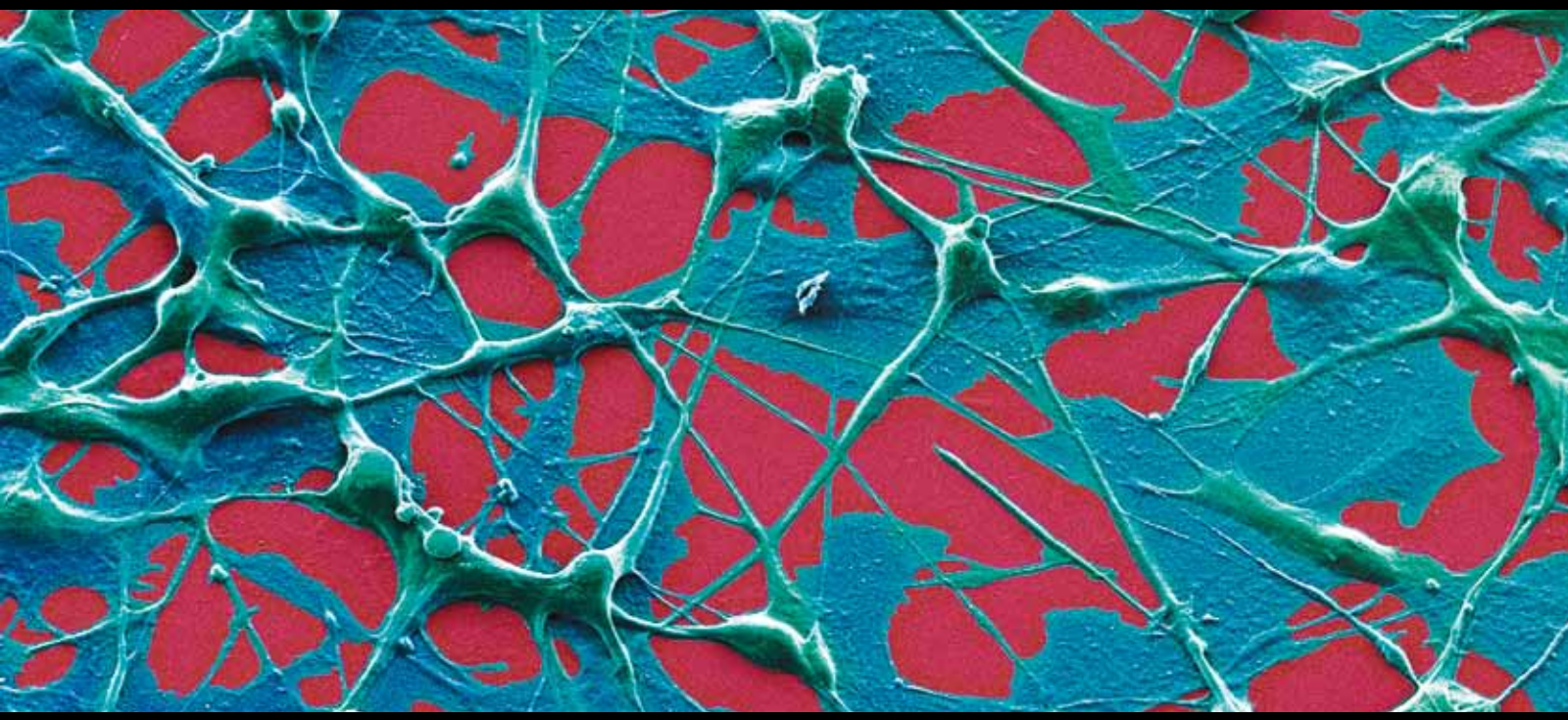
Journal of Skin Cancer

# Merkel Cell Carcinoma of the Head and Neck: Challenges in Diagnosis and Therapy

Guest Editors: Boban M. Erovic, Brett A. Miles, and Justin Lee



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# Editorial Board

# Contents

Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2013, Article ID 427984, 1 page
http://dx.doi.org/10.1155/2013/427984

*Editorial*

# Merkel Cell Carcinoma of the Head and Neck: Challenges in Diagnosis and Therapy

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Received 26 June 2013; Accepted 26 June 2013



Since the original description of the trabecular carcinoma of the skin, now known as Merkel cell carcinoma (MCC), by Toker in 1972, this malignancy has provided significant challenge to clinicians. With an increasing incidence and a known poor prognosis for advanced lesions, the disease continues to challenge physicians in the present time. New evidence indicates that not only the incidence is increasing in the overall population but also certain groups of patients such as those taking medications or immunosuppressed are at increased risk. Additionally, patients affected by MCC may be at risk for other malignant diseases. Therefore, it is likely that MCC will continue to challenge clinicians in the future.

Current clinical questions regarding the optimal management of MCC include surgical challenges such as histologic diagnosis, sentinel lymph node biopsy, and margin control, as well as issues related to reconstruction. Radiation oncologists continue to evaluate the appropriate strategy for this rare disease in terms of locoregional control and appropriate dosing strategies. Medical oncologists continue their quest for effective treatments for this rare disease, which does not lend itself to randomized controlled trials due to the small number of eligible subjects.

Recent new data regarding the analysis of MCC has resulted in a dramatic increase in our knowledge regarding this disease. The discovery of the Merkel cell polyomavirus by Feng, et al. and the subsequent work of Touze et al. which showed high antibody titers against the virus (anti-MCPyV) correlating to improved survival have provided us with new data with which to target this disease. Work in viral detection and protein expression continues to further elucidate the role of the virus in the genesis of MCC. The development of viral vaccines and targeted agents for the treatment of MCC is ongoing.

The purpose of this special issue is to update the clinician on the current literature regarding Merkel cell carcinoma and provide a consolidated review of this disease for the clinician. A historical perspective as well as the current management strategies will be reviewed. Recent data will be presented regarding current diagnostic methods, and pathological evaluation as well as an evaluation of surgical, radiotherapeutic, and chemotherapeutic strategies employed in the treatment of MCC will be examined in the articles within the issue. In addition, future areas of research will be identified to allow the reader to plot the trajectory of our current understanding of this disease and where scientific and clinical research efforts are likely to yield advances in the future.

*Brett A. Miles*

Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2013, Article ID 929364, 6 pages
http://dx.doi.org/10.1155/2013/929364

*Review Article*

# Merkel Cell Carcinoma: The Past, the Present, and the Future

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Received 20 October 2012; Revised 7 March 2013; Accepted 25 March 2013

Academic Editor: Justin Lee



Since the first description of the Merkel cell carcinoma by Cyril Toker in 1972, the number of studies has significantly increased over the last 4 decades. In this review, we will illustrate the historical background of the Merkel cell carcinoma beginning with the 19th century, the first description of the Merkel cell to the finding of the CK20 as a highly specific diagnostic marker and finally to the recently detected Merkel cell polyomavirus (MCPyV). Moreover, we will highlight the beginning of adjuvant therapeutic regimens with radiotherapy and chemotherapy and discuss the diagnostic work-up including imaging and histology of patients with Merkel cell carcinoma. Another very rapidly growing and interesting field of research is the development of patients' specific and tailored targeted therapy, in particular in patients with distant metastatic disease.

## 1. Introduction

Since the first description of the Merkel cell carcinoma by Cyril Toker in 1972, the number of studies has significantly increased over the last 4 decades. In this review, we will illustrate the historical background of the Merkel cell carcinoma beginning with the 19th century, the first description of the Merkel cell to the finding of the CK20 as a highly specific diagnostic marker and finally to the recently detected Merkel cell polyomavirus (MCPyV).

Moreover, we will highlight the beginning of adjuvant therapeutic regimens with radiotherapy and chemotherapy and discuss the diagnostic work-up including imaging and histology of patients with Merkel cell carcinoma.

Another very rapidly growing and interesting field of research is the development of patients'-specific and tailored targeted therapy, in particular in patients with distant metastatic disease.

## 2. Finding the Merkel Cell

Friedrich Sigmund Merkel was born on April 5, 1845 and died on May 28, 1919. He was a German anatomist and histopathologist who first described the so-called *Tastzellen* or touch cells in the skin [1] (Figure 1). Interestingly, three years later the term Merkel cell was born, by a young anatomist Robert Bonnet (1851–1921) who later worked with Dr. Merkel.

In mammals, Merkel cells are localized in the basal layer of the skin and mucosa [2] either as single cells or in clusters (in german *haarscheiben*). Clusters contain about 50 cells (touch domes) and are in close neighborhood to nerve terminals forming mechanoreceptors [2]. There are other cells called "Merkel-cell-like" cells, also in the skin and mucosa but without contact with nerve terminals. They are probably part of a diffuse neuroendocrine system and do not function as mechanoreceptors. Probably, these cells, rather than those acting as mechanoreceptors, are the origin of the highly malignant Merkel cell carcinoma. Recent studies could show that Merkel cells originate from the neural crest [3] and are found in the skin and parts of the mucosa that are derived from the ectoderm.

*2.1. Structure of Merkel Cells.* With the introduction of the electron microscopy in medicine in the 1960s, new significant knowledge in regard to cellular anatomy was gained. Particularly, in 1965 and 1969 Munger, Iggo and Muir showed that Merkel cells are clear and oval cells,


Figure 1: Friedrich Sigmund Merkel (1845–1919).

measuring approximately 10–15 $\mu$m in the long axis having lobulated nuclei that contain intermediate cytokeratin and neurofilaments [4, 5]. Moreover, Merkel cells have spike-like protrusions that enable them to interdigitate with the surrounding keratinocytes. The nerve terminals of the Merkel cells are packed with mitochondria and optically clear vesicles [4].

*2.2. Protein Expression in Merkel Cells.* The most interesting fact in regard to the protein expression profile is that epithelial proteins like cytokeratins but also neuroendocrine markers like neuron-specific enolase can be found in Merkel cells [2]. In particular, cytokeratin 20 is of significant value as a highly specific marker for Merkel cells in normal squamous epithelium [6]. Besides neuron-specific enolase, protein gene product 9.5, synaptophysin, and chromogranin A are found immunohistochemically in Merkel cells as well [2].

*2.3. First Description of the Merkel Cell Carcinoma.* In 1972, Toker first described a trabecular carcinoma of the skin [7]. In those days, he was a pathologist at the Mount Sinai School of Medicine, City University of New York and later Professor of Pathology and Head of the Division of Surgical Pathology at the University of Maryland Hospital and Medical School in Baltimore, MD, USA. He analyzed five cases and described clinical and histomorphological aspects. In particular, tumor cells displayed large, oval nuclei with vesicular chromatin and prominent nucleoli. The tumor growth pattern was trabecular and column-like infiltrating between dermal bundles. In regard to the origin of the trabecular carcinoma, Dr. Toker hypothesized that the carcinoma cells derived from epithelial structures are capable of forming primitive sudoriferous structures, that is, early fetal sweat glands.

Six years later, in 1978 Tang and Toker found dense-core granules in three of the original tumors by electron microscopy [8]. Merkel cells are the only cells in the skin that have dense-core granules. This fact led subsequently to the hypothesis that this trabecular skin carcinoma arises from Merkel cells. Further electron microscope studies showed that both Merkel cells and Merkel cell carcinoma cells have overlapping electron microscopic features. On the protein level, immunohistochemical expression of Cytokeratin 20 supports the hypothesis that the Merkel cell is the cellular origin of this aggressive skin tumor [6]. However, to date there is a controversy going on regarding the origin of the Merkel cell carcinoma. Some authors believe that the Merkel cell carcinoma derives from pluripotent stem cells from the skin. Our research group could show as well that Bmi-1, a stem cell marker, was homogenously and highly positive in all Merkel cell carcinoma samples [9]. Therefore, throughout the last decades Merkel cell carcinoma has been described under trabecular carcinoma of the skin, cutaneous neuroendocrine carcinoma, and Merkel cell carcinoma. The name Merkel cell carcinoma was first proposed by De Wolff-Peeters in 1980 and remains the most used and accepted term [10].

However, whether the Merkel cell carcinoma truly derives from the Merkel cell is still to date very controversially discussed. Without any doubt, more studies are needed to elucidate the origin of Merkel cell carcinoma because systemic therapy in patients with disseminated disease would probably have a significant higher impact on survival and disease-free rates due to modifications based on the origin of the cancer cells.

*2.4. CK20 as the Key Diagnostic Marker for Merkel Cell Carcinoma.* In the decades following its initial discovery, reports on the pathogenesis, course, and treatment of Merkel cell carcinoma were scarce attributing to its rarity as a disease entity, lack of biomarkers for diagnosis, and nonunified staging classifications. In 1992, Dr. Moll and colleagues recognized that Cytokeratin 20 (CK20) expression was highly specific for Merkel cell carcinoma [6]. In this study, 15 specimens with Merkel cell carcinoma were tested for CK20 using the immunoblotting and immunohistochemistry technique. All cases for CK20 were significantly positive, and the authors proposed that this marker is highly specific for Merkel cell carcinoma. Moreover, CK20 helps to distinguish between Merkel cell and small-cell lung carcinoma cells since both tumors are morphologically similar [6].

In the following years, new studies showed that approximately 5% of all Merkel cell carcinoma specimens lack CK20 expression [11]. As a consequence, Jaeger showed in a recently published review that besides CK20 expression neuron-specific-enolase (NSE) and neurofilament protein (NFP) is specific for Merkel cell carcinoma [12]. Another very important tumor marker is thyroid transcription factor-1 (TTF-1). TTF-1 is a very reliable and accurate diagnostic marker for small-cell lung carcinoma but it is not expressed by Merkel cell carcinoma [13]. Other "negative" markers are leucocyte common antigen (LCA) and cytokeratin-7 (CK7) that are positive in lymphoma [14, 15] and small-cell carcinoma of the lung (SCLC), respectively [16]. Differentiating malignant melanoma and Merkel cell carcinoma is based on CK20 positivity in Merkel cell carcinoma but negativity for HBM45, NKI/C3, and S-100 [17].

## 3. Prognostic and Predictive Factors in Merkel Cell Carcinoma

In a recently published study, it could be shown that immunosupression and advanced-stage disease was a significant predictor for decreased survival in 240 patients with Merkel cell carcinoma [18]. Interestingly, tumor size had no impact on survival [18]. Touzé and colleagues found that high antibody titers of MCPyV were a significant predictor for progression-free survival [19]. Another study performed by Poulsen and colleagues showed that again stage was a significant prognostic factor for better survival but that intratumoral CD8+ lymphocyte invasion was shown to be a significant biomarker for improved survival in MCC patients as well [20]. This observation could be underlined by the study performed by Sihto et al. This study group could show that in 116 patients that besides intratumor infiltration with CD8+ cells high CD3+ tumor count has a significant impact on patients' overall survival [21].

Clinical factors like tumor thickness, size, sex, and age are shown to not be a reliable prognostic factor for overall and disease-free survival [18, 20, 22].

*3.1. Finding of the Merkel Cell Carcinoma Polyomavirus.* In 2008, Feng and coworkers found novel viral sequences in four Merkel cell carcinoma tumor tissues [23]. After sequence analysis, it could be shown that they encoded for a polyomavirus which was subsequently named as Merkel cell polyomavirus. Further studies showed a prevalence of 40% to 100% of the MCPyV in Merkel cell carcinoma specimens [24].

