Overview and Incidence

Merkel cell carcinoma (MCC) is an uncommon, rapidly growing, and aggressive cutaneous malignancy of elderly persons, affecting mainly whites [1]. White-skinned individuals make up roughly 95 % of those affected; African Americans make up less than 1 % [2, 3]. Local recurrences, nodal involvement, metastases, and high mortality rates are more the rule than the exception in MCC. The most common region of the body affected by MCC is the head and neck, with roughly 50 % of MCCs occurring in this area [2, 4–6] and nearly one of every ten MCCs occurring on the eyelid and periocular areas [7, 8] (see Fig. 2.1). The incidence of MCC in the head and neck region increases substantially after the age of 65 years, especially in men [9]. The next most common sites are the upper and lower extremities, which are the more common sites of MCC involvement in individuals younger than 65 years [2, 5]. Upper-extremity MCC seems to carry a better prognosis and occurs in roughly 20 % of cases [4]. The lower extremities are affected in one of seven patients with MCC and seem to be associated with increased recurrence [10]. The trunk comprises 11 % of MCC development. In addition to these common sites of involvement, 5 % of MCCs occur in non-sun-exposed mucosal areas, the most common of which is the larynx [2]. Other less common locations for MCC include the breasts, buttocks, esophagus, penis, salivary glands, scrotum, and vulva [4, 11–14].

The majority (80 %) of MCCs measure less than 2 cm in diameter at diagnosis and present with localized disease clinically (50–70 %) [2, 5, 15]. The rest have regional node involvement or distant metastases, or both, at diagnosis [1, 16, 17]. Even with aggressive excision of localized MCC, the incidence of recurrence and metastasis is high, and these traits ultimately lead to death in
approximately 30% of individuals within 2 years of diagnosis \[18\] (median survival time, 33 months) \[19\]. The average age of persons affected with MCC is roughly 70 years (range, 7–104 years) \[1, 5, 6, 20–22\], with the male to female ratio believed to be 1.4:1.0 \[1\]. Of note, however, certain reports, such as one that evaluated MCC incidence in the Danish population, show a higher incidence in women than men \[23\]. In addition, this ratio moves closer to 1.0 in non-sun-exposed anatomical sites, and in these cases the average age is 60 years at diagnosis \[2\].

The estimated age-adjusted incidence of first primary MCC in the United States is currently 0.6 per 100,000 person-years (see Fig. 2.2), with the incidence rate of whites more than eight times that of African Americans and double the incidence of other ethnic groups \[4\]. From 1986 to 2001, the age-adjusted incidence of MCC increased 8% per year, which was an alarming threefold increase \[6\]. The highest incidence rates of MCC were seen in Hawaii, Washington, and Utah \[2, 6\]. This increase surprisingly was more dramatic than the 3.03% increase per year in melanoma incidence seen in that same period \[6\].

To date, the highest reported incidence rates of MCC in the medical literature come out of Western Australia, where age-adjusted incidence rates are 1.0 per 100,000 person-years in men and 0.63 per 100,000 person-years in women \[24\]. One of the first European epidemiologic studies of MCC came out of Spain and reported an age-adjusted incidence lower than that found in the United States: 0.13 per 100,000 person-years \[25\]. Similar incidence rates have been found in other European countries \[26, 27\].

The incidence of MCC has been increasing in different populations, having doubled since 1993 in the Netherlands by 2007 and tripled since 1983 in Finland by 2004 \[26, 27\]. The American Cancer Society recently estimated an increase of 1,500 new cases per year in the United States \[18\]. Several major risk factors are thought to contribute to this trend of increasing incidence: the increasing age of the general population, increased rates of immunosuppression, and increasing sun exposure habits over a lifetime \[6\]. Improved detection and reporting likely also contribute to the increasing incidence of MCC seen most prominently in the twenty-first century.

