for entry into the DNA replication (S) phase of the cell cycle[60]. Furthermore, this observation suggests that inactivation of RB1 function by mutation in *RB1* or by the binding of the LXCXE motif of LT to RB1 is required for MCC carcinogenesis[61] (FIG. 2b). When *RB1* is mutated or when MCPyV LT is present, RB1 is unable to repress E2F transcription factor-dependent gene expression, and cells are unable to arrest in the G1 phase of the cell cycle (FIG. 3). Strong genetic evidence suggests that the target of the truncated MCPyV LT is RB1 (REF. 62). An MCPyV⁺ MCC cell line with *RB1* deletion continued to proliferate after LT was knocked down by RNA interference[62]. By contrast, knock down of LT in other MCPyV⁺ MCC cell lines that contained wild-type *RB1* caused growth arrest that could be rescued when *RB1* was also knocked down[62].

In addition to loss of *RB1*, MCPyV$^-$ MCCs usually have inactivating mutations or deletions of *TP53* (REFS 57,63), whereas MCPyV$^+$ MCCs tend to contain wild-type *TP53*. Thus, both *RB1* and *TP53* are nearly always mutated in MCPyV$^-$ MCC and intact in MCPyV$^+$ MCC. Nevertheless, p53 activity is reduced in MCPyV$^+$ MCC as well[64]. However, in contrast to the well-studied Simian virus 40 LT, truncated MCPyV LT does not bind to p53, which implies that MCPyV ST, the truncated MCPyV LT or structural variations in the genome of the tumour cell caused by MCPyV insertion contribute to the reduction in activity of wild-type p53.

MCPyV$^-$ MCCs frequently contain inactivating mutations in genes involved in several signalling pathways, including Notch, DNA damage repair and chromatin-modifying pathways (FIG. 3). Loss-of-function mutations in *NOTCH1* and *NOTCH2* have been reported in MCPyV$^-$ MCCs[7,20,57,65]. It is possible that, in MCPyV$^+$ MCCs, LT and ST functionally perturb these signalling pathways, thereby bypassing the requirement for the respective inactivating mutations. Several studies have noted that both MCPyV$^+$ MCCs and MCPyV$^-$ MCCs contain mutations that activate receptor tyrosine kinases (RTKs) and the downstream PI3K–AKT–mTOR growth signalling pathway. Gain-of-function mutations in *AKT1*, *HRAS* and *PIK3CA* or loss-of-function mutations in *PTEN*, *NF1* and *TSC1* have been reported in both MCPyV$^+$ MCCs and MCPyV$^-$ MCCs[7,20,57,65,66]. Several *in vivo* and *in vitro* models of MCC are available (BOX 3).

Box 2 | **Human polyomaviruses**

In 1953, an infectious agent was reported to cause salivary gland cancer in laboratory mice[151]. The cancer-causing agent was identified as a non-enveloped DNA virus that was named polyomavirus (from the Greek roots poly-, which means many, and -oma, which means tumour). In the family *Polyomaviridae*, there are 73 recognized species that are contained within 4 genera, with 3 unassigned species[152]; 14 species can infect humans. Polyomaviruses typically do not cause illness in healthy individuals, although several viruses are associated with disease in immunocompromised hosts, as in the case of Merkel cell polyomavirus (MCPyV)-associated Merkel cell carcinoma (MCC)[153].

Human polyomavirus 6 (HPyV6), HPyV7 and trichodysplasia spinulosa-associated polyomavirus (TSPyV) have been identified on the skin[154,155]. In severely immunocompromised patients, HPyV6 and HPyV7 can cause pruritic dermatoses characterized by hyperproliferation of dyskeratotic (with premature or altered differentiation) keratinocytes that result in brownish skin plaques[156]. TSPyV can cause a hyperkeratotic folliculitis (trichodysplasia spinulosa) in recipients of solid-organ transplant[157,158].

BK polyomavirus (BKPyV) can cause polyomavirus-associated nephropathy in recipients of renal transplant and haemorrhagic cystitis in recipients of haematopoietic stem cell transplant who are treated with immunosuppressive therapy[159]. JC polyomavirus (JCPyV) can cause progressive multifocal leukoencephalopathy (PML)[160], which is characterized by lytic infection of oligodendrocytes and astrocytes. JCPyV can also cause a variety of neurological symptoms including ataxia, paresis, dementia and blindness. The incidence of PML increased in patients with AIDS between the 1980s and 2000s but now is frequently associated with immunosuppressive therapy for multiple sclerosis[161]. JCPyV can also infect neurons and cause a distinct illness called granule cell neuropathy[162].

WU polyomavirus (WUPyV) and KI polyomavirus (KIPyV) have been isolated from respiratory secretions, particularly in children and infants with severe pulmonary symptoms[163,164]; it is not clear whether WUPyV and KIPyV can cause pneumonia. WUPyV has also been detected in respiratory epithelial cells[165]. HPyV10 and Saint Louis polyomavirus (STLPyV) have been isolated from stool samples and might contribute to infectious forms of diarrhoea[166,167]. New Jersey polyomavirus (NJPyV) was originally isolated from a recipient of pancreatic transplant with severe immunosuppression, retinal blindness and vasculitic myopathy[168].

### *Immunogenicity and immune escape*

The immunogenicity of MCC is based on either the presence of MCPyV or the high mutational burden in UV-associated MCC. Cellular immunity mediated by CD8$^+$ T cells that target LT-derived and ST-derived epitopes has been observed in the majority of patients with MCPyV$^+$ MCC. Indeed, intratumoural infiltration of CD8$^+$ T cells is associated with an improved prognosis. However, substantial intratumoural CD8$^+$ T cell infiltration is rare in MCC, as it occurs in ≤20% of tumours[67]. Moreover, infiltrating T cells are often characterized by an exhausted phenotype[68,69] (a process in which T cells progressively lose their function)[70]. Lack of T cell infiltration could reflect different immune escape strategies of MCC cells, such as inhibition of cellular immune responses via programmed cell death protein 1 (PD1) and PD1 ligand 1 (PDL1) signalling or defects in human leukocyte antigen (HLA) class I expression[71]. Decreases in HLA class I antigens on the cell surface can also partially explain primary or secondary resistance of MCC to PD1–PDL1 blockade therapy, which relies on restoring adaptive T cell responses that, in turn, crucially depend on HLA class I-restricted antigen presentation[72].

## Diagnosis, screening and prevention

### *Clinical features*

MCC presents as a rapidly growing, solitary, cutaneous or subcutaneous tumour that is located mostly on sun-exposed areas, particularly the head and neck and also, less frequently, the extremities and buttocks[73–75] (FIG. 4). However, whether MCPyV$^+$ MCC and UV-associated MCPyV$^-$ MCC tend to occur at the same sites is unclear. Lesions are asymptomatic, red-to-violet nodules that might be clinically misconstrued as benign lesions[21] (such as cysts or infectious or inflammatory lesions) or other malignant lesions (such as cutaneous squamous cell carcinoma, lymphoma or metastasis; BOX 4). Ulceration is uncommon. Rarely, multiple lesions arising at different body sites have been observed[76].

Owing to the nonspecific presentation, clinical diagnosis of MCC is often delayed. The acronym AEIOU has been used to recall relevant clinical features of MCC and the patient: asymptomatic, expanding rapidly, immunosuppressed, >50 years of age and UV-exposed[21]. Because clinical diagnosis of MCC is challenging, histopathological analysis of suspected lesions is necessary to confirm it.