In particular, polyomaviruses encode for large and small T-antigens which bind to host proteins facilitating (i) viral replication and (ii) inactivation of tumor suppressor proteins p53 and pocket retinoblastoma (pRb). Feng and colleagues observed a monoclonal viral integration 5 out of 10 (50%) patient samples and interestingly primary and metastatic MCC tissues from the same patient showed an identical viral integration pattern, indicating that the integration of MCV preceded the metastatic spreading of the cancer [23].

The number of studies dealing with the MCPyV expression significantly increased over the last 3 years [11, 25]. In particular, in a large Australian cohort Paik and colleagues could show that the MCPyV large T protein was only detected in 7% of the specimens localized in the head and neck area and in 24% from other anatomic sites [11]. Since the expression of MCPyV large T-protein in Merkel cell carcinoma specimens in patients with less sun exposure is unknown, our group recently conducted a study and showed that MCPyV large T-protein was highly expressed in primary as well as metastatic lesions [25]. This observation is highly clinically relevant in two points: firstly MCPyV large T-protein can be easily and cost-effectively detected by CM2B4, a highly sensitive and specific mouse monoclonal antibody, in specimens that lack CK20 immunoreactivity.

Secondly, since the expression of MCPyV large T-protein is homogenously overexpressed in primary and more important in metastatic lymph nodes it can be used as a target protein for systemic therapy in patients with disseminated disease with very poor outcome [26, 27].

*3.2. Management of Patients with Merkel Cell Carcinoma*

*3.2.1. Surgery and Postoperative Radiotherapy.* The first retrospective study in regard to treatment and management of Merkel cell carcinoma patients was conducted at the MD Anderson Cancer Center [28]. Between 1966 and 1983, 41 patients with Merkel cell carcinoma were treated. It could be shown that wide surgical resection of the primary lesion with neck dissection and adjuvant radiotherapy is the best treatment for controlling locoregional disease [28]. The first and still to date solemn prospective trial was performed in 2003 by the TASMAN group [29]. Interestingly, this study showed that adjuvant radiotherapy significantly prolonged locoregional disease-free survival whereas radiation had no impact on patients' overall survival [29].

*3.2.2. Mohs Surgery.* Mohs micrographic surgery was introduced by Dr. Frederic Mohs in the 1930s and became over the decades a reliable technique for resection of cutaneous tumors particular at delicate sites. In case of Merkel cell carcinoma, only a few reports are available. A retrospective study conducted by Gollard and colleagues presented excellent results with no recurrence rate after 3 years. However, only 8 patients were included in this study. Another paper including 45 patients with Merkel cell carcinoma showed that Mohs surgery is a reliable and cost-effective technique [30]. The authors compared the outcome of two groups: one with Mohs surgery alone and one with adjuvant radiotherapy. In the first group only 1 (4%) marginal recurrence and 3 in transit-metastasis could be observed whereas in the second group none recurrent disease were observed in the radiation group. Nevertheless, in both groups, overall and disease-free survival were not significantly different between treatment groups. The authors conclude that radiotherapy is beside surgical resection a key factor for successful management of patients with Merkel cell carcinoma [30].

*3.2.3. Radiotherapy.* Merkel cell carcinoma is a highly radiosensitive skin tumor [10]. Studies could show that adjuvant radiotherapy to the primary site and the nodal basins significantly improves locoregional control and overall survival [23, 24]. In patients where no surgical treatment, due to low medical performance, can be offered, primary treatment with radiation shows an excellent outcome and locoregional control rates [28, 29]. Controversies still exist regarding the treatment of the neck. The majority of the cancer centers worldwide prefer doing a selective a neck dissection with adjuvant radiotherapy [31]. However, numerous studies showed that radiotherapy alone to the neck has comparable locoregional control rates to surgery [32–34].

Since the discovery of the MCPyV, future studies are showing whether its expression is able to stratify patients either to primary radiotherapy or surgery plus adjuvant radiotherapy treatment. Such stratification has already taken place in squamous cell carcinoma of the oropharynx. In these

patients, the human papilloma virus status decides whether patients will undergo primary radiotherapy or surgery with adjuvant radiotherapy [35].

*3.2.4. Chemotherapy.* In the mid-eighties, several studies were conducted to evaluate the efficacy of chemotherapy in patients with disseminated Merkel cell carcinoma disease [31, 36].

For the first attempts to treat MCC metastases, regimens were chosen similar to those used for small-cell lung carcinomas because of its neuroendocrine differentiation and histopathologic features [31]. George and colleagues introduced carboplatin and reported a positive effect on patients' progression-free survival [31]. In the following years, a huge number of case series were published presenting therapeutic outcome after single or combined treatment with radiotherapy [37–42]. Agents like carboplatin, cisplatin, 5-FU, cyclophosphamide, doxorubicin (or epirubicin), vincristine plus or minus prednisone, and etoposide were used with the hope to improve significantly patients outcome. In fact etoposide was better tolerated and showed a significant response in one study [43]. Unfortunately, still to date there is no first-line chemotherapy established for Merkel cell carcinoma patients. In fact, chemotherapy is used either in advanced-stage disease or in patients with recurrent, nonresectable, or disseminated disease. Therefore, the outcome is very controversially discussed in the literature. In particular, in a retrospective analysis including a huge number of patients' adjuvant chemotherapy was linked to a worse overall survival compared to patients who did not received chemotherapy [44].

Without doubt new systemic therapeutic strategies are needed for patients with Merkel cell carcinomas. One of such new strategies is termed as targeted anticancer therapies. Such therapies are shown to be very promising options in treating different types of cancer, that is, gastrointestinal tumors [45] or renal cell carcinomas [46]. Due to the rareness of the disease, a very limited number of studies are available. The first studies showed that c-kit, a receptor tyrosine kinase, is in 15–90% expressed by Merkel cell carcinoma cells. Recently, we conducted a study looking at a distinct panel of target proteins and we could find that therapeutically useful targets c-kit, Bmi-1, Mcl-1, VEGF-A and VEGF-C, VEGF-R2, PDGF-$\alpha$ and PDGF-$\beta$ were expressed in Merkel cell carcinoma [9]. Another recently published study showed that survivin was a promising candidate for a new target therapy in Merkel cell carcinoma [47]. Looking at these studies the results are very promising and validate further clinical studies on the use of multitargeted tyrosine kinase inhibitors and antisense oligonucleotides in Merkel cell carcinoma [9].

Recently two studies showed that targeting MCPyV can be a promising option in patients with Merkel cell carcinoma [26, 27].

## 4. Imaging

For patients with Merkel cell carcinomas, imaging and subsequently staging of the tumor are of utmost importance. Since the introduction of ultrasonography in the late seventies, sonography of the neck is a key staging tool for patients with Merkel cell carcinoma. First reports on sonography and Merkel cell carcinoma were published in the late 90s [48]. Beyond ultrasonography, CT and MRI scanning are important for determining tumor size, location, and eventual bone invasion [48, 49]. In the late nineties, octreotide scanning in Merkel cell carcinoma patients was proposed to show a reliable detecting rate compared to CT and MRI imaging [50]. In the following years, however, it was shown that the octreotide scan has a low sensitivity and specificity [50]. Another whole body imaging technique, FDG-PET and PET-CT scanning showed highly reliable and accurate images in Merkel cell carcinoma patients with metastatic disease [49].

Sentinel node biopsy was introduced by Cabanas in 1977 in patients with penile carcinoma [51] enabling detection of micrometastasis in lymph nodes. This technique gains more and more importance in the management of patients with Merkel cell carcinoma since studies showed that patients with negative neck nodes have a risk of 30% to harbor micrometastasis in the neck nodes [52]. Another significant benefit of sentinel node imaging and mapping is an option to avoid the morbidity of an elective neck dissection in sentinel node negative patients [52–58].

## 5. Perspectives

Since the discovery of the Merkel cell in the skin in the 19th century and the description of the Merkel cell carcinoma in the early 70s, many new implementations in medicine with regard to diagnosis, imaging, and treatment have been introduced.

However, the management of patients with Merkel cell carcinoma is a tremendous challenge for the clinician as well as the patient and their families. The first step for optimal treatment is clinical investigation and proper diagnostic work-up of the patient including determination of the histology, either by excision biopsy or fine needle biopsy, imaging of the tumor and any metastatic disease, and finally determination of the therapeutic plan within a multidisciplinary setting.

In particular, diagnosis of Merkel cell carcinoma is based upon the CK20 positivity determined by immunohistochemistry whereas staging relies on ultrasonography, sentinel node, and CT/MRI and PET-CT scanning. Primary treatments including surgical resection and radiotherapy are currently the treatment of choice. In patients with recurrent either locoregional or distant metastasis, treatment options are very limited. In the case of resectable locoregional disease, surgical resection is an accurate way of treatment and for most of the patients it is unfortunately the only therapeutic option. However, in the presence of distant metastatic disease, there are no established systemic therapeutic regimens. The number of studies focusing on the development of new targeted anticancer therapy is steadily rising, and thus there is hope that new drug regimes for patients with distant and systemic Merkel cell carcinoma disease will be available in the near future. In particular, many study groups are looking for new strategies to target the Merkel cell polyoma virus either to prevent infection or to inhibit viral-induced carcinogenesis.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2013, Article ID 327150, 9 pages
http://dx.doi.org/10.1155/2013/327150

*Review Article*

# Merkel Cell Carcinoma: Chemotherapy and Emerging New Therapeutic Options

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Received 25 July 2012; Accepted 10 December 2012

Academic Editor: Boban M. Erovic



Merkel cell carcinoma (MCC) is a rare neuroendocrine skin tumor that typically occurs in elderly, immunosuppressed patients. Infection with Merkel cell virus (MCV) and immunosuppression play an important role in the development of MCC. Different staging systems make it difficult to compare the existing clinical data. Furthermore, there predominantly exist single case reports and case series, but no randomized controlled trials. However, it is necessary to develop further therapy options because MCC tends to grow rapidly and metastasizes early. In the metastatic disease, therapeutic attempts were made with various chemotherapeutic combination regimens. Because of the high toxicity of these combinations, especially those established in SCLC, and regarding the unsatisfying results, the challenge is to balance the pros and cons of chemotherapy individually and carefully. Up to now, emerging new therapy options as molecular-targeted agents, for example, pazopanib, imatinib, or somatostatin analogues as well as immunologicals, for example, imiquimod and interferons, also showed less success concerning the disease-free response rates. According to the literature, neither chemotherapy nor molecular-targeted agents or immunotherapeutic strategies have shown promising effects in the therapy of the metastatic disease of MCC so far. There is a great demand for randomized controlled studies and a need for an MCC registry and multicenter clinical trials due to the tumors curiosity.

## 1. Clinical Features

Merkel cell carcinoma (MCC) of the skin, formerly called trabecular carcinoma, is a rare, highly malignant neuroendocrine tumor. Clinically only a presumptive diagnosis can be achieved. Clinical features that may serve as clues in the diagnosis of MCC are summarized in the acronym AEIOU: asymptomatic/lack of tenderness, expanding rapidly, immune suppression, older than age 50, and UV-exposed site on a person with fair skin [1]. The definitive diagnosis is made by histology and immunohistopathology depicting intermediate filaments and neuroendocrine markers [2]. The incidence of MCC has been rising in recent years [3, 4]. 5 years after diagnosis, overall survival was 40% and the age-adjusted and sex-adjusted survival was 54% [5].

Infection with the Merkel cell virus (MCV) and immunosuppression are the key factors in the development of MCC. The relative risk for MCC is about 13-fold higher in HIV [6] and about 5-fold higher in solid organ transplantation recipients [7] than in the general population. On the one hand, these features might also explain the increasing incidence of MCC. On the other hand, they might be key factors for the successful treatment of MCC.

The stage of patients with MCC has prognostic impact and influences the therapy offered. Over the years, different staging systems of MCC have been applied making it difficult to compare clinical data. In 2010, the American Joint Committee on Cancer (AJCC) Staging system first included the staging for MCC [8]. Duprat et al. [9] summarized AJCC Staging system and five-year survival data from Lemos et al. [5] in a table. Clinicians and researchers should be cautious when comparing clinical studies which applied older systems and with those which applied the recent AJCC Staging system.

MCC mostly appears as a hemispherical, firm-elastic, and reddish-livid tumor with a smooth surface. It is typically

located on sun exposed areas like head, neck, extremities, and upper body [10]. Because of its harmless appearance, this rare neuroendocrine tumor, first described by Toker in 1972 [11], is often misdiagnosed, for example, as a cyst [1]. Interestingly, the clinically suspected diagnosis has only been made correctly for one percent of the cases [1, 12]. The MCC grows rapidly, is highly aggressive, and metastasizes early locoregionally as well as distantly [1, 13] illustrating the importance of comprehensive strategies to control disseminated diseases.

## 2. Therapeutic Options

The rareness of the disease and, possibly also the comorbidities have contributed to the lack of prospective clinical studies evaluating the efficacy of therapeutic options. Up to now, only one randomized clinical study was published [34]. All other publications refer uncontrolled data from case series or even retrospective case descriptions.

The only randomized controlled clinical study published in the field of MCC compared regional adjuvant radiotherapy with observation [34]. While adjuvant radiotherapy significantly reduced the probability of regional recurrence, it had no effect on the overall survival. The authors wrote that the introduction of sentinel node dissection decreased the recruitment rate for this study. Surgery is considered the mainstay of treatment for MCC [10]. However, there is no evidence basis for this treatment option. A prospective evaluation of sentinel node dissection in MCC was described only in 9 patients [35].

## 3. Chemotherapeutic Options: Polychemotherapy and Monotherapeutic Options

Basically MCC is assumed to be a chemosensitive tumor [12, 36, 37] but to date no broadly accepted treatment algorithm exists. Supportively to primary excision, chemotherapy is used on MCC stages III (lymph node metastasis) and IV (distant metastases) after the AJCC Staging system. It may be applied either alone or in combination with radiotherapy. Furthermore, chemotherapeutics are used in locally advanced disease, as palliative measure or in case of recurrences [37].

The following data refers to retrospective case series or single case reports, except [14, 15] and (Table 1) [19], which are prospective case series. Several groups tried to treat MCC with chemotherapeutic regimens commonly used for small cell lung cancer (SCLC) because of histopathological and cytochemical similarities—besides both of them are considered as neuroendocrine tumors [16, 38–42]. These regimens combined carboplatin, cisplatin, and etoposide, cyclophosphamide with vincristine, doxorubicin, prednisone, bleomycin, or 5-fluorouracil (Table 1). They were reported to provide a good initial regression of the lesion, but recurrences occurred mainly within 4 to 15 months. All these patients had locoregional or distant metastases. These potential benefits should be weighed against the possible adverse reactions of these therapeutic attempts. Some of these rather old patients died from sepsis caused by chemotherapy-induced leukopenia [40], progressive renal failure [17], or impaired hepatic function [37].