### Ultraviolet Radiation

Strong clinical and epidemiologic evidence links ultraviolet (UV) radiation to the pathogenesis of MCC \[1, 20, 28\]. Higher incidence is found in geographic locations of higher ultraviolet radiation, in patients with fair skin, and in anatomic locations with sun exposure. In the United States, incidence of MCC increases with geographic regions of increasing sun exposure, as measured by the UV-B radiation index \[29\]. Review of the UV-B radiation index of different geographic areas designated in the Surveillance, Epidemiology, and End Results (SEER) Program shows a statistically significant linear correlation \((r = 0.84; P = 0.005)\) existing between first primary MCC of the head and neck of white persons in the United States and the UV-B radiation index.
of that SEER geographic area. The highest age-adjusted incidence rates of MCC were seen in Hawaii, a finding that correlates with the highest UV-B radiation index among the states [2]. In addition, the incidence of MCC is much greater in equatorial latitudes [6, 30] with highest incidence in Western Australia [24].

MCC is also most frequently found on sun-exposed skin. Interestingly, investigators in the United States found that MCC was much more likely to arise on the left side of the body than on the right, especially on the face and arms ($P < 0.01$) [31]. This finding suggests that driver-side automobile UV light exposure, which is fivefold stronger on the left side of the body than on the right, is a strong contributing factor to the pathogenesis of MCC [31].

UV-A also appears to play a key role. The wavelengths in the UV-A light spectrum pass through window glass. Thus, UV-A most likely is strongly correlated with automobile UV exposure and the subsequent MCC development. Psoralen (methoxsalen) and UV-A used in combination (PUVA) for the treatment of psoriasis have also been correlated with MCC development [32]. In fact, a 100-fold increase in patients with psoriasis who were treated with PUVA was found when these patients were compared with the general population [33].

Recently, Merkel cell polyomavirus (MCPyV) mRNA transcript levels in patients with MCC proved to be UV light inducible, which may suggest an association between MCPyV, MCC development, and UV light [34].

### Aging

The SEER National Database and all other cancer registries around the world confirm that MCC is a tumor of the elderly population. More than 70% of primary MCCs occur in patients older than 70 years and the incidence rates of MCC increase dramatically with age [2, 6, 9] (see Fig. 2.3). For example, the annual incidence of MCC in people older than 85 years is 15.5 per 100,000 persons in Australia [24], and less than 5% of all MCCs affect immunocompetent patients are younger than 50 years [2, 4, 5]. MCC development is exceedingly rare in children [21].

The immunological deterioration in both cell-mediated and humoral immunity that accompanies the aging process provides a possible explanation for the striking age-dependent trends of cutaneous carcinogenesis, including MCC development [35, 36]. Immunosenescence, or the gradual deterioration of the immune system brought on by the natural aging processes, results in decreasing numbers of functional immune cells, especially lymphocytes. The resulting decrease in immune function leads to a shift of
more $T_{H2}$ and fewer $T_{H1}$ cytokines, resulting in impaired immunity decreased tumor surveillance system [35].

**Immunosuppression**

Iatrogenic immunosuppression leads to decreased cell-mediated immunity and increased frequency of skin cancer, including MCC [37]. MCC is 15 times more likely to occur in individuals with long-term immunosuppression than in the general population [38]. Recent retrospective studies suggest that nearly 8% of all MCC patients have immunosuppression [30]. Furthermore, the ratio of malignant melanoma to MCC is 6:1 in patients with long-term immunosuppression vs. the 65:1 ratio normally seen in the immunocompetent population [39].

Given that MCC is strongly correlated with aging, as well as UV radiation exposure, it is interesting to consider that both aging and UV radiation exposure result in decreased immune function and a blunted tumor surveillance system, which may lead to an accumulation of oncogenic events. Other specific forms of immunosuppression are discussed below.

**Autoimmunity**

Numerous autoimmune diseases have been associated with MCC [40–45]. Rheumatoid arthritis has been found to be the most prevalent autoimmune condition associated with skin cancer in a recent report and was associated specifically with an increased risk of MCC [46]. The incidence of MCC in patients with autoimmune disorders has been increasing over the past decade and may be secondary to the potent immunosuppressant medications used to treat these conditions [47–51]. In some cases, stopping the immunosuppressant medications has led to a regression of metastatic MCC [52, 53].