MCC usually spreads to the lymph nodes first; thus, sentinel lymph node biopsy (SLNB; that is, removal and examination of the sentinel node) represents an important staging procedure[3,77]. In the most recent AJCC staging system, to be adopted in 2018, four clinical stages of MCC are recognized based on features at time of presentation (TABLE 1): stage 0 (*in situ*), stage I (localized disease, primary lesion ≤2 cm), stage II (localized disease, primary lesion >2 cm), stage III (nodal spread) and stage IV (metastatic disease beyond the local nodes)[15]. Survival depends on the stage at diagnosis: 5-year survival is 62.8% in patients with stage I MCC, 34.8–54.6% in stage II, 26.8–40.3% in stage III and 13.5% in stage IV[75]. Owing to increasing awareness of MCC,

most of the initial diagnoses are stage I or stage II MCC. Local or distant recurrences usually occur within the first 2–3 years after initial diagnosis; thus, patients whose cancer has not recurred by 3 years are at substantially diminished risk of recurrence.

In up to 10% of patients, MCC is diagnosed when enlarged lymph nodes are removed for analysis; notably, in these cases, there is no evident primary cutaneous tumour, and the prognosis is more favourable than in cases of cutaneous MCC with lymph node metastases[78]. Besides regional lymph nodes, metastases are commonly found in the skin, distant lymph nodes, lungs, adrenal glands, liver, brain and bones.

MCC might regress spontaneously. Indeed, spontaneous regression of even metastatic MCC has been reported, and is associated with improved prognosis[79]. Notably, patients with stage III MCC and an unknown primary tumour have a better prognosis than patients with stage III MCC and a known primary tumour[80]. The mechanism of regression probably involves immunological responses and apoptosis of malignant cells, and its precise understanding could provide valuable clues for new therapies.

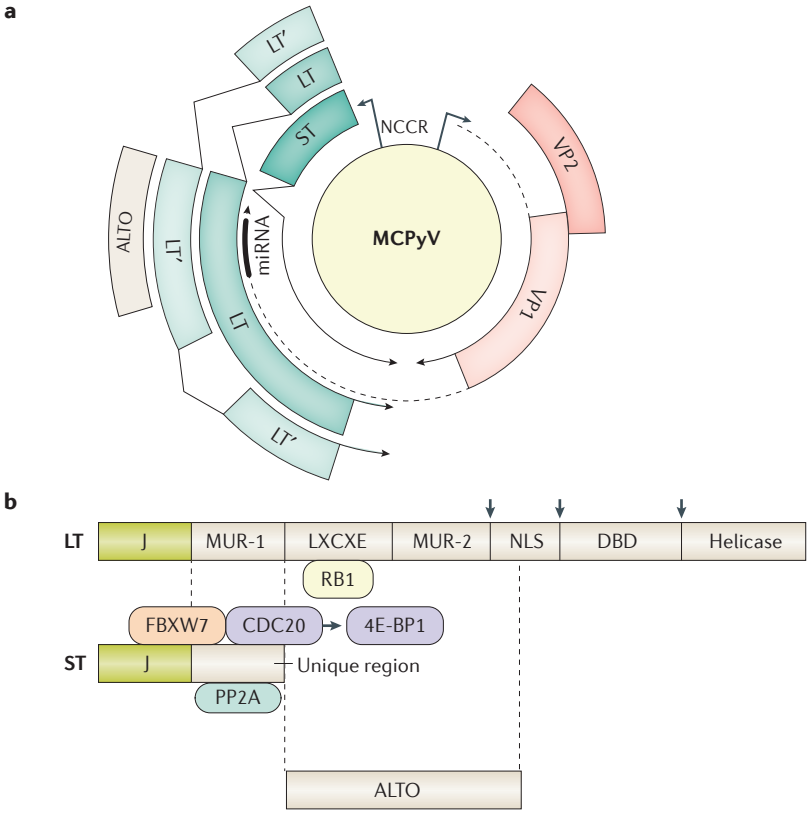


Figure 2 | **Circular map of MCPyV and linear maps of the MCPyV early genes.** **a** | Merkel cell polyomavirus (MCPyV) has a 5,387 bp circular double-stranded DNA genome with two transcriptional units[36], the early and late regions. The early region yields four spliced mRNAs encoding four proteins: two alternatively spliced isoforms of the large T antigen (LT and LT', which is also known as 57 kT), the small T antigen (ST) and ALTO (alternate frame of the LT open reading frame). The late region encodes two viral coat proteins, VP1 and VP2, and a microRNA that targets the T antigen transcripts[45,172,173]. **b** | LT contains an N-terminal J domain, MCPyV-unique region (MUR)-1 and MUR-2, LXCXE motif (where the retinoblastoma-associated protein (RB1) binds), nuclear localization signal (NLS), DNA or origin binding domain (DBD) and helicase domain. The cell growth-inhibitory domain (not shown) overlaps with the helicase domain. On the basis of its similarity to other polyomaviruses, MCPyV LT is thought to form two hexamers that bind in head-to-head fashion to the origin of replication and serves to melt, twist and unwind the viral DNA and recruit the cellular DNA polymerases of the host cell to enable viral replication[174–176]. Which cells normally support MCPyV replication in humans is unknown, as MCPyV LT expression has not yet been detected by immunohistochemistry in any normal human tissue. However, cultures of primary human dermal fibroblasts could support MCPyV replication[144]. In Merkel cell carcinoma (MCC), mutations in MCPyV DNA result in truncated LTs (indicated by arrows) that retain the LXCXE motif and sometimes the NLS and can bind and inhibit RB1. ST contains an N-terminal J domain and a unique domain not shared with LT. ST can bind to regulatory and catalytic subunits of protein phosphatase 2A (PP2A). The LT stabilizing domain (not shown) within the unique domain is distinct from the sequence that binds the phosphatase and participates in binding to F-box/WD repeat-containing protein 7 (FBXW7) and cell division cycle protein 20 homologue (CDC20). MCPyV ST binding to CDC20 could contribute to increased phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1)[177]. NCCR, non-coding control region.

### *Key imaging techniques*

Upon a confirmed histopathological diagnosis of MCC (see below), patients should be screened for the presence of extracutaneous disease[81–83]. Ultrasonography of regional lymph nodes is commonly used to screen the nodal basin. CT and MRI are effective, but, in many centres, they have been integrated with or replaced by PET–CT[84,85]. In fact, in a single-institution study, PET–CT imaging resulted in changes to the stage classification in 33% of patients and to management in 43% of patients[86].

### *Histopathology*

MCC cannot be diagnosed based on clinical examination alone. In the majority of cases, assessing the histopathological features and the immunological marker expression profile of a biopsy specimen of the lesion is sufficient for a definitive diagnosis. However, MCC cells are very sensitive to drying artefacts that can occur during the preparation of the sample (particularly in small biopsies), and, in such cases, a morphological diagnosis might be impossible. Regardless of the presence of artefacts, samples with phenotypic aberrations require a more-comprehensive (and expensive) immunohistochemical work-up (FIG. 5).