In a retrospective analysis of a series of 251 patients from a single centre treated between 1970 and 2002 (Table 1) [24], the use of adjuvant chemotherapy was associated with decreased survival. 28 of 237 patients presenting with locally advanced disease or locoregional metastases received adjuvant chemotherapy and showed a 5-year disease-specific survival rate of 28% compared to 73% of 209 patients without receiving chemotherapy. Furthermore, 67 node-positive patients receiving chemotherapy were associated with a lower survival rate compared to not-receiving chemotherapy.

Beside polychemotherapy with burdensome toxicity, there are better tolerated monotherapeutic options like etoposide and anthracyclines [10, 25, 37]. Liposomal doxorubicin together with radiotherapy ($n = 5$) yielded rapid response, but showed less adverse reactions, for example, gastrointestinal disorders. Tumor proceeded within 1 to 3 months (Table 1) [25]. Orally administered etoposide achieved complete responses in 3 out of 4 patients (75%) and two of them were comparatively long lasting (16 and 36 months) (Table 1) [26].

There are no randomized studies that compare different chemotherapy regimens. In 204 patients, the most common regimens used were cyclophosphamide, doxorubicin (or epirubicin), vincristine plus/or minus prednisone, and etoposide combined with cisplatin (or carboplatin). A relevant difference in the response rate could not be described (Table 1) [27].

Although high remission rates were reported after chemotherapy (up to 70–75% [25, 37]), but no such prolongation of survival [10]. Intensity of chemotherapeutic therapy and response rates did not correlate [37]. Main therapy still is wide excision of the tumor with or without node dissection, often in combination with radiotherapy. In comparison, chemotherapy has been used rarely [45].

Up to now, the literature does not provide adequate, sufficient data to support the use of chemotherapy.

## 4. Molecular-Targeted Agents

Davids et al. (Table 2) [28] treated a patient who suffered from metastatic pulmonary lesions with pazopanib, which is a small-molecule tyrosine kinase inhibitor acting against vascular-endothelial-growth-factor-receptors- (VEGFR-) 1, 2, and 3 and against platelet-derived-growth-factor-receptor- (PDGFR-) $\alpha$ and $\beta$. The rationale was that MCCs have been shown having upregulated VEGFR [46, 47] and PDGFR [48, 49]. Pazopanib can be administered orally. It was well tolerated and provided partial response of the pulmonary lesions as well as complete response of the primary lesion, but disease recurred or rather progressed 4 months later. In this case, every other therapy that had been tried before (surgery, radiotherapy, etoposide and carboplatin, paclitaxel, tegafur, and 5-chloro-2,4-dihydroxypyridine and oxonic acid) also led to partial or complete response and lesions recurred 4–8

Table 1: Chemotherapeutic options: polychemotherapy and monotherapeutic options.

| | Number of patients | Intent of chemotherapy | Agents used | Response | Time to progression | Survival |
|---|---|---|---|---|---|---|
| McAfee et al. [14] *prospective* | $n = 34$ 9 patients received CTx local to metastatic disease | Adjuvant | Carboplatin, cisplatin, VP-16, etoposide | NDA | 5-year local control of all cases: 94%; 5-year locoregional control of all cases: 80% | 5-year survival of all cases: 37%; 5-year DSS of all cases: 52% |
| Poulsen et al. [15] *prospective* | $n = 41$ local or locoregional disease | Adjuvant (72%); therapeutic (28%) | CTx combined with RTx; etoposide, carboplatin | NDA | NDA | 3-year OS 76%; 3-year DFS 65% |
| George et al. [16] *retrospective* | $n = 1$ metastatic disease | Adjuvant | Cyclophosphamide, doxorubicin, vincristin | CR: 4-5 months | 4 months | NDA |
| Redmond III et al. [17] *retrospective* | $n = 6$ metastatic disease | Adjuvant | Cisplatin + etoposide or Cisplatin + etoposide + cyclophosphamide or Cyclophosphamide + doxorubicin + vincristin | CR in 5 patients | CR for a median of 3,5 months | median OS of 6,5 months |
| Azagury et al. [18] *retrospective* | $n = 1$ metastatic disease | Adjuvant | First line: VP-16 + cisplatin + doxorubicin + bleomycin — Second line: RTx combined with methotrexate + cyclophosphamide + VP-16 | CR after 6 cycles — CR after 4 months | 15 months until relapse — NDA | NDA |
| Bajetta et al. [19] *prospective* | $n = 30$ NET (1 MCC among all cases) locally advanced or metastatic disease | Adjuvant | 5-Fluorouracil + dacarbazine + epirubicin | CR in 2 patients (in 1 patient with MCC); PR in 7 patients | CR of MCC for 21+ months; median duration of response of all cases was 10 months (range, 5+ to 24+) | NDA |
| Eng et al. [20] *retrospective* | $n = 88$; 43 patients received RT and/or combined CTx local to metastatic disease | Adjuvant | 19% received CTx without RTx most common regimen: VP-16 + cisplatinum | NDA; of all cases 12% had persistent disease, 40% had recurrent disease | Of all cases median time to recurrence was 8 months | NDA |
| Eng et al. [21] *retrospective* | $n = 46$ 9 patients received CTx metastatic disease | Adjuvant | +/− RTx most common regimen: carboplatin + etoposide + vinblastin | NDA | Overall median time to recurrence was 9 months | OS rate of all cases: 37% |

Table 1: Continued.

| | Number of patients | Intent of chemotherapy | Agents used | Response | Time to progression | Survival |
|---|---|---|---|---|---|---|
| Veness et al. [22] *retrospective* | $n = 86$ 7 patients received CTx locoregional disease | Adjuvant | most common: based on platinum | NDA; 55% of all cases experienced a relapse | median time to relapse was 3–7 months | 5-year OS 47%; DFS rate 25% |
| Voog et al. [23] *retrospective* | $n = 107$ advanced or metastatic disease | Adjuvant | different regimens; NDA | ORR to first line CTx: 64% | NDA | 3-year OS was 17% (metastasis) and 35% (locally advanced) |
| Allen et al. [24] *retrospective* | $n = 251$ 28 patients received CTx local or regional disease | Adjuvant | most common regimen: carboplatin + etoposide | NDA; disease recurred in 102 patients | of all cases median time to recurrence was 9 months (range, 2 to 70 months) | 5-year DFS of all cases: 48%; 5-year DSS of patients receiving CTx: 28% |
| Wobser et al. [25] *retrospective* | $n = 5$ metastatic disease | Adjuvant | +RTx liposomal doxorubicin | PR in 4 patients | an average of 2 months until progression | Survival time: range 3 to 20 months |
| Schlaak et al. [26] *retrospective* | $n = 4$ metastatic disease | Adjuvant | Etoposide | CR in 3 patients | 2 of CR lasted for 16 and 36 months | NDA |
| Tai et al. [27] *retrospective* | $n = 204$ locoregional and metastatic disease | Adjuvant | most common regimens: Cyclophosphamide + doxorubicin (or epirubicin) + vincristin +/− prednisone — Etoposide + cisplatin (or carboplatin) | ORR 75,7% (35,1% CR, 35,1% PR, 5,4% minor responses) — ORR 60% (36% CR, 24% PR) | Median response duration of patients receiving CTx: 1–12 months | Median OS of all cases: 21,5 months (range, 1 to 118 months); 2-year OS of all cases: 36%; 5-year OS of all cases: 17% |

NDA: no data available; NET: neuroendocrine tumor(s); MCC: merkel cell carcinoma; PR: partial response; CR: complete response; CTx: chemotherapy; RTx: radiation therapy; Sx: surgery; DFS: disease free survival; OS: overall survival; ORR: overall response rate; DSS: disease-specific survival.

Table 2: Molecular-targeted agents.

| | Number of patients | Agent used | Dosage | Tolerability | Response | Median time to progression |
|---|---|---|---|---|---|---|
| Davids et al. [28] | $n = 1$ metastatic disease | Pazopanib | 800 mg daily | Minimal adverse effects; dose reduction after gallstone pancreatitis to 400mg daily | After 2 months: CR of primary lesion, PR of metastatic lesions | 4 months |
| Samlowski et al. [29] | $n = 23$ metastatic or unresectable disease | Imatinib | 400 mg daily | Mainly Grade 1-2 toxicities; 3 episodes of Grade 4 toxicities; Grade 3 toxicities in 3 patients | no CR; PR: 4% | 1-2 months |
| Di Bartolomeo et al. [30] | $n = 58$ metastatic disease (neuroendocrine tumors) | Octreotide | 500 or 1000 micrograms 3 times a day | Carcinoid syndrome and abnormal urinary 5-hydroxy-indoloacetic acid excretion were reported | Median survival time of 22 months (range, 1–32+ months); PR: 3% | Disease stabilized for at least 6 months (range, 1–32+ months) |
| Meier et al. [31] | $n = 1$ locoregional disease | 90Y-DOTATOC; targeted radiotherapy | 85 mCi | Fatigue was main side effect | PR after 1 week; CR after 4 weeks | 10 weeks until locoregional relapse |
| Fakiha et al. [32] | $n = 1$ clinically locoregional disease | Lanreotide | 15 mg i.m. injection every two weeks | No side effects reported | Clinically CR after 2 months | 7 months until relapse |
| Shah et al. [33] | $n = 12$ metastatic or regionally recurrent disease | Oblimersen sodium | 7 mg per kilogram daily | Including Grade 3 and Grade 4 events, for example, lymphopenia, renal failure, cytopenia, and hyperkalemia | No responses; stable disease in 3 patients | PD in 9 patients |

CR: complete response; PR: partial response; PD: progressive disease.

and once 24 months later. In this paper, the authors conclude that pazopanib appears to have a promising antitumor and antiangiogenic function and a good oral bioavailability; as per them, this has been demonstrated in preclinical studies.

In this patient, single nucleotide polymorphism (SNP) in PDGFR-$\alpha$ gene was found, namely, 1432T>C mutation in codon 478. The same mutation was shown in two other samples of MCCs that were examined by this group and in three other patients with MCC from another study [49]. It is not clear whether this mutation leads to an activation of PDGFR-$\alpha$ and consequently to a better response to tyrosine kinase inhibitors, for example, pazopanib or not.

Similarly well tolerated is another tyrosine kinase inhibitor called imatinib mesylate (Gleevec) (Table 2) [29]. KIT (CD117), a tyrosine kinase receptor which belongs to the same family of tyrosine kinase receptors like PDGFR-$\alpha$, is reported to be highly expressed (84–95%) in MCCs [50–52]. Activating mutations of KIT were found in 88,2% ($n = 127$) of gastrointestinal stromal tumors (GISTs) and showed a significantly higher partial response rate to imatinib for exon 11 KIT mutation (83.5%) compared to exon 9 KIT mutation (47.8%) or no found mutation (0.0%) [53]. Because of the successful treatment of KIT expressing GISTs [53, 54] and because of the recent insight that KIT receptor activation through its ligand stem cell factor (SCF) stimulates growing of MCC cells in vitro [55], imatinib was assumed to be a promising therapeutic option for MCC. In fact, there were only few adverse events but imatinib appeared to provide insufficient effects on progression-free and overall survival. Just one out of 23 patients with KIT expressing MCCs responded partially and the progression happened rapidly after 1 or 2 months in most of the patients. Thus, the study was prematurely discontinued [29].

Kartha and Sundram [48] examined primary and metastatic MCCs ($n = 32$) to evaluate the expression and mutations of KIT and PDGFR in MCCs. KIT expression was found in 53% of the cases. Coexpression of KIT and SCF was shown in 16% only, whereas coexpression of PDGFR-$\alpha$ and its ligand PDGF-A was found in 81% of the cases. In this study, no activating mutations could be found (KIT exons 9, 11, 13, and 17 and PDGFR-$\alpha$ exons 10, 12, and 18 were analyzed). Therefore, efficacy of imatinib is questionable, also considering results of Samlowski et al. [29].

Somatostatin receptors were also reported to be expressed in MCCs. Somatostatin analogue octreotide showed unfruitful results concerning tumor regression with a partial response rate of 3% ($n = 58$) (Table 2) [30]. Radiopeptide therapy is used to treat neuroendocrine tumors by binding of edotreotide (DOTATOC, which contains the active peptide of somatostatin, namely, octreotid) to somatostatin receptors. In one case, the radiolabeled somatostatin analog 90Y-DOTATOC led to complete remissions after a few days, but relapse and progression occurred within weeks. It has to be pointed out that the tolerability was very good (Table 2) [31]. Lanreotide, a nonradiolabeled somatostatin analog, was intramuscularly administered in one patient every two weeks and showed a complete response of the lesion. Recurrences occurred within 7 months after the first injection (Table 2) [32].

Oblimersen sodium (Genasense), which inhibits the production of Bcl-2 (which is a protein acting against apoptosis in cancer cells), was applied intravenously to 12 patients and showed no responses (Table 2) [33].

## 5. Immunotherapeutic Strategies

MCC is associated with immunosuppression [1, 4]. Cases of spontaneous regressions of MCCs were reported that were deemed to be caused by the regained activity of the immune system [56, 57]. MCCs that showed a high infiltration with CD8+ lymphocytes were attributed to a better prognosis (100% MCC-specific survival, $n = 26$) compared to MCCs with lower infiltration (60% survival, $n = 120$) [58].

Some patients developed MCC during treatment with tumor necrosis factor (TNF) alpha inhibitors, which usually promotes inflammatory response. Therefore, TNF-alpha inhibitors are assumed to increase the risk of occurring of MCC [59, 60].

The detection of the Merkel cell polyomavirus (MCV) and its genetic material, found in MCC tumor cells of about 80% of the concerned patients, provided new opportunities and possibilities regarding therapy strategies [61, 62]. For instance, interferons ($\alpha$ and $\beta$) have been suggested to be a possible therapeutic option [63]. However, there are only few reports on the use of immunomodulating substances in MCC. In two case reports, interferon-$\alpha$-2b caused severe asthenia and depression, leading to discontinuation of the therapy, considering that no tumor regression was observed. The tumors were positive for MCV [63]. Recently, it has been shown that viral T-antigens represent an important signal for MCV-infected MCC cells concerning survival and growth [64]. Consequently, the inhibition of T-antigens might be a therapeutic option.

Imiquimod, which induces immune response by binding to TLR7 (toll like receptor-7, located on the surface of immune cells, e.g., macrophages), was topically applied to MCC ($n = 1$) and combined with radiotherapy. Complete response of the lesion lasted 7 months [65].

Another new therapeutic approach is based on cytokine inducted inflammatory response. To avoid systemic reactions, fusion proteins were developed consisting of antibodies and cytokines, which bind to their corresponding antigens located on the tumor cell surface [66]. In general, combined therapy of cytokine-based antibodies and regular chemotherapy seems to be well tolerated.

## 6. Conclusions

There is a considerable lack of prospective clinical studies and in particular randomized controlled studies that evaluated the therapeutic options for MCC. For the time being, nearly all conclusions are based on case series or even isolated cases and theoretic considerations, rather than evidence-based medicine.