**Organ Transplantation**

The incidence of MCC is unusually high in organ transplant recipients compared with the general population, highlighting the importance of a functional immune system in prevention of MCC development [39, 54]. A tenfold increase of MCC in transplant recipients has been reported [29], with the incidence of MCC in these patients representing 0.9% of all de novo cancers [39]. In
addition, MCC arises at a much earlier age (mean, 53 years) [39], presents multifocally in 20% of the cases [55], and is more often advanced at time of presentation and (stage II and III) in 70% of cases involving transplant recipients [39, 54]. An estimated 60% of organ transplant recipients with MCC die within 18 months of MCC diagnosis [39]. One recent report looking at renal transplant recipients with MCC in Finland showed that all patients died within 25 months of diagnosis. From this and other reports, it is strikingly apparent that organ transplant recipients are at much greater risk for skin cancer, including MCC. In addition, the clinical course of MCC in organ transplant recipients appears to be much more aggressive [56]. Aside from earlier age at MCC onset and seemingly more aggressive disease behavior, the other demographic characteristics and location of MCC appear similar, with a white male predominance and with the head and neck region being most commonly affected. MCC has been found to appear 6–8 years, on average, after organ transplantation, and the incidence of MCC increases remarkably 20 years after transplantation [57].

**Acquired Immunodeficiency Syndrome**

Human immunodeficiency virus (HIV) infection leads to an immunocompromised state with impaired cellular immunity, leaving patients highly susceptible to opportunistic, bacterial, and viral infections, as well as the development of certain cancers. The relative risk of MCC development in patients with HIV infection is 13.4, and HIV-infected individuals who undergo organ transplantation have an annual incidence of 12 per 100,000 persons [58]. Compared with the general population, HIV patients are diagnosed with MCC at a younger age (49 years) and tumors arise in anatomic sites other than the head and neck region in the majority of cases [59]. The average duration from HIV infection to MCC development is 9.5 years; the average CD4 count is 256 at the time of MCC diagnosis. Although the prognosis is poor in this population, treatment of AIDS with highly active antiretroviral therapy has led to remarkable improvements in patients with metastatic MCC [60].

**Non-Hodgkin Lymphoma**

Non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) are lymphoproliferative cancers. NHL ranks seventh among the most commonly diagnosed cancers in the world [61], and CLL is a member of the NHL family, representing 25% of all leukemias [62]. A low-grade lymphoproliferative malignancy, CLL is characterized by clonal proliferation of B cells. The proliferation causes a marked decrease in the person’s immune function. Investigators have shown that leukemic cells express immunosuppressive factors, as well as downregulate expression of CD40 ligand (CD154) on activated T cells, thus interfering with T-cell ability to interact with normal bystander B cells or other antigen-presenting cells [63]. Furthermore, CD154 has a role in the T-cell induction of immunoglobulin class switching and may result in a deficient IgG level of various IgG subclasses [64]. Other factors that affect the immunosuppression seen in patients with CLL include hypocomplementemia, altered expression of class 2 major histocompatibility complex antigens on leukemic cells, hypogammaglobulinemia, and impaired granulocyte function [65, 66].

A number of studies have reported an association between MCC and CLL [62, 67–73]. Individuals aged 50–69 years and those aged 70 years or older who have CLL have a striking 48- and 34-fold increase in age-adjusted incidence of MCC, respectively, compared with the incidence of the general population [74]. A small case series recently suggested that the course of MCC in the clinical setting of CLL is much more aggressive, with possible increased recurrence, metastasis, and MCC-related death [75]. A new subset of MCPyV was recently discovered in 25% of CLL patients infected with MCPyV [76]. This discovery may argue for the potential role of MCPyV in the more aggressive nature of MCC in CLL.
patients. More research is needed to clarify the relationship of CLL and MCC and how one may influence the behavior of the other.

