

## Burden of Merkel Cell Carcinoma: A Targeted Literature Review

Siva Narayanan\*, Smeeta Gala

MKTXS Market Access Solutions, LLC, Raritan, NJ, USA.

**Corresponding Author:** Siva Narayanan, Executive Vice President, MKTXS Market Access Solutions, LLC, 575 West Rt. 28, Suite 207, Raritan, NJ 08807, USA, **Tel:** +1-203-297-1208; **Email:** snarayanan@mktxs.com

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### ABSTRACT

Merkel Cell Carcinoma (MCC) is a rare, lethal cutaneous skin cancer with no approved drug therapies and limited treatment options. The incidence of MCC (per 100,000 persons per year) is reported highest in Australia (0.82-1.60), followed by the United States of America (0.6), Netherlands (0.35), Sweden (0.18-0.33), Finland (0.24-0.25), Spain (0.28), Denmark (0.22), South East Scotland (0.133), France (0.13). The 5-year and 10-year survival is 0%-68%, and 21%-65% respectively, based on factors such as disease stage and sex. Although less than 20% of patients progress to advanced metastatic stage IV MCC, they experience the highest unmet need due to lack of effective therapeutic options. Further research is warranted to quantify clinical, humanistic, and economic burden of MCC adequately and assess comparative effectiveness of evolving treatment options to better inform patients, prescribers and payer organizations.

### KEYWORDS

Merkel Cell Carcinoma; Epidemiology, Morbidity; Survival; Unmet Needs.

### INTRODUCTION

Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer characterized by high incidence of local recurrences, regional nodal metastases, distant metastases, and high mortality rates [1]. Most individuals diagnosed with MCC have a history of other skin cancers and other malignancies such as multiple myeloma, chronic lymphocytic leukemia, and Hodgkin and non-Hodgkin lymphoma [2]. MCC is commonly staged using the 2010 tumor (T) node (N) metastasis (M) staging system. Based on TNM staging, stage I involves primary tumor  $\leq 2$  cm, maximum tumor dimension, without evidence of regional lymph node involvement; stage II involves primary tumor  $>2$  cm (T2 or T3) or a primary tumor with invasion into bone, muscle, fascia, or cartilage (T4), without evidence of lymph node involvement; stage III involves any primary tumor with regional lymph node disease and stage IV involves metastasis beyond the regional lymph nodes, regardless of the status of the primary tumor and regional nodes [3].

The treatment landscape has not changed in past 20 years [4, 5]. Depending on the stage of disease and patient's health status, the primary treatment of MCC involves surgical intervention, radiotherapy, chemotherapy, or a combination of two or more [5]. Currently, MCC treatment in the pipeline includes targeted therapies and a majority of them are being studied

in phase 2/3 clinical trials. However, the optimal treatment remains uncertain and there are limited options for metastatic stage IV MCC.

A comprehensive review of global epidemiology of MCC is lacking. This review summarizes the trends in incidence of MCC, the variation in estimates based on geography, age and sex of patients, and disease-related survival. This review also highlights the broader patient burden and unmet needs associated with MCC reported in literature.

### MATERIAL AND METHODS

A targeted literature review was conducted to assess epidemiology, patient burden, and unmet needs associated with MCC. The MEDLINE database was searched for English-language studies using the search terms such as "merkel cell carcinoma", "epidemiology", "prevalence", "incidence", "survival", "morbidity", "burden of illness", "treatments", and "clinical trials". The search was limited to studies published from 2006 to 2016. The bibliography of review articles identified as part of this search was further screened for relevant articles not identified in the original search.

The resulting titles and abstracts were screened methodically, adhering to the inclusion/exclusion criteria and exported to Microsoft Excel 2007 for an additional review. An article was

retrieved for full review if the abstract met each of the following criteria: reported incidence, natural morbidity or mortality of MCC; derived from a peer-reviewed journal; and reported in English-language published since January 2010. Articles were excluded from full review, if the abstract met any of the following criteria: study was a case report, case series, editorial or commentary; study reported data for skin cancer but not for MCC specifically; data was reported for MCC as a comorbidity to a specific disease and not in general; study assessed change in morbidity and mortality as an effect of treatment.

## RESULTS

### Incidence

The incidence (reported as new cases per 100,000 persons per year throughout this review) of MCC varies by country with the highest reported in Australia followed by the United States of America (USA). The incidence of MCC increases with age, with a median age at diagnosis greater than 70 years, and it is higher in men than women in most countries.