With respect to chemotherapeutics or molecular-targeted agents, no convincing responses were reported; at best the responses lasted a few months or just several weeks. There

were no controlled studies. Thus, the question arises whether there truly is a benefit of chemotherapy for MCC; if any, the benefit is unlikely to be relevant. Because of frequent comorbidities of the older patient collective, it is necessary to develop therapy modalities that are effective and more likely to be tolerated. The recent insight of an association of MCC to MCV infection and immunosuppression enables new therapeutic options, for example, the inhibition of viral T-antigens, that requests further investigations. Currently, there is an ongoing phase II trial study with the purpose of placing the gene for interleukin-12 into MCC cells by intratumoral injection so that humans build up an immune defense and may kill tumor cells. Other promising options might be immune-response modifiers.

This emerging disease requires more clinical research. A first step might be the implementation of an MCC registry. More important, however, would be randomized controlled studies in this field, which are urgently needed. The often rapid deterioration of this cancer and the frequent comorbidities might require rather simple protocols. The rareness of the disease calls for the implementation of an MCC network to collect sufficient numbers of patients in an MCC registry and multicenter clinical trials.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2013, Article ID 973123, 6 pages
http://dx.doi.org/10.1155/2013/973123

*Review Article*

# Imaging in Patients with Merkel Cell Carcinoma

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Received 24 October 2012; Accepted 4 January 2013

Academic Editor: Justin Lee



Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine tumor of the skin with a mortality rate of approximately 25% (Peloschek et al., 2010). Accurate assessment of nodal involvement in patients with MCC predicts significantly overall outcome (Smith et al., 2012 and Ortin-Perez et al., 2007). Due to the rarity of this highly aggressive disease, only a few imaging reports on MCC were published, and subsequently still to date no accepted imaging algorithm for MCC is available. For primary staging of MCC, general recommendations have included ultrasonography, chest X-ray CT, and MRI, but recent articles show that the use of sentinel node and FDG-PET/PET-CT is gaining more and more importance.

## 1. Introduction and Overview

Merkel cell carcinoma is a rare and highly aggressive neuroendocrine tumor of the skin. It develops predominantly on sun-exposed area of the head and neck [1, 2]. In 1972, Toker described an unknown, trabecular carcinoma of the skin in five caucasian patients [3]. In 1982, Tang and Toker proposed that the MCC derives from the Merkel cell, a mechanoreceptor of the hair follicle [3, 4].

MCC typically develops rapidly and manifests as firm, nontender, dome-shaped red, purple or violet nodule [5, 6]. The overlying skin is smooth and shiny, sometimes exhibiting ulcerative, acneiform, or telangiectatic features [5, 7].

MCC tends to metastasize to the regional nodes and in 50% of the patients it spreads hematogenously to other organs [8], that is, the liver, bone, brain, and lung [2]. In 1993, Haag and colleagues defined a commonly used staging system [2, 9]: stage I is defined by local disease without lymph node involvement or distant metastases, in stage II carcinoma has spread to lymph nodes but no systemic metastases are detectable, and in stage III distant metastases are detectable [9].

Diagnosis of MCC can be challenging because in many cases MCC lesions mimic benign skin lesions [10]. Unfortunately, in clinical practice, lesions highly suspicious for Merkel cell carcinoma are often biopsied or nonaccurately resected with close margins [2]. In fact, patients presenting with unclear new skin lesions should undergo clinical examination, and lesion still highly suspicious for Merkel cell carcinoma should be excised with clear and wide margins. Diagnosis and management of nodal metastasis in patients without a primary tumor can be challenging. In particular MCC metastasis can mimic metastasis from other small cell neoplasms, that is, for example lung carcinoma [3, 11]. In 2%–19% of the patients no primary tumor can be found—defined as MCC of unknown primary (MCCUP) [11]. Due to the rarity of this disease, the literature on MCCUP is very limited [12, 13].

Agelli performed multiple epidemiological studies showing that between 1986 and 2001 the age-adapted incidence of MCC has increased 3-fold with an annual increase of 8% [14]. This growing incidence rate has given a significant input for a growing interest in disease management of patients with Merkel cell carcinoma [15, 16].

Unfortunately, there is sparse literature on imaging algorithms in patients with Merkel cell carcinoma and no widely accepted guidelines for imaging of Merkel cell carcinoma are available [5, 8]. This paper reviews the literature on imaging of Merkel cell carcinoma discussing the role of the most recent imaging and diagnostic tools.

## 2. Ultrasonography

Ultrasonography is a highly accurate and cost-effective technique in tumor staging. In regard to Merkel cell carcinoma, work up and staging of the neck should be started with an ultrasonographic examination [2].

Primary skin lesions can appear as single or multicentric hypoechoic solid nodules arising from the dermis and extending in the subcutaneous fat, with variable degrees of posterior acoustic transmission [5, 8]. Ultrasonographic features of Merkel cell carcinoma appear similar to more common skin tumors such as melanoma or basal cell carcinoma [8]. It has been shown that in sonographically easy accessible regions, such as the neck, differentiation of malignant from benign lymph nodes can be achieved with an accuracy of 89%–94% [17, 18]. Furthermore, ultrasonography has a key role in real-time imaging during fine needle biopsy of nonpalpable lesions of Merkel cell carcinoma [8]. Except for a few published case reports, ultrasound guided and nonguided fine needle aspiration biopsy has been rarely described in MCC patients [19–23]. Definitive diagnosis of metastatic disease is challenging with fine needle aspiration cytology alone [20]. The cytomorphology resembles numerous other malignancies such as malignant lymphoma and malignant melanoma [23]. Nevertheless, FNA of MCC can provide an accurate and reliable diagnosis of primary or recurrent metastatic lesions [23]. In patients where positive nodes are proven, a full body imaging should be done to detect distant metastases [16].

## 3. Sentinel Node Biopsy (SLNB)

Sentinel lymph node biopsy provides the unique capacity to detect metastasis and micrometastasis and subsequently lymph metastasis node draining [5] in patients with melanoma [5], squamous cell carcinoma [24], and MCC [5] by using lymphoscintigraphy [25]. SLNB in patients with Merkel cell carcinoma appears to be a reliable staging technique, whereas the prognostic relevance of positive tumor status of the sentinel node still remains unclear [26].

In up to two-thirds of patients with stage I MCC disease, regional nodal spread has been diagnosed at initial presentation with SNLB, and in only 7%–31% nodes are clinically palpable in patients with stage II disease [5].

Lymphatic drainage pathways in the head and neck region are more variable than in any other location of the body and are challenging to be accurately predicted [27]. Occasionally, head and neck lymphoscintigrams fail to identify a definitive lymphatic drainage pattern [27]. In particular, unexpected nodal drainage is seen in 37%–84% of cases and is often missed without the use of lymphoscintigraphic guidance [5, 28]. Negative sentinel biopsy appears to be a relevant prognostic factor for disease-free survival [26]. Consequently, false-negative findings in lymphadenectomy are leading to inadequate staging of MCC and aggressive but unnecessary complete nodal dissection in patients with true stage I disease [5].

However, Stadelmann and colleagues showed that in 5%–6,8% of patients with melanoma or Merkel cell carcinoma of the head and neck region, no nodal disease could be detected [27]. In particular, in 5 out of 74 clinically node-negative patients who underwent preoperative lymphoscintigraphy, lymphoscintigram failed to identify positive nodes metastases [27]. In 2002, Nguyen and colleagues recommended lymphoscintigraphy in combination with perioperative lymphatic mapping.

## 4. Computed Tomography (CT)

Due to the usefulness of CT for imaging lymph nodes of the head and neck as well as for nodular metastases in subcutaneous fat and visceral metastases, several authors proposed that CT is a reliable imaging method for the initial staging of patients with Merkel cell carcinoma [2, 5, 8]. In particular, Colgan and colleagues proposed sensitivity and specificity rates of 47% and 97%, respectively, with positive and negative predictive values of 94% and 68%, respectively, for diagnosis of lymph node involvement by CT imaging [29]. However, Peloschek and coworkers claimed a specificity of 96.2% and a sensitivity of 89.1% for CT in diagnostic imaging of Merkel cell carcinoma including lymph node involvement as well as evaluation of distant metastasis [2].

Compared to the muscle, primary skin lesions appear as isodense to slightly hyperdense cutaneous rounded nodules extending below the skin [30]. Cutaneous fat stranding adjacent to the primary lesion suggests engorgement and edema from lymphatic invasion [8]. Furthermore, enhanced CT scan is able to demonstrate high-attenuation lymphadenopathy and soft CT scan is able to demonstrate high-attenuation tissue nodules, which are often clinically silent [5, 8, 30], suggesting focal metastases [30]. Lymphadenopathy mostly occurs in the neck, especially in the parotid region followed by the axilla, mediastinum, retroperitoneum, and groin. Distant metastases include local and retroperitoneal lymph nodes, liver, bone, brain, and lung [31]. Using CT-imaging, metastases of abdominal organs manifest as hypervascular lesions with ring-like enhancement [5]. Soft-tissue metastases may involve the chest wall or abdominal wall with musculoskeletal invasion. Gollub and colleagues conducted a study in 12 patients with MCC and showed the ability of CT scanning to detect visceral and nodal metastases. They suggest follow-up CT scans at 3, 6, 12, and 18 months after initial treatment to discover recurrent disease [30].

## 5. Magnetic Resonance Imaging (MRI)

There are only a few studies and case reports describing the usefulness of MRI in patients with MCC. In particular, case reports on large primary tumors of the sinonasal region [32], and abdominal wall [33] described MCC lesions as inhomogeneous in signal intensity on T1- and T2-weighted images [33, 34]. Focal central increased signal intensity on T2-weighted images within large lesions has been described as being associated with histologically proven central necrosis and hemorrhage [33, 34]. In MRI scans, lymphatic satellite lesions are reflected by reticular stranding and subcutaneous masses. The same appearance of satellite lesions can be

observed by CT imaging. Large lymph node metastases appear as lesions with fine, compressed, retained fatty tissue [34].

Colgan showed in a study of 7 patients who underwent first MRI followed by sentinel lymph node biopsy or regional lymph node dissection a positive predictive value of 0% and a negative predictive value of 67% for the MRI [29]. However, Anderson and colleagues showed in 15 patients that MRI improves differentiation of distant metastases [34]. Furthermore, intramuscular masses and perifascial tumors were better defined on MRI than by CT imaging [34].

MRI in Merkel cell carcinomas is highly accurate for evaluating soft tissue metastases, as well as involvement of brain and bone marrow. Invasion of the central nervous system is rare; however, in case of neurologic symptoms, workup should be performed with MRI [5, 35].

## 6. Somatostatin Receptor Scintigraphy (SRS)

The rational for performing somatostatin receptor scintigraphy in MCC patients to detect locoregional and distant metastatic disease is based on the neuroendocrine characteristics of MCC. In 1992, Kweekeboom and colleagues presented data for the effectiveness of SRS in 4 patients with MCC. In all 4 patients, in whom the tumor was detected by CT and sonography, tumor sites were also detected in SRS. They showed that SRS had an equal or greater sensitivity than CT for imaging of MCC [36].

Nevertheless, more recent studies observed a limited sensitivity of SRS as well as a high rate of false positive and negative results [37–39]. Guiltera presented their 7-year experience with 20 patients with MCC. In particular, sensitivity of 78% and specificity of 96% for SRS of Merkel cell carcinoma could be observed [38].

A comparison between SRS, CT and MRI showed that tissue SRS is less affected by inflammation, edema, granulation tissue at surgically pretreated or irradiated sites [5]. However, there is a significantly limited value in organs showing a physiological uptake of radiolabelled octreotide such as liver, adrenal glands, pancreas, thyroid gland, and spleen [5, 37]. This causes a low tumor-to-background ratio, which hampers detection of metastasis near organs with a high physiological uptake of the tracer [37]. Further, other systemic diseases such as sarcoidosis, tuberculosis, Wegener's granulomatosis, non-Hodgkin lymphoma, or Hodgkin's disease have also led to false positive SRS results [37, 40].

Unfortunately, a limited use of SRS in diagnostic evaluation of Merkel cell carcinoma. Therefore many authors do not recommend SRS for routine imaging [37, 38].

## 7. Positron Emission Tomography (PET) and Positron Emission Computed Tomography (PET-CT)

Within the last years nuclear medicine, especially PET and PET-CT, has gained importance in diagnostic imaging of Merkel cell carcinoma. Since MCC is a rapid growing tumor, it is expected that tumor cells have an increased glycolysis [2].

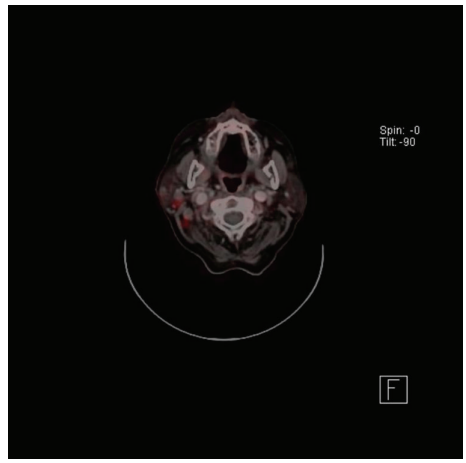


Figure 1: PET/CT: pathologic enhancement in the right parotideal region.

$^{18}$F-FDG is a glucose analog and a surrogate marker for glucose metabolism [41]. In particular, increased glycolysis in certain areas compared to healthy tissue is a distinctive feature of malignant transformation. Increased glycolysis can be captured using the FDG positron emission tomography (PET) technique allowing differentiation between normal and malignant tissue [5] as shown in Figure 1.

The main difficulty with PET alone is the lack of an anatomical reference frame. The hybrid of FDG-PET and the morphological data of CT have potential to improve specificity of PET [2].

Several studies in $^{18}$FDG-PET and PET-CT supported the effectiveness in detecting locoregional nodal and distant metastatic disease and subsequently staging in patients with MCC [2, 42–47].

Unfortunately, only few data are available comparing $^{18}$FDG-PET and PET-CT with the gold standard of histopathologic nodal evaluation and other imaging tools in MCC patients.

In a study comparing FDG-PET-CT, MRI, bone scan, and computerized tomography in 11 patients, the authors could show that FDG-PET has a sensitivity of 92% and specificity of 100%, and in 3 patients FDG-PET-CT allowed a more precise anatomic localization of lesions [42]. Furthermore, Concannon et al. found, in a retrospective study of 18 patients with MCC who underwent FDG-PET-CT imaging, that FDG-PET-CT resulted in altered staging in 33% of patients and in changes in disease management in 43% of the patients [36]. However, a retrospective study in 15 patients showed a significant advantage of FDG-PET-CT compared to clinical examination in 46% of patients, whereas sensitivity, specificity, and positive and negative predictive value were the same for PET-CT and CT, respectively [48].

In a retrospective study, Peloschek and colleagues described that FDG-PET has a sensitivity of 85,7% and a specificity of 96,2% compared to a sensitivity of 95,5% and specificity of 89,1% for conventional imaging methods [2]. In another study, Grewal et al. reported the sensitivity and specificity of FDG-PET in MCC as 79% to 92% [49].