**Association with Other Cancers**

Patients with a diagnosis of MCC are at considerably increased risk of secondary malignancy, especially other skin cancers and hematologic cancers. The frequency of secondary malignancy in patients with MCC is as high as 25% [32, 77, 78]. The risk of development of a secondary malignancy is estimated to be 2.1% for each year after the diagnosis of a primary MCC [78]. The risk of a secondary malignancy is highest during the first year of follow-up [77, 78]. The cancer most commonly linked to MCC is squamous cell carcinoma, with reported associations as high as 40% [79–81]. In Scandinavia, patients with NMSC and with melanoma had 8.35- and 4.29-fold increases for risk of second cancers compared with persons without primary MCC [82]. A population-based study from Denmark found that the overall cancer incidence more than 1 year after the diagnosis of MCC is twice that of the general population [23] and a national cohort study demonstrated similar findings [83]. Conversely, patients with other forms of cancer are at increased risk of MCC. A three- to seven-fold increase in MCC occurs after multiple myeloma, CLL, NHL, and malignant melanoma [77]. The MCC incidence rate at 12 months after the diagnosis of another cancer was 2.6 times higher than the expected incidence in the Danish population [23] and 1.7 times higher than in the United States [77].

**Arsenic**

Arsenic is a well-documented human carcinogen. NMSCs are the most common types of cancers that arise because of arsenic exposure. Contrary to the usual distribution of most NMSCs on sun-exposed sites, arsenic-related cancer typically occurs on sites not exposed to the sun [84]. MCC has been documented to be increased in geographic areas of high arsenic exposure. Data collected from two medical centers in Taiwan revealed that greater than 50% of all MCCs occurred in residents with long-term arsenic exposure [85]. The exact mechanism by which arsenic influences the development of MCC has not been elucidated.

**Merkel Cell Polyomavirus**

In 2008, authors of published data theorized that a novel polyomavirus, termed Merkel cell polyomavirus (MCPyV), may influence MCC pathogenesis [86]. This virus was clonally integrated in the MCC tumor genome at various locations, strongly suggestive of viral infection and integration occurring in tumor cells before clonal expansion and tumor growth. In that study, the investigators detected viral levels in 80% of MCC tumors and only 8% of noncancerous tissue, with all but one MCC showing high viral loads. Since the report, efforts around the world have researched the possibility of human polyomavirus-associated tumorigenesis. Table 2.1 highlights the reproducible results published by independent researchers since 2008.

MCPyV belongs to a family of small nonenveloped, circular, double-stranded DNA viruses. Six of the polyomaviruses are known to infect humans, but for years these six viruses only produced tumor formation in animal models (hence, the term incorporates poly + oma) [87]. The link between this virus family and tumorigenesis has fueled research for decades, which in turn has led to the knowledge that all polyomaviruses encode T antigen oncoproteins and capsid proteins important for structural support, viral replication, virion assembly, host integration, and cellular transformation [88]. Feng et al. [86] described large T (LT) antigen mutations resulting in truncation in all MCPyV-positive tumor samples but not in MCPyV-positive control samples. The unique mutation found in MCPyV-positive tumor cells has been studied [89], and multiple distinct LT antigen mutations have been described in the MCPyV of MCC tumors. Normally, this antigen contains binding sites for the retinoblastoma (RB) tumor suppressor protein, cell-cycle regulatory heat shock proteins, and helicase domain.
The mutating events classic for MCPyV in MCC result in LT antigen truncation and loss of helicase function only, thus causing the virus to lose its ability to replicate epigenomically. This chain of events implies an integration before clonal expansion. In addition, recent reports of LT antigen mutations disrupting lysosome clustering and function and capsid mutations of VP1 altering viral integration have surfaced [90, 91]. These findings are in line with data supporting the monoclonal integration of the polyomavirus into Merkel cell tumors [90, 92–94]. Moreover, primary and metastatic specimens from the same patient have showed identical viral integration patterns, indicating that the integration process occurs before metastatic spread of tumor [86].