#### Australia

The age-standardized incidence (to 2000 USA standard population) was 0.82 in Western Australia, 1.0 in males and 0.63 in females, as identified from analysis of Cancer Registry from 1993-2007 [6]. The age-specific incidence rates increased multi-folds with increasing age from 0.1 in the age group of 30-34 years to 15.5 in the age group  $\geq 85$  years [6]. The age-standardized incidence (to 2000 USA standard population) was 1.6 in Queensland (South-Eastern part of Australia), 2.5 in males and 0.9 in females, as identified from Queensland Cancer Registry from 2006-2010 [7]. The incidence rates increased rapidly by age peaking at 20.7 for patients aged 80 years or older [7].

#### North America

In the USA, an analysis of 1986-2011 Surveillance Epidemiology and End Results (SEER) registry showed that the non-standardized incidence of MCC in 1986 was 0.22 and increased to 0.79 in 2011 [8]. The incidence of MCC was 0.60 in 2006 [9]. Albores-Saavedra et al. found in an analysis of 3,870 patients with MCC from 1973-2006 that 4% of the patients were 49 years or younger, 24% were between 50 to 69 years and 72% were aged 70 and above. The overall age-standardized incidence rate of MCC for men was 0.41 and for women was 0.18 [9]. The incidence of MCC in Canada is not available in the literature of last 11 years.

#### Europe

The annual age-standardized incidence (adjusted to European standard population) doubled in the Netherlands from 0.17 in 1993-1997 to 0.35 in 2003-2007 as observed in a study analyzing the Netherlands Cancer Registry [10]. The same study also reported the age-standardized incidence as 0.28 in males and

0.25 in females, and the incidence of MCC octuplicated from the age group of 60-64 years to 85-89 years [10].

A retrospective cohort study of Swedish Cancer Registry reported the increase in age-standardized incidence (adjusted to 2000 USA standard population) from 0.18 to 0.33 in Sweden during the study period (1993-2012) [11]. From 1993 to 2012, it increased from 0.16 to 0.34 in men and 0.19 to 0.31 in women [11]. Another study reported that the age-standardized incidence (adjusted to 2000 Swedish population) increased from 0.05 among patients who were 64 years or younger to 0.15 among those between 65-84 years and 0.45 among those who were 85 years or older during 1990-2005 [12]. The age-standardized incidence was 0.42 among men and 0.33 among women [12]. In Finland (1989-2008), the age-standardized incidence (adjusted to 2000 US standard population) of MCC was comparable in both sexes with 0.24 for women and 0.25 for men [13].

A systematic literature review and meta-analysis reported the non-standardized incidence of MCC as 0.28 in Spain [14]. An analysis of Danish national health and population registers reported the age-standardized incidence (adjusted to Danish population) in Denmark between 1995 and 2006 was 0.22, with 0.25 among women and 0.20 among men [2]. The incidence of MCC increased from 0.19 cases among individuals who were younger than 60 years to 1.13, 1.95, and 5.03 cases among those who were 70-79 years old, 80-89 years old, and 90 years or older, respectively, between 1978 and 2006 [2]. Another analysis of Danish Cancer Registry by Lhyne et al. reported that non-standardized incidence of MCC in Denmark increased from 0.06 cases in 1989 to 0.31 cases in 2002, about 5.2 fold higher [15]. The incidence increased from 0.39 cases in 1986 to 1.76 cases in 2002 among patients aged over 65 years, which was approximately 4.5 times higher than that among patients less than 65 years [15].

The non-standardized incidence of MCC was 0.13 in South East of Scotland during 1993-2003 [16]. During a 10-year period, 20 MCC cases were diagnosed of which 35% were males and 65% were females [16]. An analysis of population-based cancer registry in Doubs, France from 1980 to 2004 found that the age-standardized incidence (adjusted to world population) of MCC was 0.13 [17].

Any study reporting the incidence of MCC in Germany, Iceland, Ireland, Norway, Switzerland, United Kingdom (UK), and other European countries was not identified.