The most significant drawback of this technique is the fact that in some cases metabolic trapping can be nonspecific and in addition to tumor cells it can also be found in sites of inflammation or infection [50]. In case of brain metastases FDG-PET scanning is significantly hampered due to the high metabolic rate. Subsequently high cerebral background impairs detection of metastatic lesions in the brain [51]. Furthermore, some authors describe a failure of FDG-PET-CT in detection of lymph nodes micrometastases and distant metastatic disease [29, 48].

*7.1. Alternative Tracers.* Biogenic amines are enhanced and accumulated in neuroendocrine tumors and are an alternative PET tracer for MCC to visualize malignant tissue [2]. A case report described that, due to the less intense uptake of $^{18}$F-DOPA, it is more accurate in diagnosis of brain metastases $^{18}$F-DOPA compared to FDG-PET and is as accurate in detection of more extracranial metastases [45]. However, Peloschek et al. showed in a study, superior value of FDG-PET in detection of malignant sites of MCC, showing two false negative regions in $^{18}$F-DOPA-PET [2]. Furthermore, diffuse $^{18}$F-DOPA uptake was $^{18}$F-DOPA seen in a region pretreated with surgery and $^{18}$F-DOPA irradiation, which was similar to that in FDG-PET that hampers the idea of a benefit of $^{18}$F-DOPA. Thus, $^{18}$F-DOPA-PET cannot be recommended for diagnostic imaging $^{18}$F-DOPA in Merkel cell carcinoma [2].

*7.2. Follow-Up Imaging.* After treatment of primary lesions of MCC, a close monitoring is required.

For follow-up imaging, we would suggest a routine chest X-ray as well as a computed tomography of the head and neck region 3 months after therapy. Every year after therapy, a chest X-ray, CT and MRI of the head and neck region are recommended. 6, 9, 15, 18, 21, and 30 months after therapy a cervical ultrasonography and a chest X-ray should be performed. Because of the low cost of sonography, it has a high value in routine follow-up imaging of Merkel cell carcinoma [2]. Chest X-ray is a routine imaging technique to evaluate possible pulmonary involvement. Peloschek et al. recommend repetition of FDG-PET 3 months and 1 year after treatment [2].

## 8. Discussion

The key task of imaging in patients with Merkel cell carcinoma is staging at the initial presentation and post-therapeutical.

Early recommendations for imaging in MCC included ultrasonography CT, MRI, and octreotide scans [29]. Recently, $^{18}$FDG-PET has become a valuable and useful imaging technique for staging in patients suffering from MCC. Its diagnostic value is comparable to conventional imaging methods that have a restricted field of view [2].

Peloschek et al. recommend that initial staging workup should be started with ultrasonography as it is cost-effective and an accurate imaging method in easy accessible lymph node regions such as the head and neck [2]. There is rarely literature available dealing with ultrasound-guided fine needle biopsy of Merkel cell carcinoma. Definitive diagnosis is difficult but possible and accurate with FNA [19, 20].

In oncologic patients with suspected distant metastases FDG-PET, CT or MRI imaging should be performed. Somatostatin receptor scintigraphy is no longer recommended for routine imaging of Merkel cell carcinoma, as studies showed a high rate of false-positive or false-negative results in detection of Merkel cell carcinomas and metastatic disease [37].

As Merkel cell carcinoma has a high rate of distant metastasis, PET scan has a particular value in imaging and staging workup.

MRI has a particular value in assessing soft-tissue involvement, whereas CT is used for imaging of thorax and abdomen. Three months and 1 year after treatment, FDG-PET should be repeated for follow-up imaging. Moreover, fusion of FDG-PET with CT or MRI would improve specificity of PET analysis [2].

Colgan et al. reported that the use of FDG-PET when compared with traditional computed tomography is significantly more sensitive and equally specific than FDG-PET alone in evaluation of regional lymph node basins in primary MCC [29].

The role of FDG-PET-CT in management of MCC remains to be a matter of debate. However, PET-CT has been shown to have a potential high impact of staging and management of MCC patients with stage I and II disease [43].

To date, there is still no imaging algorithm for Merkel cell carcinoma. Due to the rarity of Merkel cell carcinoma imaging, findings have been reported only in small trials and case reports. On the basis of the existing literature, we would recommend FDG-PET CT as first line imaging of Merkel cell carcinoma. It is a noninvasive imaging technique that has potential to detect occult lesions bigger than 5–8 mm in minimal diameter [48] that are not detectable by other imaging techniques. We suggest that further diagnostic imaging should be obtained depending on the results of lymph node involvement and distant metastases.

However, in case of negative lymph node involvement, we would recommend sentinel lymph node mapping with subsequently performing an ipsilateral neck dissection to confirm lymph node status histopathologically. In our opinion, due to the low morbidity of a neck dissection, it has a high diagnostic and preventive value.

In summary, Merkel cell carcinoma is a highly aggressive skin cancer with a high rate of metastasis and mortality. Since no imaging guidelines are available, more studies are required to define an evidence-based imaging algorithm.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2013, Article ID 189342, 6 pages
http://dx.doi.org/10.1155/2013/189342

*Review Article*

# Merkel Cell Carcinoma: Interdisciplinary Management of a Rare Disease

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Received 24 October 2012; Revised 21 December 2012; Accepted 28 December 2012

Academic Editor: Brett A. Miles



*Background*. The goal of this paper is to review contemporary multidisciplinary treatment with reference to Merkel cell carcinoma. Management of this rare but highly aggressive skin cancer is a complex undertaking that necessitates an understanding of its etiology, epidemiology, clinical presentation, and the coordinated work of several clinical specializations. *Recent Findings*. The contemporary literature employs a multidisciplinary approach to achieve the best patient's treatment. *Conclusion*. This paper presents an algorithm for contemporary management for the rare and aggressive Merkel cell carcinoma. Multidisciplinary approach in a tumor center provides high-quality care for patients with Merkel cell carcinoma.

## 1. Introduction

Merkel cell carcinoma (MCC) is a rare neuroendocrine skin tumor, with a high risk of local and distant spread. The incidence of MCC is 0.32 per 100.000 [1], showing an increasing incidence with advanced age and in male Caucasians [2].

Progression in incidence might be linked to the constantly increasing exposure to ultraviolet B radiation considering the fact that MCCs are localized frequently in sun-exposed areas of the body. Other known risk factors are immunosuppression in transplant recipients [3], HIV [4], and in particular Merkel cell carcinoma polyomavirus infection [5].

The head and neck area is the most frequently affected site (29–40.6%), followed by extremities (21–38%), trunk (7–23%), and unknown primary sites (3.4–12%) [6–8]. Unfortunately, clinical appearance of MCC is heterogeneous. It frequently presents as an asymptomatic, reddish, bluish, or purple tumor of the skin. Size at the time of first consultation is usually smaller than 2 cm, although MCC is characterized by rapid growth [9]. Due to the long list of, mostly, benign skin tumors, diagnosis based on clinical parameters is challenging. A recently performed study showed that in 56% of patients with MCC a benign tumor was initially presumed, mirroring the problems in clinical examination and challenges in clinical diagnosis [8]. However, diagnosis is finally achieved by histopathological analysis of small biopsies or samples of totally excised tumor.

Additionally, people's awareness of this disease is very low compared to malignant melanoma. This suggestion might be supported by the observation that most patients are seen with an advanced stage of disease.

The 5-year survival rate ranges from 30 to 64% [6, 10], although survival is strongly dependent on the presence of regional and distant metastasis with a far worse outcome in advanced stages of disease. About 50% of patients showed localized stage of disease at the initial presentation. A recent single institution study shows the impact of stage of disease on 5-year survival showing MCC-specific survival of 87, 63, 42, and 0% for stages I, II, III, and IV, respectively [11].

High awareness to this rare cancer type among the population as well as among physicians can provide the key to early diagnosis. Besides the consideration of clinical risk factors, improved diagnostic tools like specific protein markers in immunohistochemistry [12] increased significantly the rate of diagnosis in Merkel cell carcinoma patients. Hence, improvement in diagnostics should be accompanied by optimization of multidisciplinary treatment strategies to

deliver high-quality cancer care for patients with Merkel cell carcinoma.

The rareness of MCC accompanied by the lack of outcome reports as well as relative treatment inconsistence raises further barriers to general treatment recommendations. However, there is evidence of improvement in recurrence and survival rate due to either adjuvant radiotherapy or chemotherapy following surgical management [13, 14]. Furthermore, in an early stage patients not receiving multimodality treatment increased locoregional recurrence was observed [15, 16]. Thus, multidisciplinary management of MCC appears as the most favorable approach.

In this paper we will review the contemporary interdisciplinary management of patients with Merkel cell carcinoma and present our experience at the University of Otolaryngology, Head and Neck Surgery, Vienna.

## 2. Multidisciplinary Management

MCC is an extraordinary rare disease. Thus, there is still little knowledge to guide the care of patients with MCC. Furthermore, limited data on interdisciplinary treatment evaluation and outcome analysis of multidisciplinary decision-making exist in general.

Although until now there is no evaluation of tumor board decisions in patients with Merkel cell carcinoma, several other types of cancer multidisciplinary discussions on patients showed relevant impact on their clinical outcome. In ovarian cancer it could be shown that management by a multidisciplinary team at a joint clinic significantly increased patients' survival [17]. Also in gastroesophageal cancer, patients managed by a multidisciplinary team were more likely to survive 5 years compared to patients who were managed independently by surgeons [18]. Furthermore, several studies have shown that discussion in tumor board conferences altered the final diagnosis [19, 20], led to treatment alterations [21] or changes in management [22], and improved staging accuracy [23].

Treatment of MCC often requires a wide field of specialties like dermatologists, head and neck surgeons, radiooncologists, oncologists, pathologists, radiologists, speech pathologists, and nursing which goes along with extensive coordination management.

Although a heterogeneous field of therapeutic strategies exists, wide resection of the tumor followed by sentinel lymph node biopsy is standard treatment. According to pathological examination, total lymph node dissection is frequently performed. Surgical treatment is carried out by dermatologists and head and neck surgeons. Furthermore, oncologists and radiooncologists are frequently involved in adjuvant therapy in patients with advanced stage of disease. Thus, the key for successful management of patients with this highly aggressive disease is a multidisciplinary clinic, at which coordination of care with multiple medical specialties is established [24]. High-quality care for patients with MCC as well as their relatives can be provided in an interdisciplinary setting.

According to the aims of the Institute of Medicine of the National Academics, high-quality care must follow six proposed aims [25]. Care must be safe, meaning that injuries by the treatment have to be free of avoidable errors. Care must be effective by providing services based on scientific knowledge to all who could benefit. Moreover, care is supposed to be patient centered within the meaning of respectfulness and response to individual patient preferences, needs, and values. A timely and efficient process characterizes high-quality cancer care. Waits and delays as well as waste of equipment, supplies, ideas, and energy must be avoided. Finally, providing care must be equitable in terms of consistence in quality and independence of sociodemographic characteristics.

Considering the need for multidisciplinary evaluation, special attention should be paid to time-efficient clinical evaluation and patients' treatment according to high-quality cancer care aims. Coordination of care among specialists is considered as essential for high-quality oncologic care, whereas lack of coordination is a main drawback for patients' treatment and improvement of care [26].

One of the essential cornerstones in treatment of MCC is a multidisciplinary tumor board for implementation of the goals of high-quality treatment in an interdisciplinary fashion.

Management of all cancer patients should be discussed and planned in multidisciplinary meetings, due to the fact that it facilitates ensuring quality of care and decreasing organizational difficulties in the treatment of cancer [27]. According to the French Cancer Plan, a definition for multidisciplinary meetings has been established [28], emphasizing main quality criteria. First, a multidisciplinary approach means that specialists from at least three medical disciplines have to be present. Formal structure concerning frequency of meetings, paperwork, and conclusion reports must be given. Moreover, it is essential that every cancer case must have a conclusion report, in which medical decisions must be based on clinical practice guidelines. Board recommendations must be communicated to the patient to implement therapeutically decisions. Importantly, recommendations of multidisciplinary meetings must be periodically evaluated.

Another benefit of multidisciplinary management is cost efficiency. Although no cost analysis of a multidisciplinary setting of MCC patients is currently available, it has been demonstrated for melanoma treatment that multidisciplinary care at a large academic medical center can be more cost efficient than a less organized traditional community-based approach [29]. It leads to the assumption that cost reduction is also possible in MCC treatment by specialists in an academic, multidisciplinary setting.

It is favorable that each patient is presented in this board as soon as possible after histologic diagnosis for further discussion of treatment options. During the last decades, cancer treatment shows an increasing complexity. Regarding the progressing specialization as well as more sophisticated treatment options in every discipline involved in cancer treatment, planning of high-quality therapeutic approaches is not possible for an independent physician. According to this way of thinking, multimodal treatment is a consequence of interdisciplinary discussion and planning. Clearly, development of therapeutic strategies in a tumor board is the

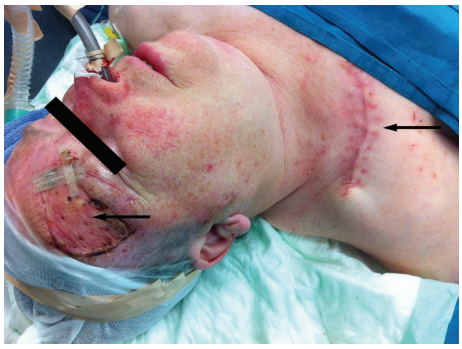

Figure 1: Patient with Merkel cell carcinoma of the right eyebrow (arrow). Primary excision site was covered by full thickness skin taken from the right clavicular/subclavicular region (arrow).

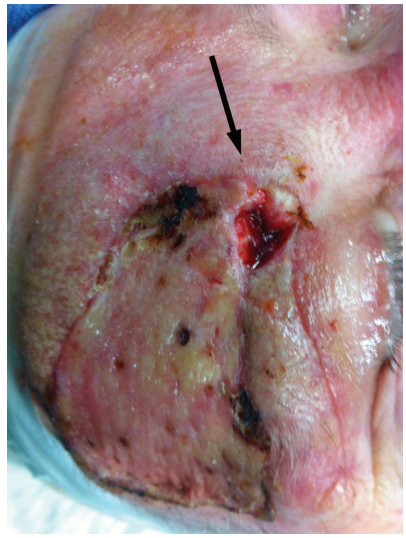

Figure 2: Wound dehiscence at the primary site (arrow).

most time efficient way to enhance patient management by gathering experts of each discipline, but also long-term effects on patients' outcome have to be considered.

Despite the benefits of multidisciplinary management, there are also several pitfalls in this setting. Noteworthy, there is no standardized expert panel for several cancer types. This may influence therapeutic decisions by the presence or absence of a certain specialist and might reflect personal preferences. Furthermore, definition of being an expert of a certain specialty is rarely given. No standardized qualification criteria for attending a tumor-board as a decision maker so far exists.

Considering these facts, treatment decisions may depend on the presence or absence as well as on the qualification of several specialists, which can make it hard to relate to certain decisions.