MCC belongs to the so-called small-blue-round-cell tumours and is composed of dermal and/or subcutaneous nodules or sheets (FIG. 5a) of small, monomorphic, round-to-oval cells with a vesicular nucleus and scanty cytoplasm[87] (FIG. 5b). Three main types of MCC have been described — small-cell, trabecular (FIG. 5c) and intermediate — but most cases present with overlapping features, and the classification of MCC according to these three variants does not have practical implications. Neoplastic cells might be large (particularly in recurrences after radiotherapy) and, in some cases, show a more-pleomorphic morphology. The nucleoli are multiple and usually not prominent. Necrosis can be prominent, and microscopic features of individual cell necrosis are common.

Large tumour thickness, high mitotic rate, an infiltrative (rather than circumscribed) growth pattern and the presence of lymphovascular invasion have been associated with increased risk of microscopic nodal metastases and a poor prognosis, but none of these features is generally used in clinical practice for prognostic purposes.

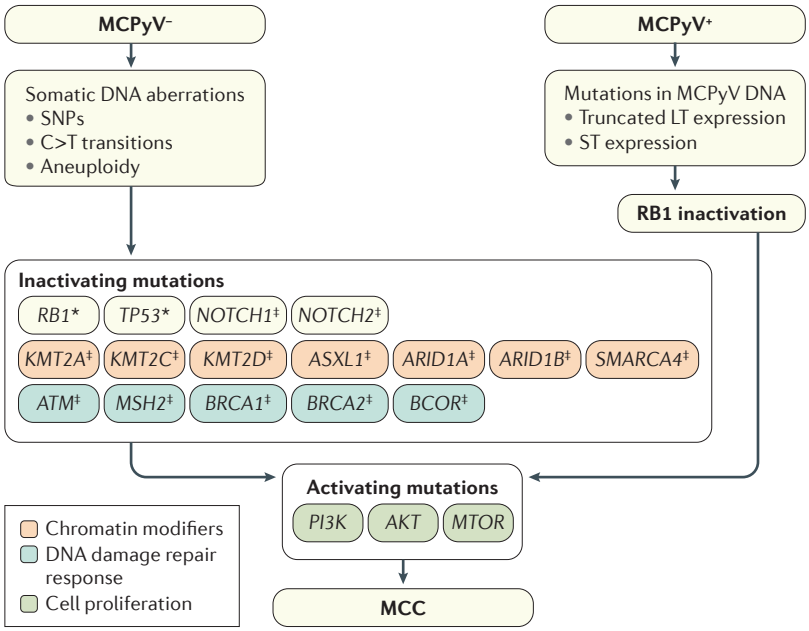


Figure 3 | **Genetic aberrations in MCC.** Merkel cell carcinoma (MCC) develops from substantial changes in the genome that originate from ultraviolet light damage (including point mutations, amplifications, deletions and translocations) or integration of the Merkel cell polyomavirus (MCPyV) genome and expression of large T antigen (LT) and small T antigen (ST) that lead to perturbations in a variety of signalling pathways. The retinoblastoma-associated protein (RB1) pathway, which normally has tumour-suppressive roles, is altered by mutations in *RB1* in MCPyV⁻ MCC and by LT in MCPyV⁺ MCC, which perturbs the ability of RB1 to inhibit transcription factors of the E2F family. Cellular tumour antigen p53 (encoded by *TP53*) contributes to regulating the cell cycle by activating genes that negatively regulate cell division; *NOTCH1* and *NOTCH2* encode receptors involved in cell differentiation and proliferation. SNPs, single-nucleotide polymorphisms. *Mutation observed in most cases; ‡mutation observed frequently.

Epidermotropism (invasion of tumour cells to the epidermis) can be observed in ~10% of cases[88]. Rare, purely intraepidermal tumours have been described[89]. Intralymphatic invasion is common (FIG. 5d) and, in the author's experience (L.C.), isolated tumour cells far from the main tumour mass and often in proximity of the surgical margins are a moderately frequent finding (FIG. 5e). The presence of intralymphatic complexes and isolated tumour cells close to the surgical margins can explain the high rate of local recurrences and should be accurately searched for and documented in the histological report.

MCC has been observed contiguous to or intermingled with other skin malignancies, particularly cutaneous squamous cell carcinoma, including Bowen disease[90,91] (a red and scaly patch on the skin that is the sign of very early cutaneous squamous cell carcinoma). The relatively frequent association between MCC and cutaneous squamous cell carcinoma could be explained by both tumours originating from a common multipotent stem cell, divergent differentiation of neoplastic cells or simultaneous growth of two unrelated malignancies. Overexpression of p53 has been observed in combined tumours[92]. MCC has been occasionally found at the same site as other benign or malignant tumours, but these cases probably represent chance associations.

***Immunohistological markers.*** MCC has a characteristic immunohistological profile, in terms of antigens expressed and expression patterns. Notably, although these markers are helpful and important for diagnosis, particularly in the presence of artefacts, no convincing evidence supports the use of any such markers to predict the prognosis or response to therapy. Furthermore, no marker has been reliably associated selectively with either MCPyV⁺ MCC or MCPyV⁻ MCC and, therefore, no differential diagnosis between the two MCC types can be made on the basis of immunohistochemistry alone. Whereas positive staining for MCPyV LT probably strongly suggests an MCPyV⁺ MCC, negative staining does not necessarily rule it out.

MCC cells express several type I or type II cytoskeletal keratins, in particular CK20 (FIG. 5f), but also CK8, CK18 and CK19. In addition to cytoskeletal keratins, neoplastic cells also express neuroendocrine markers such as synaptophysin (FIG. 5g) and several others (FIG. 1). Consistent with the genetic findings, a large subset of MCCs stain positive for the MCPyV T antigens (FIG. 5h). Positivity for the oncoprotein huntingtin-interacting protein 1 (HIP1) has been observed in the majority of cases[93]. Staining for tumour protein 63 (p63) has been observed in one-third of cases and has been linked to a worse prognosis[94,95], but available data suggest that it cannot prognosticate patients independent of stage.

A small subset of MCCs (<10%) are negative for CK20; these cases are characterized by a high mutational burden and are generally MCPyV⁻ MCCs. MCC is usually negative for thyroid transcription factor 1 (TTF1, also known as homeobox protein Nkx-2.1), mammalian achaete-scute homologue 1 (ASH1), vimentin, S100B and CK7. However, rare cases of MCC can be positive for TTF1 or CK7; thus, the staining patterns of these two antigens should be interpreted with caution. Variable numbers of tumour-infiltrating cytotoxic T lymphocytes are found in a subset of cases of MCC (FIG. 5i), and their presence is associated with a better prognosis[67,96–99].

***Differential diagnosis.*** Several tumours might show a small-blue-round-cell morphology (BOX 4). In most cases, morphological features, positive staining for CK20 and neuroendocrine markers and negative staining for TTF1, CK7 and lymphoid markers are sufficient to confirm the diagnosis of MCC. Of note, metastatic small-cell carcinoma of the lung can rarely be positive for CK20, and, conversely, MCC can rarely be positive for TTF1 or negative for CK20 (or both); in such cases, all available markers should be used to make a precise diagnosis. Notably, MCPyV is absent in neuroendocrine carcinomas arising in other organs; thus, screening for MCPyV is a potential tool to differentiate MCC from other neuroendocrine tumours[42].

### *Screening, surveillance and prevention*

Owing to the very low incidence of MCC, specific screening programmes are unwarranted. Indeed, in the United States, the Surgeon General (in 2014) and the US Preventive Services Task Force (in 2009) concluded that insufficient evidence exists to assess the balance of the benefits and harms of skin cancer screening[100,101].