Since its discovery in 2008, MCPyV has been detected in normal tissue and in non-MCC cancerous tissue in small percentages (see Table 2.1). The only association reported between malignancy

### Table 2.1 Summary of findings on Merkel cell polyomavirus

<table>
<thead>
<tr>
<th>Study authors</th>
<th>Year</th>
<th>Country</th>
<th>Positivity in MCC, % (n)</th>
<th>Positivity in Noncancerous tissue (n)</th>
<th>Other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng et al. [86]</td>
<td>2008</td>
<td>United States</td>
<td>80 [10]</td>
<td>8 % [59]</td>
<td>16 % of 25 skin and skin tumor tissue</td>
</tr>
<tr>
<td>Carter et al. [141]</td>
<td>2009</td>
<td>United States</td>
<td>77 [29]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Duncavage et al. [142]</td>
<td>2009</td>
<td>United States</td>
<td>76 [33]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Garnesi et al. [92]</td>
<td>2009</td>
<td>United States/Australia</td>
<td>43 [37]</td>
<td>0 % [15]</td>
<td>13 % of 15 SCC</td>
</tr>
<tr>
<td>Paulson et al. [102]</td>
<td>2009</td>
<td>United States</td>
<td>59 [22]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ridd et al. [143]</td>
<td>2009</td>
<td>United States</td>
<td>54 [13]</td>
<td>3 % [37]</td>
<td>0 % of 119 other skin cancers</td>
</tr>
<tr>
<td>Bhatia et al. [106]</td>
<td>2010</td>
<td>United States</td>
<td>74 [23]</td>
<td>–</td>
<td>1 % of 52 non-MCC</td>
</tr>
<tr>
<td>Loyo et al. [144]</td>
<td>2010</td>
<td>United States</td>
<td>87 [7]</td>
<td>26 % [82]</td>
<td>11 % of 192 non-MCC</td>
</tr>
<tr>
<td>Sihto et al. [135]</td>
<td>2009</td>
<td>Finland</td>
<td>80 [88]</td>
<td>0 % [7]</td>
<td>0 % of 15 glioblastomas and melanomas</td>
</tr>
<tr>
<td>Sastre-Garau et al. [93]</td>
<td>2009</td>
<td>France</td>
<td>100 [10]</td>
<td>–</td>
<td>0 % of 1,241 non-MCC</td>
</tr>
<tr>
<td>Touze et al. [136]</td>
<td>2009</td>
<td>France</td>
<td>66 [31]</td>
<td>–</td>
<td>0 % of 9 other neuroendocrine tumors</td>
</tr>
<tr>
<td>Kassem et al. [90]</td>
<td>2008</td>
<td>Germany</td>
<td>77 [39]</td>
<td>0 % [45]</td>
<td>–</td>
</tr>
<tr>
<td>Becker et al. [94]</td>
<td>2009</td>
<td>Germany</td>
<td>85 [53]</td>
<td>–</td>
<td>13 % of 24 BCC</td>
</tr>
<tr>
<td>Wieland et al. [95]</td>
<td>2009</td>
<td>Germany</td>
<td>88 [34]</td>
<td>18 % [45]</td>
<td>16 % of other skin cancers</td>
</tr>
<tr>
<td>Andres et al. [147]</td>
<td>2010</td>
<td>Germany</td>
<td>64 [32]</td>
<td>17 % [12]</td>
<td>0 % of other skin cancers</td>
</tr>
<tr>
<td>Houben et al. [103]</td>
<td>2010</td>
<td>Germany</td>
<td>86 [50]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Varga et al. [148]</td>
<td>2009</td>
<td>Hungary</td>
<td>83 [6]</td>
<td>–</td>
<td>0 % of 29 other skin cancers</td>
</tr>
<tr>
<td>Wetzels et al. [149]</td>
<td>2009</td>
<td>Netherlands</td>
<td>40 [5]</td>
<td>–</td>
<td>0 % of 10 small-cell lung cancers</td>
</tr>
<tr>
<td>Mangana et al. [150]</td>
<td>2010</td>
<td>Switzerland</td>
<td>67 [28]</td>
<td>0 % [19]</td>
<td>–</td>
</tr>
<tr>
<td>Nakajima et al. [152]</td>
<td>2009</td>
<td>Japan</td>
<td>79 [14]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kuwamoto et al. [153]</td>
<td>2011</td>
<td>Japan</td>
<td>77 [26]</td>
<td>–</td>
<td>0 % of 4 mixed MCC and SCC; 0 % of 3 other skin cancers</td>
</tr>
<tr>
<td>Woo et al. [154]</td>
<td>2010</td>
<td>South Korea</td>
<td>100 [7]</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*SCC, squamous cell carcinoma; MCC, Merkel cell carcinoma; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; –, not available*
(other than MCC) and MCPyV is from a subset of patients who had CLL and tested positive for MCPyV, in whom rates were as high as 25% [76]. Otherwise, no connection between MCPyV and other tumors has been seen [90, 95, 96]. MCPyV is ubiquitous in nature and infects nearly 90% of healthy individuals by adulthood, as shown through seropositivity [97–99]. Some investigators have linked initial viral acquisition to respiratory tract infections [100] or to possible tonsillar persistence of the virus in childhood, or both [99]. Nevertheless, the exact mechanism through which this new human polyomavirus mediates carcinogenesis in MCC is still not clear. More than 1 pathway most likely exists for MCC tumorigenesis, however, because roughly 20% of MCCs are negative for MCPyV (see Table 2.1). These MCPyV-negative MCCs have been theorized to arise from the accumulation of more complicated genetic aberrations [101] and develop together with MCPyV-positive MCC in the clinical setting of immunosuppression from long-term UV light exposure, aging, organ transplantation, concomitant cancers, and other factors.