Particularly in Merkel cell carcinoma, it is important to arrange a setting in which treatment options can be discussed and recommendations are well documented. Due to the rarity of MCC, the lack of prospective clinical studies and conflicting literature on the treatment and outcome of Merkel cell carcinoma, standardized management is often not established. Taking one step forward, one can say that high-quality care and improvement of treatment are only provided in a multidisciplinary, academic setting. The number of patients to collect data in an effort to improve patient care as well as clinical and basic research might not be obtained outside a multidisciplinary center.

Therefore, a multidisciplinary approach in a center, most favorable in an academic setting, is the only possibility to provide high-quality care as well as improvement of therapeutic strategies so patients with this rare and aggressive disease benefit the most.

## 3. Case Report

To illustrate the need for multidisciplinary management we consecutively describe the case of a 77-year-old women who was diagnosed with Merkel cell carcinoma in April of 2012. Her medical history included treatment for a melanoma on the leg in 1997 and CLL since 2007.

Initially, this patient was seen in a private praxis by a dermatologist. She had a slow growing nodular tumor above her left eyebrow. Unfortunately, clinically this tumor was not suspicious for a malignancy and thus an open biopsy was carried out. As soon as the histological workup showed an R2 resection of a Merkel cell carcinoma, the patient was sent to the outpatient clinic at a department of dermatology in Vienna. At this time, the tumor measured 1.5 cm in diameter and was localized superior of the right eyebrow, paramedian, and close to the supratrochlear vessels. Subsequently, in May 2012 wide local resection of the tumor with sentinel lymph node biopsy was carried out. The primary site was closed with full thickness skin harvested from the right chest.

At the primary site, resection margins were negative, however, the sentinel node, localized in the ipsilateral parotid gland, was positive for Merkel cell carcinoma. Staging by computed tomography of the head and neck, thorax, and abdomen was conducted after the sentinel node biopsy. Imaging showed that the patient had at least two intraparotideal lymph node metastases and multiple ipsilateral cervical lymph nodes highly suspicious for metastatic disease.

Two and a half weeks later the patient was seen at the Department of Otolaryngology, Head and Neck Surgery, Vienna Medical University, and was presented at the interdisciplinary tumor board for head and neck tumors. Therapeutic options were discussed as followed: either adjuvant radiotherapy at the primary site including the ipsilateral parotid gland and neck or surgery followed by postoperative radiotherapy. Meanwhile the patient developed a wound dehiscence at the primary tumor site, highly suspicious for local recurrence (Figures 1 and 2). The first line recommendation of the multidisciplinary board was to perform a subtotal parotidectomy, selective ipsilateral neck dissection followed by radiotherapy. The patient agreed and surgery was performed in June 2012. Intraoperatively biopsy from the wound dehiscence was carried out and pathological examination by frozen sectioning showed Merkel cell carcinoma. Again wide local

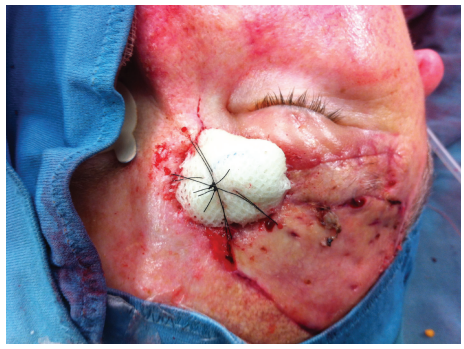

Figure 3: Wound dehiscence was biopsied and frozen sections showed to be positive for recurrent MCC disease. Carcinoma was resected again and STSG was used to cover the defect over the right eyebrow.

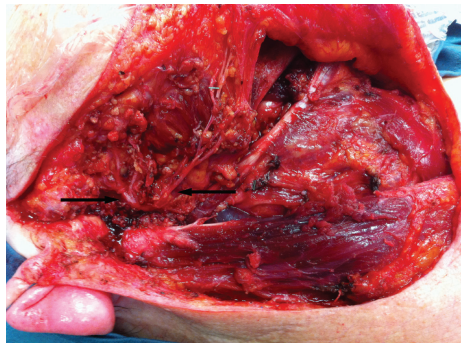

Figure 4: After right parotidectomy and selective neck dissection all branches of the facial nerve could be preserved (arrows).

resection was performed and the defect was closed with a split thickness skin graft (Figure 3). Subsequently, subtotal parotidectomy and selective neck dissection was performed (Figures 4 and 5). In the final pathology report the parotid gland was positive for Merkel cell carcinoma and multiple lymph nodes were infiltrated as well. In particular, level 1a showed 2 out of 13, level 1b 6 out of 6, level 2a 6 out of 8, level 2b 2 out of 3, level 3 6 out of 8, and level 4 16 out of 22 lymph nodes positive for Merkel cell carcinoma.

At the time of writing up the paper the patient finished adjuvant radiotherapy and is currently free of tumor disease.

## 4. What Could Have Been Done Better?

Although it is obvious that physicians always intent to provide high-quality treatment to their patients, the case report shows that there are several pitfalls in clinical work-up with Merkel cell carcinoma patients. According to the goals of high-quality treatment, effective, safe, equitable, and patient-centered treatment could be achieved, but this patients' medical history shows a lack of in time and efficient management.

In particular, at our institution such small tumors would be completely excised and sent to pathology. Imaging work-up is always initiated at the initial presentation of the patient

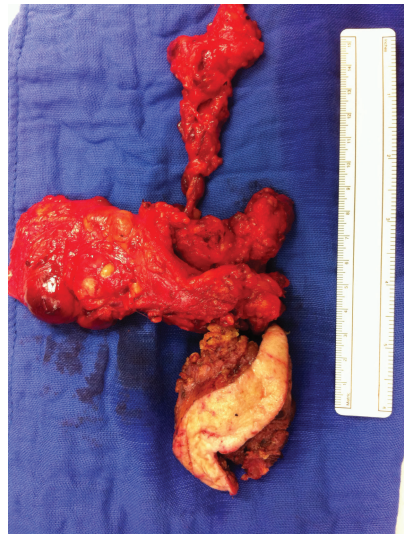

Figure 5: Parotidectomy and neck dissection specimen measuring 20 cm × 15 cm.

and in particular before performing sentinel node biopsy. To the best of our knowledge, in this presented case we were not able not find any imaging that has been done before sentinel node biopsy. As a second open biopsy in the parotid gland was carried out that represents a significant drawback in regards to possible spread of tumor cell into surrounding tissue.

In regards to waiting time, this case shows an unnecessary loss of time from the point of histological diagnosis to planning and initiating treatment. An early presentation of the patient in a multidisciplinary tumor board would have avoided loss of time as well as facilitated the planning of multidisciplinary treatment.

## 5. Multidisciplinary Tumor Board for Head and Neck Cancer at the Medical University of Vienna

At the initial presentation of tumor patients a careful and meticulous examination of the head and neck, including endoscopic examination, is performed. Consecutively, an excision biopsy, depending on the size of the primary tumor, is taken under local anesthesia in the clinic. In case of suspicious lymph nodes, fine needle aspiration is performed. Additionally, all patients with skin malignancies are seen by a dermatologist.

As a second step, an ultrasonography, CT or MRI of the neck, and, if possible, a PET-CT are carried out. With all histological and imaging reports patients are presented at the weekly tumor board for head and neck cancer. Patient's history and all diagnostic findings are presented either by a resident or attending physician. Presentation includes the medical history as well as the by the patient itself preferred therapy.

Best therapeutic strategy is discussed in a multidisciplinary approach among all members of the tumor board

including head and neck surgeons, dermatologists, radiooncologists, oncologists, and radiologists. In case of the need of further examination or planning of therapy, appointments are made at the same meeting to provide time efficient management.

Considering all the provided facts, the tumor board members give a treatment recommendation that will be offered to the patient and its family members at the next appointment.

## 6. Conclusion

Management of Merkel cell carcinoma is a huge challenge for physicians and patients and their social surrounding.

In our case paper we could clearly show that the need for a multidisciplinary planning of therapy is highly time and cost efficient and linked to best-treatment outcome. Immediate presentation after histological diagnosis in a multidisciplinary setting can reduce waiting time for treatment. Furthermore, an interdisciplinary surgical approach can be planned and carried out and thereby reduce length of inpatient stays and frequency of surgery.

For best patients' care, especially for patients with rare diseases, a multidisciplinary tumor board is the most favorable treatment tool.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2013, Article ID 325086, 7 pages
http://dx.doi.org/10.1155/2013/325086

*Research Article*

# Merkel Cell Carcinoma of the Head and Neck: A Single Institutional Experience

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Received 28 October 2012; Accepted 22 December 2012

Academic Editor: Boban M. Erovic



Merkel cell carcinoma (MCC) is a rare cutaneous malignancy occurring mostly in older immunocompromized Caucasian males. A growing incidence of MCC has been reported in epidemiological studies. Treatment of MCC usually consists of surgical excision, pathological lymph node evaluation, and adjuvant radiotherapy. This paper reports the experience of a single tertiary center institution with 17 head and neck Merkel cell carcinoma patients. Median followup for the cohort was 37.5 months. After five years, recurrence-free survival, disease specific survival, and overall survival were 85%, 90%, and 83%, respectively. Our limited data support the use of adjuvant radiotherapy. We also report two cases of MCC located at the vestibule of the nose and two cases of spontaneous regression after diagnostic biopsy. About 40% of our patients were referred to our center for surgical revision and pathological lymph node evaluation. Increased awareness of MCC and an interdisciplinary approach are essential in the management of MCC.

## 1. Introduction

In 1875, Merkel, professor of anatomy at the University of Rostock, Germany, for the first time described "Tastzellen" (touch cells)—later known as Merkel cells—in the epidermis of domestic animals and humans [1]. In 1972, Toker first reported a case series of five patients with "trabecular carcinoma" and recognized a "distinct pathological entity," with a "capricious clinical behaviour" [2]. It took Tang and Toker another six years to determine that trabecular carcinoma "most probably" derives from Merkel cells [3].

More recently, in 2008, a previously unknown polyomavirus was found to be integrated in Merkel cell carcinoma (MCC) [4]. Now known as Merkel Cell polyomavirus (MCV), this virus is indeed thought to be a causative agent in MCC [5, 6] and has been associated with about 80% of MCC cases [4, 7–10]. A previous study from our institution reported similar prevalence of MCV in MCC [11]. Conflicting evidence exists about the prognostic value of MCV status [7, 8, 12–14].

Important differential diagnoses of MCC are basal cell carcinoma, small cell melanoma, lymphoma, small blue round cell tumours, and especially metastatic small cell lung carcinoma [15]. A thorough histo- or cytopathological workup including immunohistochemistry (e.g., CK20, TTF-1, and neuroendocrine markers) [16] combined with entire examination and clinical history usually allows to differentiate the above mentioned entities.

A recent study by Smith et al. [17] drawn from an US-population based database (SEER) with over 4,300 MCC patients showed that 48% of all MCC are primarily located in the head and neck area (HN-MCC), with men representing about 61% of the patient population. The overwhelming majority of patients were Caucasian.

Hodgson [18] reported a incidence of Merkel cell carcinoma of 0.44/100,000/year in 2001 from the same database. Interestingly, there seems to be a sharp increase in the number of cases being reported. Hodgson performed a comparative analysis and showed an 8% estimated annual percentage change (EAPC) in MCC incidence from 1986 until 2001. This change was attributed to the ageing of population and the growing prevalence of immunocompromized

patients, two known risk factors for MCC [18–22]. Furthermore, the authors noted that this change might also result from increased awareness and reporting of MCC [18]. A further risk factor for MCC is UVB exposure, as shown in epidemiological studies [23] and mutations analysis of TP53 [24]. Expression of p53 has been correlated to MCV-negative MCC [13, 14, 25], thus suggesting a different pathogenesis in MCV-positive and MCV-negative MCC.

The authors of another epidemiological study from The Netherlands [19] reported similar incidence trends of MCC with an EAPC of 8%. For the same period, the EAPC for melanoma and squamous cell carcinoma of the skin were 4% and about 2%, respectively.

The prognosis of MCC remains poor, with a 5-year relative survival for local, regional, and metastatic disease of about 75%, 50%, and 20%, respectively [19]. Smith et al. reported a 5-year disease specific survival for pN0, pN1, and M1 in HN-MCC patients of 83.3%, 58.3%, and 31.3%, respectively [17]. Epidemiological analyses have established several prognostic factors in HN-MCC [17]: male sex, >T2-primaries, N-positive, M-positive, and tumour location at the lip were shown to be independent negative risk factors. Unlike for nonhead and neck-MCC (NHN-MCC), increasing tumour size was not a prognostic factor for HN-MCC [17].

Lemos et al. have shown the critical impact of pathological lymph node evaluation for MCC patients [26]. For example, in the management of cutaneous melanoma, sentinel lymph node biopsy (SLNB) is now a standard of care [27]. Analogically, SLNB has gained popularity in the past years in the management of MCC, currently being recommended as standard treatment [28], independently of the size of the primary tumour [29–32], as SLNB permits a pathological lymph node evaluation with less morbidity compared to elective neck dissection [33, 34]. SLNB studies have shown that about 30% of cN0 MCC patients harbour occult metastasis [35, 36], with up to 20% false negative rate [37, 38].

Prophylactic irradiation is usually accepted as an alternative in the management of the clinically negative neck [39].

The superiority of adjuvant radiotherapy in local and regional control has been shown in a meta-analysis of observational studies [40]. A recent multicentric prospective randomized controlled trial conducted in France again showed improved locoregional control [41]. Both studies could not prove a significant advantage of adjuvant radiotherapy on disease specific survival.

For inoperable patients, an in-field control rate of 75% has been reported with radiotherapy alone, with 55 Gy as a minimum dose for macroscopic disease [42]. Other studies also show acceptable results for radiotherapy alone [43, 44].

The aim of this study was to report the experience of a single institution tertiary center in Switzerland.

## 2. Methods

After local ethics committee approval, we performed a retrospective chart review of all patients treated for a Merkel cell carcinoma in the department for Otorhinolaryngology—Head and Neck Surgery—at the University Hospital of Zurich, Switzerland, between January 1990 and August 2012. We searched our electronic patient database using the following keywords: "Merkel cell carcinoma," "Merkel cell," and the ICD-10-Code for Merkel cell carcinoma (C44.*). A single reviewer (GM) was responsible for sorting the eligible patients out of the generated list.

Inclusion criteria were confirmed histopathological diagnosis of Merkel cell carcinoma and location of the primary tumour in the head and neck. Only patients treated at our department were included. Patients treated by other departments (e.g., plastic surgery) were not included.

For each patient, the following parameters were assessed: tumour site, age, sex, immunosuppression, TNM-stadium (AJCC, 7th Edition 2010 [39]), treatment modality of local and regional disease, location of primary tumour, surgical margins, recurrence-free survival (RFS), disease specific survival (DSS), and overall survival (OS).

Descriptive statistics were performed using Microsoft Excel 2007. Kaplan Meier estimates were calculated using IBM SPSS 19 and the survival functions were compared by log rank tests.