Box 3 | ***In vitro* and *in vivo* models of MCC**

**Cell lines**

- MCPyV$^+$ Merkel cell carcinoma (MCC) cell lines frequently used include MKL-1, MKL-2, MS-1, WaGa, PeTa, BroLi and LoKe[63].
- MCPyV$^-$ MCC cell lines include MCC13, MCC26 and possibly UISO[169,170].
- The classic growth pattern of MCC cell lines is characterized by a neuroendocrine appearance (that is, cells grow in suspension and form clusters or spheroids). Notably, the above-listed MCPyV$^-$ MCC cell lines grow as adherent cells; thus, these are also referred to as variant MCC cell lines. Data based on these variant MCC cell lines should be interpreted with appropriate care[169].

**Xenotransplantation models**

- In mice, WaGa and MKL-1 cells form xenograft tumours with neuroendocrine features that recapitulate MCC, whereas tumours derived from UISO cells lack neuroendocrine features[149,169].

**Genetically engineered mouse models**

- MCPyV full-length small T antigen (ST) and truncated large T antigen (LT) were inserted in the *Rosa26* locus in knock-in mice and expressed in the stratified squamous epithelial cells via Cre recombinase driven by the *Krt14* promoter[171]. Their expression resulted in Merkel cells with hyperplasia, hyperkeratosis (increased thickness of the stratum corneum) and acanthosis (thickening) of the skin, but no MCC.
- Mice that expressed MCPyV ST by Cre recombinase driven by the ubiquitously expressed *Ubc* promoter (ST floxed strain) developed hyperkeratosis and hypergranulosis (increased thickness of the granular layer) of the ear lobes.
- Crossing the ST floxed strain with a *Trp53* floxed strain resulted in highly anaplastic tumours in the spleen and liver[51].
- Crossing the ST floxed strain with an *Atoh1*-Cre strain resulted in an increased number of Merkel cells in the embryo.
- When the preceding ST floxed, *Atoh1*-Cre strain was crossed with the *Trp53* floxed strain, no additional effects were observed.
- Constitutive expression of ST driven by the promoter of bovine keratin 5 showed an expanded and disorganized epithelium with decreased differentiation, increased levels of proliferation markers, evidence for apoptosis and DNA damage[52]. Notably, when ST was co-expressed with *Atoh1*, epidermis-derived MCC-like tumours developed[53].

MCPyV, Merkel cell polyomavirus.

The link between MCC and immune suppression is well demonstrated; the selection of tailored immunosuppressive medications in patients who require them could have a crucial role in the prevention of skin cancer in general[102]. However, at present, there are no data supporting the association between specific immunosuppressive treatments and the development of MCC. Dermatological screening with a risk-stratified surveillance represents a crucial part of the management of immunosuppressed patients, especially in patients who received a transplant and in patients with B cell chronic lymphocytic leukaemia[82,103]. In particular, in high-risk patients, biopsy of suspicious cutaneous lesions should not be postponed.

Appropriate surveillance is particularly important for patients with MCC for several reasons. First, the 33–46% mortality of MCC is substantially higher than that of malignant melanoma[75]. Second, the emerging immunotherapy options for MCC could be more-effective in patients with less-advanced disease, with corresponding lower disease burden[104]. As 80% of MCC recurrences occur within 2 years of the initial diagnosis[105,106], gradually decreasing the frequency of surveillance is justified, based on the diminishing risk of recurrence at later times. If patients remain recurrence-free >5 years after diagnosis, they probably do not need to be followed-up closely (for example, once per year).

Appropriate surveillance for MCC recurrence includes physical examination (including a complete skin and lymph node evaluation), which should be performed every 3–6 months for the first 2 years and every 6–12 months thereafter[81,82]. Current guidelines recommend imaging as clinically indicated, with more-frequent imaging in high-risk patients[28] (for example, immunosuppressed patients or those with more-advanced disease). Some studies indicate that PET–CT could be more accurate than CT or MRI alone[107]. Nevertheless, if PET–CT is not available, CT or MRI with contrast could be used.

Unlike invasive tissue-based analyses, blood-based biomarkers as surrogates of tumour burden can be repeatedly checked to monitor the clinical course of patients. The titres of antibodies against MCPyV T antigens (which are present in 52% of patients with MCC) have been shown to correlate with disease burden[108]. In another prospective validation study of 219 patients, measuring anti-ST antibodies provided useful clinical guidance[109]. Patients in whom no anti-ST antibodies could be detected had a 42% greater risk of recurrence, perhaps indicating either a less-robust immune response or an MCPyV$^-$ tumour status. Seropositive patients whose anti-ST antibody titres decreased over time had a 97% chance of being free of detectable disease at the time of the blood draw. By contrast, if the titre increased, 88% of patients either had detectable disease at the time of the blood draw or subsequently developed recurrent disease. However, validation of the results of this study in different patient cohorts and laboratories is required before antibody titres can be adopted for routine use in MCC surveillance[109].

UV radiation exposure (either from sunlight or artificial light sources) has been associated with an increased risk of developing MCC and is the most easily preventable risk factor for MCC. However, although UV avoidance (for example, staying indoors, seeking shade when outdoors and avoiding the use of tanning beds) and UV protection (for example, wearing wide-brimmed hats, clothing and sunscreens) are generally advised as the principal strategies for MCC prevention, the efficacy of these strategies has not yet been demonstrated. Moreover, controversy persists regarding UV protection measures, especially given the role of UV radiation in the cutaneous synthesis of vitamin D and the reported association between chronic sunscreen use and low serum 25-hydroxyvitamin D levels[110], particularly in the elderly population. Another study reported a correlation between vitamin D deficiency and MCC characteristics and outcome[111]. Other well-established risk factors for MCC, such as advanced age and disease-associated or iatrogenic immune suppression, cannot realistically be avoided. Notably, some immunosuppressive agents, such as calcineurin inhibitors, have a direct effect on cutaneous squamous cell carcinoma carcinogenesis[112–114], but such an effect has not been suspected for MCC.

## Management

After the analysis of the biopsy specimen of the initial lesion confirms the diagnosis of MCC, the lymph nodes of the draining basin are examined (clinically and/or with ultrasonography), as the following management steps should take into account whether they are clinically positive (enlarged) or negative (FIG. 6). If these nodes are clinically negative, SLNB should be considered; if they are clinically positive, tissue biopsies should be performed.

### *Primary tumour*

Wide local excision of the primary tumour is the standard of care, but it is not always feasible[81,82]. In fact, ~40–50% of MCCs are located on the head and neck, and wide excision can have unacceptable functional or cosmetic implications. Similarly, patients can be ineligible for extensive surgery if this entails high-risk general anaesthesia and potential postoperative complications. Furthermore, in the literature, there is no formal evaluation of appropriate excision margins and the risk of recurrence. However, the local recurrence rate is significantly higher with small excisions and is particularly high in case of positive surgical resection margins[105,115] (that is, if tumour cells are present at the edge of the excised tissue). The National Comprehensive Cancer Network (NCCN) and the European Association of Dermato-Oncology (EADO)–European Organisation for Research and Treatment of Cancer (EORTC) guidelines recommend a 1–2 cm excision margin down to the muscle fascia or the pericranium (the membrane that externally covers the skull), regardless of tumour size[81,82,116]. When functional considerations are important, excision can be performed with microscopically controlled surgery and complete histological inspection of the margins of the excised material to confirm complete resection of the tumour can be considered, but experience is limited in MCC[115,117,118]. Of note, the safety margin is intended to remove microscopic satellite metastases rather than to ensure clear resection margins of the primary tumour[81,82]. Any reconstruction involving tissue displacement should be postponed until negative margins have been confirmed and SLNB is performed, if applicable. Surgical techniques for reconstruction of the skin defect should take further adjuvant radiotherapy into account.