In conclusion, the tight association of MCPyV with MCC; the clonal pattern of integration in tumor tissue, as well as in its metastasis; the expression of the mutant viral oncoproteins; and the striking incidence of this cancer in persons who have immunosuppression all strongly support a factor of causality for MCPyV in tumorigenesis [93]. However, it is abundantly clear is that other mechanisms are involved in the etiology and pathogenesis of MCC as well.

**Genetics and Molecular Biology**

The data presented in prior paragraphs show that the LT antigen of MCPyV-positive Merkel cell tumors interacts with RB protein for sustained tumor growth. Recently, Paulson et al. [102] analyzed chromosomal aberrations in 28 MCC tumors of 25 patients by using comparative genomic hybridization. They reported deletions from the long arm of chromosomes 5 and 13 and amplification of the short arm of chromosome 1. The Rbl tumor suppressor gene, which is encoded within 13q14-21, was deleted in 26% of the tumors studied. Aberrant DNA methylation in promoter regions is now thought to be one of the most common molecular alterations in tumorigenesis [101]. Hypermethylation of promoter regions to the common locus gene for p14ARF and p16INK4a (alpha) has been reported in association with small percentages of Merkel cell tumors, which result in destabilization of p53 activity and improper signaling (phosphorylation) of the RB protein [38, 103]. The p14ARF gene works by inhibiting ubiquitin ligase necessary for p53 stability. One recent study suggests that p53 may be inactivated in about 50% of Merkel cell tumors through hypermethylation of the promotor region [104]. Waltari et al. [105] reviewed 87 confirmed cases of MCC with DNA available in Finland. Among the tumors, 77% were positive for MCPyV and only 22% showed expression of tumor p53, with greater viral loads correlating with less p53 expression [106]. Tumor p53 expression was associated with absence of MCPyV DNA ($P = 0.01$) and unfavorable MCC-specific survival ($P = 0.02$) [105]. Increasing evidence suggests p53 and RB may have a role in one of the many pathways involved in MCC pathogenesis. Whether they are aberrantly expressed in MCPyV-positive or MCPyV-negative tumor cell lines, or both, is unclear.

Several studies have found recurrent chromosomal abnormalities in MCC through comparative genomic hybridization and fluorescence in situ hybridization techniques, in chromosomes 1, 3, 5, 6, 8, 10, 11, 13, 17, 19, and X [107–109]. The most common aberration is chromosomal 1p amplification in 39–63% of MCC cases [102, 107]. L-myc, which is closely related to c-myc, is encoded within 1p34, suggesting involvement in tumor development in a subset of patients [102]. The proto-oncogene myc family is partially regulated by the E-cadherin $\beta$(beta)-catenin complex. Interestingly, p16INK4a (alpha) is a target gene of $\beta$(beta)-catenin, and its overexpression has been linked to poor outcomes in other carcinomas, including colorectal tumors [110]. Recently, downregulation of the E-cadherin $\beta$(beta)-catenin complex has been linked to MCC and is thought to possibly contribute to local invasion and metastasis [111].