#### Morbidity

The primary site of MCC occurrence is more frequently head and neck (44-56%), upper limbs and shoulder (12-22%), lower limbs and hip (13-15%), and trunk (2-11%) [2, 9, 18]. Typically, stage I-II MCC is observed in approximately 60-75% patients,

stage III in 10-30% patients, and stage IV (metastatic) in 2-16% patients [6,7,8,13]. About 79% patients with MCC have Merkel cell polyomavirus, which is non-enveloped, double-stranded deoxyribonucleic acid (DNA) virus linked to the development of MCC [19]. It is established that MCC is associated with diagnosis of other cancers, mostly Hodgkin lymphoma and cutaneous squamous cell carcinoma [2], and immune suppression induced by human immunodeficiency virus (HIV) [20]. However, the association of MCC occurrence and its management with other comorbidities such as cardiovascular, digestive, endocrine, immunological and mental diseases, which are prevalent in older adults, is not studied. No evidence is found on patient quality of life, health resource utilization, and cost related to diagnosis and treatment of MCC.

### Survival/Mortality

The survival rate varies by country and stage of MCC. In Western Australia, 1-year and 5-year overall survival (OS) was 90% and 64%, respectively [6] while in Queensland, Australia (2006-2010), it was 77% and 41%, respectively [7]. In the USA, a SEER database analysis revealed that the mortality rate (per 100,000) of MCC in 1986 were 0.03 and increased to 0.43 in 2011 [8]. Liang et al. conducted a database analysis of MCC patients from 1984 to 2014 treated at the University of Wisconsin Hospital and clinics in the USA and found that the 2-year and 5-year OS was 54% and 33%, respectively with a median OS of 31 months (95% CI: 18-47 months) [18]. Another study in the USA reported that the 10-year survival rate was 51% in men and 65% in women [9]. In Denmark, the 1-year mortality rates in patients (mean age = 77.1 years) with localized and non-localized MCC were 22% and 54%, and 5-year mortality rates were 55% and 84%, respectively [2]. In Sweden, the 10-year OS rates were 21% in patients with MCC as compared to 37% in an age-matched Swedish population [11]. In Finland, the 5-year relative survival (approximately the disease-specific survival) was 68% for stage I disease, 67% for stage II, 16% for stage III and 0% for stage IV [13]. In the Netherlands, 1-, 5- and 10-year survival of MCC was 85%, 62%, and 47%, respectively [10]. In Italy, a review of approximately 6.7 million death certificates from 1995-2006 identified 351 MCC-related deaths resulting in age-adjusted mortality of 0.027 (per 100,000) [21]. Mortality rates were not reported for South East Scotland and France, in addition to other countries with missing epidemiological data.

### DISCUSSION

The epidemiological review of MCC shows that its incidence is increasing; however, the epidemiology of MCC in key regions such as Canada, UK, Germany, and most of the Asia-Pacific region is not clearly understood. The clinical burden associated

with MCC is sporadically available, while information on humanistic burden (e.g., impact on quality of life), and economic burden (to payers or national healthcare systems) of MCC are not studied comprehensively.

The largest unmet need arise from the lack of Food and Drug Administration (FDA) approved treatment for MCC. The existing treatments of MCC mainly involve combination of surgery, radiotherapy, and chemotherapy, which have not changed in last two decades [5]. While early-stage MCC can be cured, more advanced stages are difficult to treat [22]. The primary treatment of localized MCC is complete surgical removal. Although surgery is considered as the standard approach, there is a lack of prospective randomized trials showing its benefits in terms of long-term survival. The use of surgical interventions is limited in stage IV metastatic disease. Adjuvant radiotherapy is recommended to the primary site, and it is an alternative therapy if the patient is not a surgical candidate or do not prefer surgery [23]. Sentinel lymph node biopsy (SLNB) is recommended for all patients with localized disease for the purpose of staging and it is associated with improved survival in stage I and II MCC [24, 25, 26]. However, there is a lack of adequate evidence to demonstrate the impact of SLNB on survival in advance stage MCC. Mohs surgery is recommended when MCC occurs on the face or at places where it is important to save the surrounding skin tissue [27]. The role of chemotherapy in MCC is not clear; however, adjuvant chemotherapy such as cisplatin and carboplatin with or without etoposide is considered in cases of lymph node involvement [3]. Despite appropriate treatment, the survival benefits are limited, and MCC often recur and metastasize [6]. Besides cisplatin and carboplatin with or without etoposide, topotecan, and cyclophosphamide in combination with doxorubicin and vincristine are administered based on patient profile, albeit, with sub-optimal impact on relapse-free or overall survival [3, 28, 29]. Survival with MCC is low as compared to other non-melanoma [30] and melanoma [6] skin cancer, which represents an added clinical burden. Thus, there is a need for an effective therapy in MCC which can increase the survival especially in advanced stages.