The surgical management of local recurrences is not well established. In many cases, these are handled similarly to the primary tumour, but no formal studies have been conducted to test this approach.

### *Loco-regional disease*

If the lymph nodes of the draining basin are clinically negative, SLNB should be considered and planned at the same time as the wide local excision (FIG. 6), as clinically occult nodal micrometastases are present in ~30% of patients. Although a retrospective study suggested that patients with a tumour diameter <10 mm had a lower probability of having regional lymph node metastasis, a systematic review of 36 studies involving 692 patients revealed that 30% of patients had a positive SLNB, consistent with the propensity of MCC to metastasize to lymph nodes even if the primary tumour is small[119,120]. The presence of occult nodal metastasis is a strong prognostic factor[15,119,121]; the reported 3-year overall survival was 88% for patients with negative SLNB versus 57.2% for patients with positive SLNB[121]. SLNB is, therefore, recommended whenever possible in patients with clinically negative lymph nodes, regardless of the size of the primary tumour[81–83]. Detection of occult tumour metastasis should be based on the analysis of haematoxylin and eosin stained sections and the appropriate immunological markers panel described above[81,82]. Still, the rate of false-negative results has been estimated to be up to 14.3% and is higher in MCCs located on the head and neck[122].

Owing to limited data, there is a lack of consensus on the optimal approach in case a nodal micrometastasis is detected. It is generally assumed that a subset of patients (for example, up to 30% in a published study)[121] will harbour subclinical MCC in the next-echelon lymph nodes and could progress to clinical nodal metastases if untreated. The treatment options include complete nodal dissection and/or elective regional radiotherapy to the draining lymph node basin, but none of these have been compared in a randomized fashion. As a rule, patients will require adjuvant wide-field radiotherapy to the primary tumour site, and these patients might, therefore, be considered for loco-regional radiotherapy to reduce the risk of nodal spread or recurrence. Notably, one study in patients with lymph node

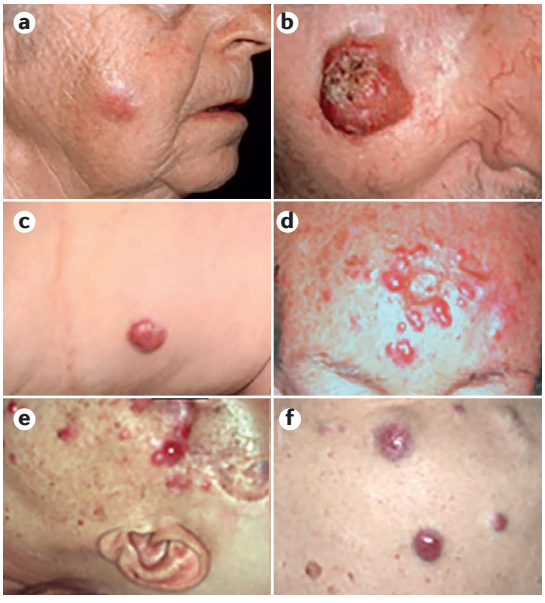


Figure 4 | **Clinical presentations of MCC. a** | Cutaneous–subcutaneous nodule on sun-exposed skin of an elderly woman. **b** | Large, partly ulcerated tumour on sun-exposed skin of an elderly man. **c** | Small cutaneous tumour on the thigh of an immunosuppressed woman. **d** | Satellite metastases on the forehead of an elderly woman. **e** | In-transit metastases on the face of an immunocompromised woman. **f** | Multiple cutaneous distant metastases on the back of a woman.

involvement demonstrated that radiotherapy alone to positive regional lymph nodes conferred benefits comparable to those of complete lymph node dissection (with or without adjuvant radiotherapy). After 2 years, there was no difference in regional relapse-free survival or disease-specific survival[123]. Nevertheless, until these observations are confirmed by additional clinical trials, patients with clinically positive lymph nodes should undergo complete lymph node dissection[81,82].

Isolated satellite or in-transit metastases around the primary tumour should be removed surgically if a complete resection is feasible[81,82]; otherwise, radiotherapy or systemic therapy should be considered.

### *Radiotherapy*

In many cases, wide-field adjuvant radiotherapy to the site of the primary tumour and, in some cases, to the draining lymph node basin is recommended following surgery. The adverse events associated with radiotherapy can often be limited with the use of highly conformal radiotherapy delivery, in which imaging scans are used to pinpoint the treatment area very precisely in three dimensions. However, most patients require 4–5 weeks of daily treatment and will experience cutaneous desquamation, fatigue and site-specific issues, for example xerostomia (dry mouth) and taste dysfunction with parotid radiotherapy. Even though the clinical benefit of adjuvant radiotherapy is not supported by all retrospective studies[105], it is recommended[124] in the current American[81,125] and European[82,83,121] guidelines for diagnosis and treatment of MCC.

MCC is very responsive to radiotherapy; thus, single-modality radiotherapy can be considered in patients who are deemed inoperable[126]. Radiotherapy to tumours and/or positive lymph nodes can control the disease in 75–85% of cases. With careful planning, even elderly patients can tolerate radiotherapy, as the treated volume is usually relatively superficial and ipsilateral (on the same side of the body). In patients with very poor performance status, a shorter, hypofractionated course of radiotherapy (in which the full treatment dose is administered in 5–10 fractions) might improve the patient's quality of life, by reducing the size of an enlarging lesion and potentially delaying or preventing fungation that results in ulceration and bleeding. In patients with visceral or skeletal metastasis, a single 8 Gy fraction can offer excellent palliation and decrease debilitating skeletal pain[127].

If SLNB cannot be performed, adjuvant radiotherapy to the lymph node basin might be beneficial for local control[128], but this benefit must be balanced with the potential for long-term adverse effects. This option should be discussed on an individual basis using a multidisciplinary approach. Follow-up of the regional lymph nodes with ultrasonography and clinical examination should be planned[81,82].

A retrospective analysis of data from the US National Cancer Database from 2,065 patients with stage III MCC concluded that adjuvant radiotherapy in these patients did not provide survival benefit[125]. Thus, adjuvant radiotherapy to the draining lymph node basin after therapeutic node dissection cannot be universally recommended, but it should be considered on a case-by-case basis to balance disease control with the increased risk of developing lymphoedema, especially in the lower limbs[129].

### *Systemic therapy*

***Chemotherapy.*** Until 2016, before the introduction of immunotherapy, the most common treatments for metastatic MCC not amenable to surgery were chemotherapeutic regimens often used for other small-cell carcinomas; these include platinum-based regimens, etoposide[130], taxanes and anthracyclines, either alone or in various combinations. The rationale for this approach was the observation that MCC has a cell morphology similar to that of other small-cell carcinomas as well as the fact that this treatment led to clinically meaningful responses in a subset of patients with MCC; however, these responses were short-lived.