Many studies have investigated the several oncogenic pathways involved in carcinogenesis,
in attempts to find key genetic alterations in MCC (see Table 2.2). Unfortunately, the vast majority of studies show little involvement of such pathways. Bcl-2, an antiapoptotic protein, has been studied, and the results appear relevant. In 1996, two separate studies were conducted and found that 75% of MCC expressed Bcl-2 [112, 113]. Furthermore, decreasing Bcl-2 in vivo in SCID mouse/human tumor xenograft model resulted in tumor shrinkage [114]. The antiapoptotic effect of Bcl-2 may be one of the mechanisms through which MCC avoids cell death, but it does little to explain the promitotic pathways seen in MCC [18]. Currently, hedgehog and kit signaling pathways are showing promise [105, 115] and investigations have led to speculation of their involvement in MCC. Research is ongoing to illuminate the molecular biology driving MCC.

**Prognostic Factors**

A fascinating and unusual form of skin cancer, MCC is defined with local and satellite recurrences, nodal involvement, metastases, high mortality rates, and overall poor prognosis. The initial tumor is typically small and fast growing with a high frequency of lymphovascular invasion. Investigators have suggested that the overall risk of lymphatic involvement or hematogenous metastasis, or both, is greater than 50% at some point during the disease process [116]. MCC presents localized in 70–80% of cases [32, 117–119], with the head and neck region most commonly affected. When relative rates of survival have been stratified in accordance with anatomical site, MCC of the upper and lower limbs is associated with the best prognosis and the worst prognosis, respectively [4, 10]. Not surprisingly, recurrent or second tumors are associated with a much dimmer prognosis [78]. When assessing prognostic indicators for MCC, conflicting studies pepper the literature because the natural history of MCC is not clear. Because of the relative rarity of this tumor, no prospective randomized trials have evaluated the prognostic factors in MCC. Further studies are needed.

The majority of studies suggest that tumors larger than 2 cm portend a worse prognosis, especially in elderly men [118–123]. For example, a review of all 251 cases of MCC in Memorial Sloan-Kettering Cancer Center’s database between 1970 and 2002 found that tumor size and disease stage were the only independent predictors of survival [28]. However, published reports evaluating clinical tumor diameter as related to survival did not find that tumors smaller than 2 cm (stage I) were associated with better prognosis [124, 125].

Both melanoma and MCC are aggressive neoplasms of the skin. The paucity of data for MCC has led researchers to look to published data from large, randomized trials for malignant melanoma. Depth of invasion (Breslow depth) is well established as a prognostic indicator for melanoma. Unfortunately, depth of MCC as a reproducible histologic prognostic factor has not been elucidated [20]. Retrospective studies are drawn upon to make this connection. For instance, invasion into subcutaneous fat has been found to be significantly associated with poor outcomes, as defined by metastasis or death [126]. Skelton et al. [127] reviewed 132 cases and reported that depth of invasion was associated with worse survival, but without statistical significance. Tumor depth has been correlated with local recurrence [10, 124]. More recently, however, numerous authors have not been able to find a correlation between tumor thickness (depth of invasion) and overall survival [124, 125, 128].

Although diameter and thickness of primary tumors are inconsistent in prognostic value, stage of MCC at diagnosis is still considered a major determinant of survival [1, 4, 28, 119]. (Stages of disease are covered in full detail later in this book.) The 5-year disease-specific survival rate for MCC has been found to be roughly 65% [28, 32], with stage I at 81%, stage II at 67%, stage III at 52%, and stage IV at 11%. Nodal involvement is a known prognostic indicator of many malignant neoplasms, including MCC. Clinically negative nodes in patients with MCC portend better prognosis than the presence of lymphadenopathy on physical examination. Furthermore, negative nodes confirmed by pathologic evaluation compared with clinically negative nodes are associated with significantly better prognosis [129]. Lemos et al. evaluated 5,823
cases from the National Cancer Data Base of MCC (median follow-up, 64 months) showing that patients with pathologically proven negative nodes had a survival rate of 76% at 5 years whereas those with negative nodes by clinical evaluation alone had a survival rate of only 59%. Evidence to date may support sentinel lymph node biopsy (SLNB) as the best staging tool for lymph node evaluation. Survival rates have reached 97% at 5 years for patients with pathologically node-negative disease determined through SLNB [28]. The recurrence rate for patients with negative SLNB is three times less, at 20%, than the 60% recurrence in patients with a finding of node-positive disease through SLNB [130]. But, as with all prognostic indicators in MCC, authors from Memorial Sloan-Kettering Cancer Center published data in 2011 refuting whether sentinel lymph node status is associated with recurrence or survival [123].