Several new and approved drugs (for indications other than MCC) are currently being studied for the treatment of MCC. Immune checkpoint inhibitors such as pembrolizumab, nivolumab, and ipilimumab which are approved for melanoma and somatostatin analogue such as lanreotide and pasireotide which are approved for acromegaly are being tested for efficacy in MCC. New drugs such as <sup>177</sup>Lu-DOTATATE (combination of a somatostatin analog with a radioactive atom, the lutetium-177) and new targeted treatments such as avelumab, MLN0128, and cabozantinib are also being studied against

advanced metastatic MCC. In an ongoing single-arm phase 2 trial, avelumab showed a manageable safety profile with durable responses in patients with metastatic MCC who had progressed on chemotherapy [31]. The phase 2 trials evaluating the activity of cabozantinib and MLN0128 are currently recruiting patients. An evaluation of on-going phase 2/3 clinical trial for MCC, in ClinicalTrials.gov site, showed that 21 out of 25 trials were phase 2 studies and four were phase 1/2. Of the 25 trials, 21 were single-arm studies. While lack of randomized two-arm trials comparing new drugs to current standard care (or best supportive care) will not impede regulatory approvals, such comparative information may however prove to be valuable for Health Technology Assessment (HTA) agencies and payer organizations to assess the value of new drugs. Establishing historical cohorts (to assess current standard of care or best supportive care) may help set benchmarks for indirect comparisons with the new drug entering the market and enable stakeholders to make informed decisions aiding appropriate product choice and use to alleviate patient burden and be economical to healthcare systems. The expectations of patient and healthcare provider communities surrounding the new drugs studied to manage MCC are enormous; availability of these new drugs may change the treatment landscape of MCC and potentially alleviate patient burden. It remains to be seen as to what extent they fulfill these expectations, and at what cost to the healthcare systems.

With the advent of new treatments (mostly studied in single-arm clinical trials), it is crucial to characterize the clinical, humanistic, and economic burden associated with MCC and set the stage for future comparative evaluations of treatment options to inform optimal clinical decision making. Clinical burden appear to be substantial, especially among elderly/fragile population, and current lack of approved treatments accentuates it. The responses to available chemotherapies are not durable and have not demonstrated a significant survival advantage [32]. The locoregional recurrence of MCC is about 41% and nearly 29% of patients eventually develop distant metastasis, which is difficult to manage with the existing treatment options [33]. Thus, humanistic burden may be significant as the disease progresses, coupled by psycho-social issues associated with the visibility of body area of MCC occurrence (e.g. head and neck). As per the guidelines, patients with MCC should get a complete skin and regional lymph node examination 2-4 times (every 3 to 6 months) for the first three years, then every 1-2 times (every 6 to 12 months) thereafter [3]. Depending on the disease stage, the need for chemotherapy, surgery and radiation therapy may increase. Economic burden as a result of high healthcare resource use (including skin examinations, treatments, related adverse events, hospi-

talizations, etc) may be considerable, but this remains largely unquantified. It is imperative to adequately quantify the disease burden (clinical, economic and humanistic) to fully understand the disease landscape from patient, prescriber and payer's perspective and pave the path for optimal care delivery for better patient outcomes.

## CONCLUSION

MCC is a rare disease and an aggressive skin cancer with no currently approved drug and limited treatment options. The incidence is the highest in Australia followed by the US and various European countries. Incidence increases with age and is mostly higher in men than women. More than half patients with MCC die in 5 years and three-quarter die in 10 years, and the mortality increases with the stage of the disease. The current treatment options usually include a combination of surgery, radiotherapy, and chemotherapy, but there is a significant need of newer, better treatments which can increase the survival. No evidence is found in the literature that reports the humanistic and economic burden related to MCC. Additionally, epidemiology is not clear in key countries such as Canada, UK, and Germany. Future research is warranted to adequately quantify the burden of illness of MCC and assess comparative effectiveness of evolving treatment options to better inform patients, prescribers and payer organizations concerning optimal modalities of disease management.

## DISCLOSURE STATEMENT

Authors have no conflict of interest to disclose.

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