Furthermore, reports of chemotherapy for MCC are sparse, with most studies being case series or case reports. Across all studies, response rates ranged from 20–61%, with higher response rates in the first-line setting (53–61%) than in the second-line setting (23–45%), and the duration of response was short in both settings. The largest single-centre retrospective analysis of patients with distant metastatic MCC (62 patients) showed a 55% response rate in those who received first-line chemotherapy; however, the median progression-free survival was 94 days, and the median overall survival was 9.5 months[131]. In the 30 patients who also received second-line chemotherapy, the response rate was 23%, median progression-free survival was 61 days and median overall survival was 5.7 months[131]. Similar poor results of second-line chemotherapy were reported in another retrospective analysis of 34 European patients[131,132].

Box 4 | **Differential diagnosis of MCC**

- Cyst
- Dermatofibroma
- Amelanotic melanoma
- Cutaneous metastasis of other tumours (for example, small-cell lung cancer)
- Lymphoma
- Cutaneous squamous cell carcinoma
- Adnexal tumour
- Histopathological differential diagnoses, that is, with small-blue-round-cell morphology
  - Basal cell carcinoma
  - Metastatic small-cell carcinoma (in particular, of the lung)
  - Cutaneous lymphoma (in particular, lymphoblastic lymphoma)
  - Anaplastic sweat gland carcinoma
  - Malignant melanoma
  - Ewing sarcoma
  - Neuroblastoma
  - Rhabdomyosarcoma
  - Undifferentiated epidermoid carcinoma

Table 1 | **Staging of Merkel cell carcinoma**

| Stage | | Primary tumour | Lymph node | Metastasis |
|---|---|---|---|---|
| 0 | NA | *In situ* (within epidermis only) | No regional lymph node metastasis | No distant metastasis |
| I | Clinical* | ≤2 cm maximum tumour dimension | Nodes negative by clinical exam (no pathological exam performed) | No distant metastasis |
| I | Pathological‡ | ≤2 cm maximum tumour dimension | Nodes negative by pathological exam | No distant metastasis |
| IIA | Clinical | >2 cm tumour dimension | Nodes negative by clinical exam (no pathological exam performed) | No distant metastasis |
| IIA | Pathological | >2 cm tumour dimension | Nodes negative by pathological exam | No distant metastasis |
| IIB | Clinical | Primary tumour invasion of bone, muscle, fascia or cartilage | Nodes negative by clinical exam (no pathological exam performed) | No distant metastasis |
| IIB | Pathological | Primary tumour invasion of bone, muscle, fascia or cartilage | Nodes negative by pathological exam | No distant metastasis |
| III | Clinical | Tumour of any size or depth | Nodes positive by clinical exam (no pathological exam performed) | No distant metastasis |
| IIIA | Pathological | Tumour of any size or depth | Nodes positive by pathological exam only (nodal disease not apparent on clinical exam) | No distant metastasis |
| | | Not detected (unknown primary) | Nodes positive by clinical exam and confirmed via pathological exam | No distant metastasis |
| IIIB | Pathological | Tumour of any size or depth | Nodes positive by clinical exam, and confirmed via pathological exam or in-transit metastasis | No distant metastasis |
| IV | Clinical | Any | With or without regional nodal involvement | Distant metastasis detected via clinical exam |
| IV | Pathological | Any | With or without regional nodal involvement | Distant metastasis confirmed via pathological exam |

Staging according to the American Joint Committee on Cancer 8th Edition Cancer Staging System[178]. NA; not applicable. *Clinical detection of nodal or metastatic disease can be via inspection, palpation and/or imaging. ‡Pathological detection or confirmation of nodal disease can be via sentinel lymph node biopsy, lymphadenectomy or fine-needle biopsy; pathological confirmation of metastatic disease can be via biopsy of the suspected metastasis.

When chemotherapy was used as an adjuvant treatment after surgical removal of all evident MCC lesions, the results were even less compelling. A retrospective study of 6,908 cases in the US National Cancer Database found that, in multivariable analysis, adjuvant chemotherapy was not associated with overall survival benefit in patients who presented with either local or nodal MCC[125].

***Immunotherapy.*** The PD1–PDL1 immune-checkpoint pathway is a key therapeutic target in reactivating immune responses against various types of cancers[133]. Several lines of evidence indicate that targeting this pathway could be an effective approach in MCC: MCC was identified as an immunogenic cancer (on the basis of the higher incidence and poorer prognosis in immunosuppressed individuals)[28], immune responses to MCPyV T antigens are present in the blood of patients with MCC[134] and tumour-infiltrating T cells (specific to MCPyV proteins or unspecific) are enriched in some MCCs[135]. MCC immunogenicity is readily explained by the constitutive expression of viral proteins in $MCPyV^+$ MCCs and by the very high frequency of DNA mutations associated with UV damage in $MCPyV^-$ MCCs.

Importantly, three phase II open-label clinical trials of therapeutic antibodies against PD1 or PDL1 have demonstrated high and durable response rates[104,136,137] (TABLE 2) that are more durable than those reported in historical data of patients treated with chemotherapy. In the first study to report immune-checkpoint blockade using the anti-PD1 antibody pembrolizumab in patients with advanced-stage MCC, the response rate was 56%[136]. The rate of progression-free survival at 6 months was 67%, compared with 24% for chemotherapy, based on historical data[130,131]. These promising results led to the inclusion of pembrolizumab as a systemic therapy option for disseminated disease in the 2017 NCCN guidelines for MCC management[81]. The second, larger study explored immune-checkpoint inhibition using the anti-PDL1 antibody avelumab as second-line therapy in patients with MCC that progressed following chemotherapy[104]. Of the 28 patients who responded, 23 (82%) still maintained their initial response at a median follow-up of 10.4 months. The efficacy of avelumab in chemotherapy-refractory advanced-stage MCC led to the accelerated evaluation and US FDA approval of avelumab for MCC in March 2017. Notably, initial results from a cohort of chemotherapy-naive patients show that avelumab has a response rate similar to those