## 3. Results

*3.1. Demographics, Tumour Location, Staging, and Risk Factors.* Seventeen patients (4 male, 13 female, ratio 1 : 3.3) met the inclusion criteria (Table 1). The mean age was 71 y (SD 15.8, median 73, range 40–89). Ten primaries (58%) were located on the cheek, two on the external ear (12%), two in the vestibule of the nose (12%), one at the lower lip (6%), one at the eyelid (6%), and one at the glabella (6%). Diabetes was reported for one patient (6%); HIV/AIDS or immunosuppression after organ transplant was not reported for any patients.

According to AJCC, 7th Edition 2010 [45], stage Ia was present in four cases (24%); stage Ib in one (6%); stage IIa in two (12%); stage IIb in two (12%); stages IIc and IIIa in zero; stage IIIb in four (24%); and stage IV in zero cases. In four patients (24%), tumour stage was not available because of missing data.

Median followup for the cohort was 37.5 months (mean 62, SD 72, range 5–288). One patient (6%) died of Merkel cell carcinoma, three (18%) of other causes. After five years, recurrence-free survival (RFS), disease specific survival (DSS), and overall survival (OS) were 85%, 90%, and 83%, respectively (Figure 1).

*3.2. Treatment Options, Surgical Margins, Pathological Lymph Node Evaluation.* Sixteen patients (94%) underwent primary surgical resection. One patient (6%) underwent primary radiotherapy, as surgical excision would have resulted in complete removal of the nose, which was unacceptable to the patient. This patient was excluded from further analysis.

In three out of sixteen patients (19%), surgical excision margins of 2 cm were reported and in two cases margins of 1 cm (13%). In one case (6%), Mohs surgery was used.

In three cases (19%), margins smaller than 1 cm were used, twice because the surgeon did not consider MCC in the

Table 1: Summary of patients characteristics.

| ◦ | Age | Sex | Location | Side | T | N | M | Therapy | Recurrence | Followup | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 73 | f | Cheek | Right | pT2 | cN0 | M0 | Excision only | No | 170 | MCC unrelated death |
| 2 | 81 | f | Cheek | Left | pT2 | pN0 (0/31) | M0 | Excision + ND + RT | No | 9 | RFS |
| 3 | 52 | f | Vestibule of nose | Right | pT1 | pN0 (sn 0/4) | M0 | Excision + SLNB | No | 18 | RFS |
| 4 | 88 | f | Glabella | Middle | pT1 | cN0 | M0 | Excision only | Yes[§] | 27 | disease specific death |
| 5 | 86 | f | Pinna | left | pTx | cN0 | M0 | Excision + RT[*] | No | 0 | lost to followup |
| 6 | 64 | m | Cheek | Right | pT1 | pN0 (sn 0/1) | M0 | Excision + SLNB + RT | No | 72 | RFS |
| 7 | 57 | f | Cheek | Right | pT1 | pN0 (sn 0/3) | M0 | Excision + SLNB | No | 66 | RFS |
| 8 | 73 | f | Lower lid | Left | pTx | pN0 (sn 0/1) | M0 | Excision + SLNB | Yes[♯] | 74 | MCC unrelated death |
| 9 | 86 | m | Cheek | Left | pT2 | pN0 (0/23) | M0 | Excision + ND + RT[**] | No | 36 | RFS |
| 10 | 65 | f | Cheek | Left | pTx | pN0 (sn 0/2) | M0 | Excision + SLNB + RT | No | 39 | RFS |
| 11 | 40 | f | Cheek | Left | pT1 | pN1b (4/26) | M0 | Excision + ND + RT | No | 21 | RFS |
| 12 | 62 | f | Cheek | Right | pT1 | pN0 (0/40) | M0 | Excision + ND + RT | No | 24 | RFS |
| 13 | 86 | m | Pinna | Right | pT1 | pN2 (3/21) | M0 | Excision + ND + RT | No | 11 | MCC unrelated death |
| 14 | 51 | f | Cheek | Right | pTx | cN0 | M0 | Excision + RT | No | 288 | RFS |
| 15 | 72 | m | Lower lip | Middle | pTx | pN1b (3/28)[$] | M0 | Excision + ND + RT | No | 63 | RFS |
| 16 | 77 | f | Cheek | Right | pT2 | pN1b (1/25) | M0 | Excision + ND + RT | No | 72 | RFS |
| 17 | 89 | f | Vestibule of nose | Left | cT2 | cN0 | M0 | Radiotherapy only | No | 5 | RFS |

Age in years; f: female; m: male. TNM stadium according to AJCC, 7th Edition, 2010. RT: radiotherapy. [$]bilateral neck dissection, left 3/14, right 0/14. [*]RT refused by patient. [**]RT could not be performed because of wound healing problems. [§]regional recurrence after 11 months. [♯]local recurrence after 12 months. Followup in months. SLNB: sentinel lymph node biopsy. ND: neck dissection. RFS: recurrence-free survival. MCC: Merkel cell carcinoma.

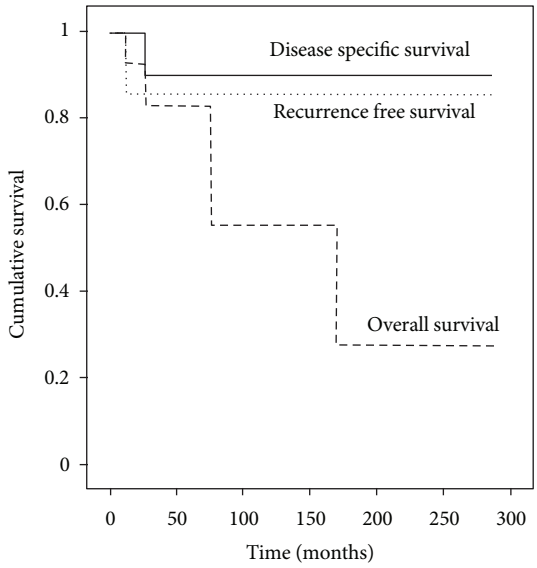


Figure 1: Survival analysis.

clinical differential diagnosis. For the remaining case, a two-step surgery was chosen, with the use of artificial skin graft, whilst a definitive histological margin was performed which led to a further excision a week later.

In seven cases (44%), surgical margins were not available; all these patients were referred to our institution after having primary surgery elsewhere.

All of the patients who had planned 2 cm excision margins had clear histological margins. One of the two patients with a planned 1 cm margin had to undergo a second operation to obtain clear histological margins. This patient (number 8) did not receive adjuvant radiotherapy as the primary was located at the lower lid and concerns were raised about the irradiation of the eye. He suffered a local recurrence one year later and had to undergo extended resection with orbital exenteration, free flap reconstruction, and adjuvant radiotherapy.

Of the patients who were initially operated in other hospitals and for those with planned excision margins of <1 cm, nine out of ten (90%) had to undergo at least one second surgical intervention. Data is incomplete for the last patient.

There was not statistical relation between surgical margins and recurrence-free survival ($P = 0.47$).

Of the sixteen patients who underwent primary surgical excision, sentinel lymph node biopsy was performed in five patients (31%) and was always negative. Mean number of sentinel nodes was 2.2 (range 1–4).

Two patients (12%) underwent therapeutic selective neck dissection for clinically positive neck disease (patients 11 and 13).

Five patients (31%) had elective selective neck dissections, showing regional disease in two cases (12%).

Five patients (31%) underwent, in addition to neck dissection, superficial parotidectomy, due to the localisation of the primary tumour and the expected lymphatic drainage. No disease was found in any of the parotid specimens.

Five patients (31%) did not have any pathological node evaluation, in one case because of the patient comorbidities. This patient (number 4) went on to develop regional recurrence 11 months later. He could not undergo salvage neck dissection and was treated with locoregional radiotherapy.

A few months later, he had distant metastatic disease and died twenty-six months after the initial surgery.

*3.3. Recurrence, Radiotherapy, and Outcome.* Two patients (12%) developed the locoregional recurrence. Patient 8 had a primary at the lower eyelid with a local recurrence 12 months after primary surgery. Patient 4 showed a regional recurrence, as discussed above. These patients received radiotherapy after locoregional recurrence.

In eleven patients (69%), adjuvant radiotherapy was recommended. One patient (6%) refused and another patient could not undergo radiotherapy because of severe wound healing problems.

Three patients (31%) did not have any radiation. Two of them underwent excision biopsy outside our clinic and were referred for revision surgery and pathological node evaluation. For both patients, the revision specimens and SLNB were free of tumour in the histopathological analysis. Adjuvant radiotherapy was therefore not performed.

Of the nine patients who had adjuvant radiotherapy following surgery, none suffered recurrence. Without adjuvant radiotherapy following surgery, two of six patients (33%) developed locoregional recurrence. There was a trend to a better RFS in patients who underwent adjuvant radiation ($P = 0.051$, log rank test).

Mean adjuvant radiation dose was 62.4 Gy (SD 4.8, median 62, range 54–70).

## 4. Discussion

MCC is a rare malignancy, occurring mostly in older immunocompromized Caucasian males. As the population in most Western countries continues ageing [46] and the prevalence of immunosuppression increases [47], epidemiological studies have shown an increase in MCC incidence.

The growing incidence of MCC has led to an increased awareness and reporting of MCC. Searching for "Merkel cell carcinoma" in PubMed database reveals a steady increase in results by year, with about 40 publications per year in the 90s, to over 160 publications for the year 2010 or 2011.

We report here a single institution retrospective analysis. The demographics of our patient cohort differ from other retrospective reports, as do our survival rates [17, 48–51]. The mean age is slightly lower than in other larger reports [17] and we have a predominance of women and no immunosuppressed patients, which could be explained by our relatively small patient cohort.

Considering a cohort with elderly patients, a difference between the OS and the DSS can be explained by comorbidities. We had in fact more disease unrelated deaths as disease specific deaths in the follow-up period.

In comparison to other reports [26, 40, 52], our favourable DSS and DFS could be explained by high rate of combined therapy, high rate of pathological lymph node dissection, low rate of distant disease at diagnosis, a predominance of women [17], and lack of immunosuppressed patients [22]. Our results must however been interpreted in light of the small cohort size.

As reported elsewhere [53], we did not find surgical margins to significantly affect recurrence-free survival. This is consistent with the fact that clear histological margins were obtained for every patient, independently of the surgical excision margins chosen initially. For HN-MCC, we recommend margins of 1 cm, or nonfeasible, two-step or Mohs surgery [28, 54, 55].

We observed a trend supporting the use of adjuvant radiotherapy. Although not significant, this result complies with stronger evidence [40, 41].

We report two cases of MCC occurring in the vestibule of the nose. This location has been reported very rarely in the literature [56]. One patient was treated using Mohs surgery. For the other patient, primary radiotherapy was chosen because an ablation of the nose would have been necessary to obtain clear surgical margins.

We also report two cases of surgical revision after external excision biopsy with lack of MCC cells in the revision specimen and SLNB, thus who either had been fully excised surgically or with spontaneous regression following biopsy, as already described in many other reports [56–61].

Analogically, MCC of unknown primary has also been described [62, 63]. Although the mechanism of regression is not known, immune infiltration has been proposed [64]. However, in a recent study with 37 patients, no significant increase in intratumoral CD8 T-cell infiltration after biopsy could be found [65].

As seven out of seventeen of the patients (41%) in this study were referred to surgical revision and pathological lymph node evaluation, we think that continuing education is essential, particularly for house physicians and general practitioners, who need to be aware of this rare but increasing malignancy, usually gentle in presentation [66, 67].

Our results should be interpreted cautiously, as biased by missing data and heterogeneous population. Our statistical analysis lacks power due to our low number of patientS and events. As a tertiary center, we also suffer referral bias. Nevertheless, bearing these caveats in mind, we believe that a few lessons can be learned from this paper.

In conclusion, we believe that increased awareness of MCC is essential to ensure an optimal initial management. Failure to do so can lead to a higher number of surgical interventions and missing or incomplete pathological staging.

Surgical removal of HN-MCC should assure oncological sufficient treatment, while preserving cosmetic or functional essential structure. An alternate surgical technique should be used, as appropriate.

To overcome these challenges, we strongly believe that a multidisciplinary approach and collaboration is essential. In accordance with the available literature, in Zurich, we have established an internal guideline, with a systematic assessing of several variables, thus allowing high quality data for further studies.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2012, Article ID 680410, 6 pages
doi:10.1155/2012/680410

*Review Article*

# Which Are the Cells of Origin in Merkel Cell Carcinoma?

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Received 12 October 2012; Accepted 27 November 2012

Academic Editor: Boban M. Erovic



Merkel cell carcinoma (MCC), a highly aggressive skin tumour with increasing incidence, is associated with the newly discovered Merkel cell polyomavirus (MCPyV). Studies on MCC and MCPyV as well as other risk factors have significantly increased our knowledge of MCC pathogenesis, but the cells of origin, which could be important targets in future therapies, are still unknown. Merkel cells (MCs), the neuroendocrine cells of the skin, were believed to be at the origin of MCC due to their phenotypic similarities. However, for several reasons, for example, heterogeneous differentiation of MCCs and postmitotic character of MCs, it is not very likely that MCC develops from differentiated MCs. Skin stem cells, probably from the epidermal lineage, are more likely to be cells of origin in MCC. Future studies will have to address these questions more directly in order to identify the physiological cells which are transformed to MCC cells.

## 1. Introduction

Merkel cell carcinoma (MCC) is a highly aggressive skin malignancy mainly affecting elderly and immunosuppressed people [1]. MCC is a rare tumour, but its incidence, especially in men, has risen during the last two decades in several countries [2]. For instance, an annual increase of 8% between 1986 and 2001 has been reported for the United States [3], and in the Netherlands, MCC incidence rates have doubled between 1993 and 2007 [4]. In Scandinavia, however, incidence of MCC did not rise between 1995 and 2005 [2]. MCC owes its name to characteristics it shares with Merkel cells (MCs), the neuroendocrine cells of the skin [5, 6]. Interest in MCC has significantly increased during the last years due to the discovery of Merkel cell polyomavirus (MCPyV) and its implication in MCC pathogenesis [7–9]. Studies on MCPyV and other molecular risk factors like mutations in the *ATOH1* gene [10] have greatly advanced our understanding of MCC pathogenesis. The monoclonal integration of viral DNA in a large proportion of MCCs suggests that viral infection precedes tumourigenesis [7, 11]. Furthermore, MCPyV T antigens are required for maintenance of virus-carrying MCC cell lines [12]. Binding of large T antigen to cell cycle regulators or of small T antigen to the translation regulator 4E-BP1 are potential mechanisms by which integrated MCPyV could transform cells [11, 13]. MCPyV may thus at least contribute to MCC formation, being the first molecular risk factor identified in MCC [9]. Additionally, mutations in several genes, including the tumour suppressor *ATOH1*, encoding a transcription factor involved in Merkel cell differentiation, and *PIK3CA*, which codes for phosphatidylinositol 4,5-bisphosphate 3-kinase, catalytic subunit, alpha isoform, have been found in subsets of MCC [10, 14]. Such mutations might either act in concert with MCPyV during tumourigenesis, or cause MCC formation in the absence of the virus. However, the question for the cell of origin in MCC remains unresolved. If it was known from which cell type MCC originates, one could develop more specific therapies which target these particular cells. In the present paper, we therefore reconsider potential cells of origin in MCC. We start with a brief discussion of cells of origin in cancer and subsequently elaborate on different cell types which have been hypothesized to be at the origin of MCC. Last but not least, we briefly discuss how MCPyV might affect the potential MCC precursors.