Histologic growth patterns, cell types and size, mitotic activity, necrosis, lymphocytic infiltration, perineural invasion, and immunohistochemistry have all been evaluated in individual studies and have shown inconsistent associations with MCC prognosis [124, 126–128]. Diffuse growth patterns, lymphovascular invasion, and heavy lymphocytic infiltration have been associated with poor outcomes [122, 126]. Moreover, MCC tumors that are heavily infiltrated by CD8+ cells are dramatically less likely to recur or metastasize after treatment [131], as are tumors with large numbers of mast cells [122]. Mitotic index in MCC has not been shown to be related to patient survival [132].

In addition, kit mutations, but not c-myc oncogene activity, have been associated with a worse prognosis [132, 133].

Current evidence suggests that MCPyV is a causal factor that underlies the vast majority of MCC cases. There is no questioning the striking occurrence of the virus in Merkel cell tumors (see Table 2.1). However, whether it affects the prognosis is still unclear. Recently, no correlation between detection of MCPyV in the primary tumor and better survival was demonstrated by Handschel et al. [134]. However, the vast majority of studies show increased survival and less recurrence in patients in whom MCPyV positivity was found compared with control subjects [135–138]. Moreover, patients with high levels of serum antibodies against MCPyV have been found to have better progression-free survival [139]. High titers of MCPyV, coupled with better disease-free survival, in patients with CD8+ infiltrated MCC tumors [131] suggest that stronger immune function correlates with better clinical outcomes.

**Table 2.2** Cancer-associated pathways and genes studied in MCC oncogenesis

<table>
<thead>
<tr>
<th>Cancer-associated pathway/gene</th>
<th>Likely relevant</th>
<th>Summary of findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>–</td>
<td>No mutations found in 12 of 15 samples</td>
<td>Van Gele, et al. [155]</td>
</tr>
<tr>
<td>Ras</td>
<td>–</td>
<td>No activating mutations in H-ras, K-ras, or N-ras found in 6 MCC cell lines</td>
<td>Popp et al. [80]</td>
</tr>
<tr>
<td>B-RAF&lt;sup&gt;V600E&lt;/sup&gt;</td>
<td>–</td>
<td>No mutations in 46 MCCs</td>
<td>Houben et al. [156]</td>
</tr>
<tr>
<td>MAP kinase activity</td>
<td>–</td>
<td>MAP kinase silenced in 42/44 MCCs</td>
<td>Houben et al. [156]</td>
</tr>
<tr>
<td>WNT</td>
<td>–</td>
<td>No mutations in β(beta)-catenin, APC, AXIN1, or AXIN2 in 12 MCC tumors</td>
<td>Liu et al. [157]</td>
</tr>
<tr>
<td>c-kit</td>
<td>–</td>
<td>No activating mutations in 9 MCC tumors</td>
<td>Swick et al. [158]</td>
</tr>
<tr>
<td>PTEN</td>
<td>?</td>
<td>No mutations in 20 of 21 samples but loss of heterozygosity for region in 43%</td>
<td>Van Gele et al. [159]</td>
</tr>
<tr>
<td>bcl-2</td>
<td>+</td>
<td>High expression in 15 of 20 MCC tumors; bcl-2 antisense decreases tumor size in xenograft model</td>
<td>Kennedy et al. [112]; Plettenberg et al. [113]; Schlagbauer-Wadl et al. [114]</td>
</tr>
</tbody>
</table>

* MCC, Merkel cell carcinoma; –, negative; +, positive; ?, not known

References