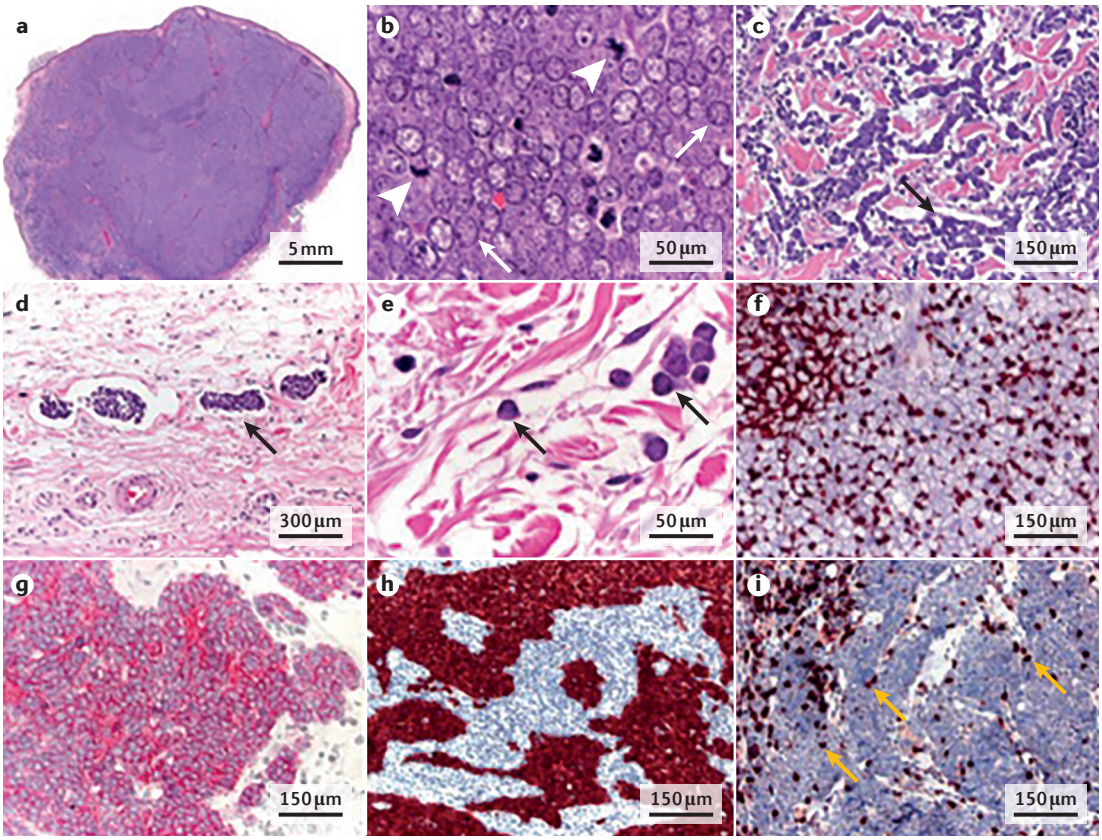


Figure 5 | **Histopathological and immunohistochemical features of MCC.** Small-blue-round-cell tumours such as Merkel cell carcinoma (MCC) owe their name to the colour of the cancerous cells after haematoxylin and eosin staining. **a** | Large dermal and subcutaneous nodule. **b** | Higher-magnification view of the tissue in part **a** shows monomorphic mid-sized cells with vesicular nuclei, scanty cytoplasm (arrows) and several mitoses (arrowheads). **c** | The trabecular pattern characterized by anastomosing (connecting) cords of tumour cells (arrow) was the feature that gave MCC its first name of trabecular carcinoma of the skin. This feature is relatively uncommon and is usually found at the periphery of the tumour. **d** | Intra-lymphatic complexes of tumour cells (arrow). **e** | Isolated tumour cells near the margin of the surgical excision (arrows). **f** | Strong positivity for cytokeratin 20 (CK20) staining (brown), with a dot-like perinuclear accentuation, although a more-diffuse cytoplasmic pattern can also be observed. **g** | Positivity for synaptophysin (dark pink). **h** | Strong positivity for the Merkel cell polyomavirus (MCPyV) large T antigen (brownish red). **i** | Staining for CD8, which reveals some intratumoural (arrows) and several peritumoural $CD8^+$ T lymphocytes.

reported for anti-PD1 antibodies[138] (TABLE 2). Of note, in all three trials, the response to immune-checkpoint blockade therapy was independent of MCPyV or PDL1 expression status.

These studies demonstrate that immunotherapy can benefit patients with advanced-stage disease and is superior to any form of therapy used hitherto; however, a substantial portion of advanced-stage MCCs do not respond to PD1–PDL1 inhibitors. Thus, several clinical trials of immune-checkpoint inhibitors for MCC are ongoing, including combinations with cytotoxic T lymphocyte protein 4 (CTLA4) inhibitors, adoptive T cell or natural killer cell transfer or other new therapeutic agents[139].

## Quality of life

Quality-of-life considerations are relevant in patients diagnosed with MCC; these individuals are generally elderly and often have other medical comorbidities. Patients >75 years of age are less tolerant to multi-modal treatment[140], which could involve combinations of loco-regional surgery, loco-regional radiotherapy and systemic cytotoxic, targeted or immune therapy. Consequently, seeking an onco-geriatric assessment in selected patients before deciding a management course should be considered. Clinicians must always balance the goal of curing a patient with the need to limit the adverse effects of the treatment, as acute toxicity is potentially fatal, and long-term toxicity has an ongoing effect on patient quality of life.

As MCC is a rare cancer, there are no validated MCC-specific quality-of-life measurement instruments; other generic or dermatology-specific instruments have not been validated for patients with MCC. In addition to the effect of receiving a diagnosis of this aggressive cutaneous malignancy, treatment-related toxicity can have a major effect on quality of life. Thus, in very old patients with multiple comorbidities, fast-acting and straightforward-to-use interventions (often radiotherapy alone) might be considered.

The use of systemic cytotoxic treatments in MCC management remains controversial and not without concerns in elderly patients. In the palliative setting, the responses are often short-lived, and patient quality of life might be affected more by the treatment than by the disease. In a study of chemotherapy compliance in patients with advanced-stage MCC, older age was associated with failure to complete the planned chemotherapy course[141]. However, evidence suggests that the efficacy and adverse-effect profile of immune-checkpoint inhibitors warrant their use to treat this population of patients[142].

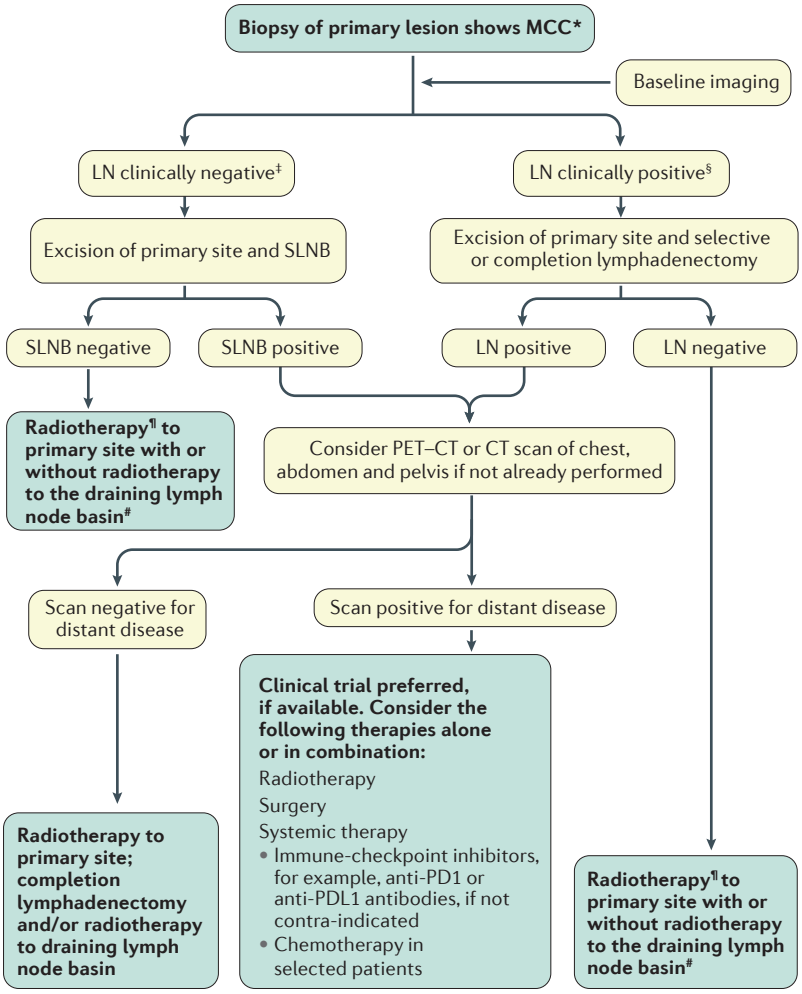


Figure 6 | **Simplified evaluation and treatment of primary MCC.** Algorithm for diagnostic and therapeutic decisions for managing patients with Merkel cell carcinoma (MCC). The flowchart begins with the assessment of the extent of disease spread to distant sites (baseline imaging) and regional nodal disease (typically including pathological assessment of clinically negative nodes). After staging is complete, the appropriate therapy can be identified. See the National Comprehensive Cancer Network guidelines[81] and http://www.merkelcell.org/ for further information, including surveillance guidance. LN, lymph node; PD1, programmed cell death protein 1; PDL1, PD1 ligand 1; SLNB, sentinel lymph node biopsy. *Consider baseline Merkel cell polyomavirus serology for prognostic significance and to track disease. ‡No pathologically enlarged nodes on physical examination and by imaging study. §Pathologically enlarged nodes on physical examination or by imaging study. ¶Radiotherapy is indicated in most patients, with the exception of low-risk disease (for example, primary tumour ≤1 cm on the extremities or trunk, no lymphovascular invasion or negative surgical margin) in patients who are not immunosuppressed. #Consider radiotherapy to the nodal basin in high-risk patients.

The effect on quality of life that treatment can have should not be underestimated: limiting treatment-related toxicity should be one of the goals of any management course and the objective of future research.

## Outlook

Despite major advances in the understanding of the carcinogenesis, biology and immunology of MCC, as well as the breakthrough in the therapy of advanced-stage disease using immune-checkpoint inhibitors, much work remains. The open questions include determining the cell of origin of MCC, susceptibility factors for and exact mechanism of viral carcinogenesis and — of greater clinical relevance — primary and secondary immune escape mechanisms. In addition, there could be opportunities for the development of targeted therapies for both MCPyV$^+$ MCC and MCPyV$^-$ MCC.

The cellular origin of MCC is still controversial. Initially, the favoured theory was that MCC originates from Merkel cells, which was followed by the hypothesis that a Merkel cell precursor, for example epidermal or dermal stem cells, is the possible cell of origin of MCC[34]. Later, the hypothesis that MCC derives from pro-B cells or pre-B cells was suggested[33,143], based on the observation that early B cell antigens are expressed in MCC. However, to date, expression of the MCPyV T antigens has not been able to transform any of these cells *in vitro*. Notably, human dermal fibroblasts support productive MCPyV infection[144]. Induction of genes encoding matrix metalloproteinases by the WNT–β-catenin signalling pathway stimulated MCPyV infection, a finding that suggests that UV exposure and ageing (that is, well-established risk factors for MCC), which are known to stimulate WNT signalling and the expression of matrix metalloproteinases, could promote MCPyV infection of fibroblasts and, therefore, drive MCC development[144]. Identification of the cell of origin together with an improved understanding of the mechanism of viral carcinogenesis might also enable the identification of susceptibility factors for MCPyV-driven MCC carcinogenesis. However, even with the currently available *in vitro* and *in vivo* models (BOX 3), this will be a challenging task.

Given the high prevalence of MCPyV seropositivity in the general population and the frequent detection of MCPyV in the skin of healthy individuals who do not seem to be adversely affected by this virus[145], the possibility of a preventive vaccine is probably not justified[146] based on public health criteria. By contrast, a preventive vaccine targeting the MCPyV T antigens could be considered for patients who need medical immunosuppression, as they have an increased risk of developing MCPyV$^+$ MCC[147].

Primary and secondary immune resistance is of utmost importance for planning future therapy strategies of MCC. Only around half of patients with advanced-stage MCC respond to immune-checkpoint blockade[104,136,137]. Moreover, even during the very short follow-up period of the reported immunotherapy trials, a substantial number of patients developed acquired resistance. Consequently, an understanding of these immune

Table 2 | **Immune-checkpoint blockade trials for therapy of advanced-stage MCC**

| Drug (trial) | Target | *n* | Median age (years) | Stage | MCPyV⁺ (%) | Prior lines of therapy | Response rate; complete response rate (%) | 6-month PFS (%); median PFS (months) | 6-month OS (%); median OS (months) | Median follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab (NCT02267603) | PD1 | 26 | 68 | IIIB or IV | 65 | 0 | 56; 15.4 | 67; 9 | Not reported | 7.6 |
| Avelumab (NCT02155647) | PDL1 | 88 | 72.5 | IV | 52 | ≥1 | 32.8; 9.1 | 40; 2.7 | 69; 11.3 | 10.4 |
| Avelumab (NCT02155647 ext) | PDL1 | 29 | 75 | IV | Not reported | 0 | 56.3; 18.8 (REF. 138) | Not reported | Not reported | 3 |
| Nivolumab (NCT02488759) | PD1 | 25 | 66 | III or IV | 48 | 0, 1, and 2* | 64‡; 32 | 75; not reached | 80; not reached | 12 |

MCPyV⁺, Merkel cell polyomavirus-positive; OS, overall survival; PD1, programmed cell death protein 1; PDL1, PD1 ligand 1; PFS, progression-free survival. *60%, 24%, and 28% of patients, respectively. ‡This response rate increased to 73% if only treatment-naive patients were considered.

escape mechanisms is necessary to overcome these issues. MCC cells might lack expression of classical and non-classical major histocompatibility complex (MHC) molecules, a phenotype that can impair both adaptive and innate immune responses[71,148–150]. The downregulation of MHC class I molecules can be reversed either by therapy with class I interferons or by epigenetic modifications. However, interferon therapy also leads to suppression of the MCPyV T antigens, which are the dominant immunogenic epitopes, and, therefore, can render MCC cells less-prone to immune recognition[149]. In preclinical models, epigenetic modulation of the expression of HLA class I molecules does not interfere with the expression of the T antigens; moreover, this treatment also reinduced molecules that activate innate immune responses[150]. Ongoing clinical trials of immune-checkpoint inhibitors for MCC combine multiple treatment strategies to avoid or to overcome immune escape mechanisms[139]. Furthermore, in the new era of immunotherapy, chemotherapy will probably be reserved for patients who are not candidates for immune-checkpoint inhibitors, such as those with solid organ transplants or an autoimmune disease.


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J.C.B. has received speaker honoraria from Amgen, Merck Serono and Pfizer; he has received advisory board honoraria from Amgen, CureVac, eTheRNA, Lytix, Merck Serono, Novartis, Rigontec, and Takeda; and he has received research funding from Boehringer Ingelheim, Bristol-Myers Squibb (BMS) and Merck Serono. J.C.B.'s activities with BMS, Merck Serono and Pfizer are related to the submitted report (therapy for advanced-stage MCC). A research project in J.A.D.'s laboratory is supported by Constellation Pharmaceuticals. C.L. has received honoraria from Amgen, BMS, MSD, Novartis and Roche, and research funding from BMS and Roche; she has a consulting or advisory role for Amgen, BMS, MSD, Novartis and Roche; she is part of speakers' bureaus for Amgen, BMS, Novartis and Roche; and she has received compensation for travel, accommodation and expenses from Amgen, BMS, Novartis and Roche. P.N. has served as a consultant for EMD Serono, Merck and Pfizer and has received research support to his institution from BMS. A.S., L.C. and M.V. declare no competing interests.

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