## 2. Cells of Origin in Cancer

Cells of origin in cancer have been defined as cells which "acquire the first genetic hit or hits that culminate in

the initiation of cancer" [15]. Given the extended lifetime and self-renewal of physiological stem cells, these cells which assure homeostasis of rapidly self-renewing tissues—like skin—appear particularly prone to accumulate oncogenic mutations [15–17]. Therefore, it is not surprising that various studies have identified stem cells as cells of origin in cancer, for example, hematopoietic stem cells in chronic myeloid leukemia (CML) [18] or crypt stem cells in intestinal cancer [19]. In the skin, Youssef et al. [20] identified long-term resident progenitor cells of the interfollicular epidermis and the upper infundibulum as cells of origin in basal cell carcinoma (BCC), using clonal analysis in mice. These long-lived progenitor cells could, however, also be called "epidermal stem cells" according to Sellheyer [21]. It is noteworthy that this stem cell population is also the cell of origin of Merkel cells in mice [22–24]. Furthermore, squamous cell carcinoma (SCC) could be induced in hair follicle stem cells as well as in cells immediately exiting the bulge, but not in transit amplifying cells, which are more developmentally restricted [25, 26]. Generally, it should be noted that the terms "stem cells" and "progenitor cells" are often used interchangeably, as a sharp distinction is not always easy.

The second group of cells of origin in cancer are committed progenitor cells [15] which differ from stem cells by their much more restricted differentiation potential. Such cells play an important role in the acute phase of CML [27], but have also been identified as cells of origin in solid tumours. Examples include medulloblastoma arising from granule neuron progenitors [28, 29] and breast cancer developing from luminal epithelial progenitors [30].

Third, even differentiated cells could give rise to cancer, as any cell which is able to proliferate could become a cell of origin in cancer, provided it acquires mutations which restore the ability to self-renew and prevent differentiation to a postmitotic state [15]. For instance, a study in mice strongly suggests that malignant peripheral nerve sheath tumours arise from differentiated glia [31]. Moreover, differentiated endocrine cells in the pancreas appear to be a target for oncogenic transformation [32]. However, it should be noted that in both cases, less differentiated progenitor cells cannot be definitively excluded as cells of origin [15].

Before turning to the origin of MCC, it is important to keep in mind that the terms "cell-of-origin in cancer" and "cancer stem cell" are different [15, 33]. The "cell-of-origin" is a physiological cell which becomes tumourigenic due to genetic alterations. By contrast, "cancer stem cells" are a cell population within a tumour which constantly self-renews and is able to generate all types of cells present in this tumour, thus preserving the tumour. Briefly, the "cell-of-origin" *acquires* tumourigenic properties, whereas the "cancer stem cell" *sustains* tumourigenic properties. Regarding the cancer stem cell concept, the reader is referred to recently published excellent review articles [33–35].

## 3. Putative Cells of Origin for MCC

*3.1. Merkel Cells.* Early histological and ultrastructural analyses of the so-called "trabecular carcinoma of the skin" [36, 37] revealed similarities to Merkel cells [5, 6, 36], leading to the currently used designation "Merkel cell carcinoma" [5, 6]. Moreover, the reported morphological observations led to the conclusion that MCC may most probably originate from Merkel cells (MCs) [5, 6, 36]. This traditional view of MCC origin (Figure 1) was further corroborated by the discovery that MCC and MCs share a similar immunophenotype [1, 38]. Shared features include presence of the Merkel cell marker cytokeratin 20 (CK20) in MCC [39, 40] as well as biosynthesis of synaptophysin [41–44], NCAM/CD56 [41, 45, 46], and numerous endocrine markers [38].

Although at first glance, these observations strongly support the hypothesis that MCC emerges from transformed MCs, there are quite a few data which question this view. First, MCs and MCC differ in some aspects of their immunophenotype. For instance, the neural cell adhesion molecule L1 (CD171), a relative of NCAM, is produced by MCC cells, but not by MCs [47]. Moreover, the arrangement of intermediate filaments, including CK20 and neurofilaments, differs between MCC and MCs: in MCCs, whirl-or plaque-like aggregates are observed, whereas in MCs, the intermediate filament cytoskeleton is loosely and diffusely arranged [48]. Last but not least, the tyrosine kinase receptor c-kit, which has been detected in the majority of MCCs [49], is mostly absent from human MCs [48].

Second, in a study on fetal and human skin, no proliferative Merkel cells could be detected, strongly suggesting that human Merkel cells are postmitotic [50]. In line with these findings, more recent lineage tracing analyses revealed that in mice, adult Merkel cell homeostasis is ensured by differentiation of epidermal progenitors, not through the proliferation of differentiated MCs [22]. Given that the possibility to restore proliferative potential is a prerequisite for a cell to become cell-of-origin in cancer [15], it is highly unlikely that postmitotic MCs would be the source of a malignancy.

Third, differences in tissue localization argue against MCs as cells-of-origin for MCC. Whereas the majority of MCs is located in the basal layer of the epidermis [48], MCCs are mostly found in the dermis and subcutis [51]. However, it should be noted that a minority of 3.2% to 9.1% of reported cases are partly or even fully localized in the epidermis [1]. The "localization argument" thus has to be handled with care.

Finally, the observed heterogeneity in MCC rather favors less differentiated cells as cells of origin [1]. In detail, MCCs associated with diverse differentiation patterns have been described: squamous [52], squamous and sarcomatous [53], melanocytic [54], eccrine [55], leiomyosarcomatous [56], rhabdomyoblastic [57], and fibrosarcomatous [58] differentiation. Although there is a certain immunophenotypical diversity in MCs themselves [41], the multitude of differentiation patterns in MCC rather points to stem or early progenitor cells as cells-of-origin. Such cells would possess the potential to differentiate along different lineages. It is, of course, conceivable that distinct stem or progenitor populations account for MCCs with distinct differentiation patterns. In the following sections, we will therefore discuss

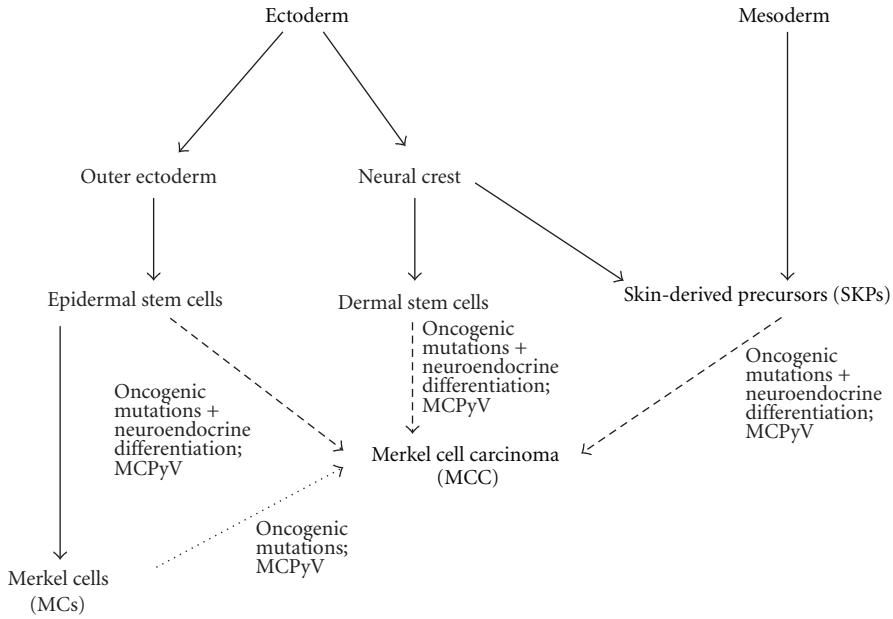


Figure 1: Scheme of potential cells of origin of Merkel cell carcinoma (MCC), shown from an ontogenetic perspective. All arrows with a *scattered* line represent thus far hypothetic lineage relationships. However, whereas MCC derivation from Merkel cells is not very likely, there are hints implying epidermal stem cells in MCC genesis, and dermal stem cells as well as SKPs at least cannot be excluded as cells of origin for MCC. For each putative cell type of origin, an involvement of MCPyV in MCC genesis is highly probable, at least in a large fraction of MCCs.

stem cell populations in skin which might serve as cell of origin in MCC.

*3.2. Epidermal Stem Cells.* As mentioned before, in mice, MCs arise from stem/progenitor cells of the epidermal lineage [22–24]. Therefore, epidermal stem cells or long-lived epidermal progenitor cells appear to be good candidates for a MCC cell-of origin (Figure 1). Along this line, Lemasson et al. have detected CK14-positive cells in MCC samples [59]. As CK14 is a marker of the basal epidermal layer which comprises the epidermal stem cells [60], and as MCs in mice have CK14-positive progenitors [22–24], the authors argued that a malignant transformation of epidermal stem cells could underlie MCC, and that the transformed cells could then serve as cancer stem cells for MCC [59]. In the same study, nestin immunoreactivity was detected in 20–30% of MCC tumoural cells. Nestin is regarded as a marker of multilineage progenitor cells [61]. However, contradictory to the findings of Lemasson et al., Abbas and Bhawan [62] reported the absence of nestin in all 11 MCC cases investigated. It cannot be excluded that these discrepancies were caused by different immunostaining protocols, as high variability of nestin immunoreactivity in skin due to procedural differences has been described [63]. Nevertheless, both studies showed the presence of CK19-positive cells in MCC [59, 62]. CK19 has been used as an epidermal stem cell marker [64], but is also present on mature Merkel cells [65]. Moreover, Abbas and Bhawan found no CK15-positive cells in MCC [62]. This might be an argument against hair follicle bulge stem cells as cells of origin in MCC, as CK15 is found in these cells [66]. Summarizing, there are several hints pointing to an epidermal stem/progenitor cell origin of MCC, but no experimental proof so far.

*3.3. Dermal Stem Cells Derived from the Neural Crest.* Based on their histomorphological pattern as well as results of immunohistochemical stainings, dermal neuroendocrine cells have been suggested as a potential source for MCC [51, 67]. This suggestion points to a second stem cell population present in skin, dermal stem cells (DSCs) derived from the neural crest lineage [68, 69] (Figure 1). Interestingly, the transcription factor Sox2, which is expressed by neural crest-derived stem cells from human skin [70], has been detected in MCC by immunohistochemistry [71]. Nine MCC samples were all Sox2-positive, with more than 50% of cells exhibiting nuclear staining. On the other hand, Sox2 is expressed by epidermal progenitors in the mouse tongue during their differentiation to sensory cells [72], demonstrating that it cannot be regarded as an exclusive neural crest-derived stem cell marker. Therefore, although MCC cells express several proteins abundant in neural cells, strong hints to a neural crest origin of MCC are currently missing.

*3.4. Skin-Derived Precursors.* In addition to the neural crest-derived stem cells mentioned before, a further stem cell population has been isolated from murine and human dermis and termed skin-derived precursors (SKPs) [73, 74]. These cells are able to differentiate into both neural and mesodermal cell types. In mice, facial SKPs are generated from the neural crest, whereas dorsal trunk SKPs derive from the somites [75] (Figure 1). Although there are a lot of similarities between SKPs and the DSCs mentioned before,

both cell types differ in that SKPs lack the robust expression of the neurotrophin receptor p75 which is characteristic for DSCs [69]. Given their dermal localization and their broad differentiation potential, SKPs should be regarded as a further potential cell of origin for MCC.

## 4. MCC Cells of Origin and the MCPyV

If the MCPyV plays an important role in MCC genesis, as suggested by several recent studies (reviewed in [8, 9]), it should target the putative cells of origin (Figure 1). It is noteworthy that JC polyomaviruses have been shown to preferentially infect stem cells or progenitor cells with a low degree of differentiation [76]. If MCPyV exhibits a similar preference, this would argue for a stem rather than a Merkel cell at the origin of MCC. Along the same line, unpublished findings from our laboratory suggest that human Merkel cells are normally devoid of MCPyV large T antigen (LTAg). Among 733 MCs detected by CK20 immunostaining in human skin areas prone to MCC development, none exhibited LTAg immunopositivity in the adjacent section. Although this does not prove the absence of MCPyV from differentiated MCs, it makes them less likely as a target for MCPyV infection.

## 5. Summary and Conclusions

Despite intense research on MCC during the last years, the cells of origin of this cutaneous malignancy remain elusive. Merkel cells (MCs), originally the favourite candidate for such a role, appear less likely to give rise to MCC now, mainly because of MCC heterogeneity and the postmitotic character of MCs. Stem cells located in the skin, most probably of the epidermal lineage, appear to be more probable cells of origin for MCC. However, as experimental evidence for a stem cell origin is missing, too, more direct approaches to tackle the "origin-of-MCC-question" are needed. These could include genetic lineage tracing or reprogramming of MCC cells.

## Acknowledgment

The authors thank Ewa Wladykowski for expert technical assistance.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2012, Article ID 563829, 6 pages
doi:10.1155/2012/563829

*Review Article*

# A Review of Radiotherapy for Merkel Cell Carcinoma of the Head and Neck

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Received 24 May 2012; Accepted 18 September 2012

Academic Editor: Brett A. Miles



Merkel cell carcinoma of the head and neck (MCCHN) presents a clinical challenge due to its aggressive natural history, unpredictable lymphatic drainage, and high degree of treatment related morbidity. Histological examination of the regional lymph nodes is very important in determining the optimal treatment and is usually achieved by sentinel lymph node biopsy. Radiotherapy plays a critical role in the treatment of most patients with MCCHN. Surgery with adjuvant radiotherapy to the primary tumour site is associated with high local control rates. If lymph nodes are clinically or microscopically positive, adjuvant radiotherapy is indicated to decrease the risk of regional recurrence. The majority of locoregional recurrences occur at the edge or just outside of the radiation field, reflecting both the inherent radiosensitivity of MCC and the importance of relatively large volumes to include "in-transit" dermal lymphatic pathways. When surgical excision of the primary or nodal disease is not feasible, primary radiotherapy alone should be considered as a potentially curative modality and confers good loco-regional control. Concurrent chemoradiotherapy is well tolerated and may further improve outcomes.

## 1. Introduction

Merkel cell carcinoma (MCC) of the skin is an uncommon, neuroendocrine malignancy often associated with a rapidly progressive primary tumour, regional nodal disease, and a high risk of distant metastases. The overall incidence is low, approximately 0.44 cases per 100 000 but appears to be increasing with the aging population [1]. The overall cure rates for MCC are approximately 50% with a high degree of variability amongst reported series based on stage, patient comorbidities, and treatment factors [2]. The most common primary tumour location in 3870 cases reviewed from the Surveillance, Epidemiology, and End Results (SEER) database was the head and neck, which represented half of all cases, among which lesions located on the face were the most common (29%).

The management of cancer of the head and neck region presents unique challenges to diagnosis and treatment. Given the high predilection of MCC to originate in these regions, the purpose of this study is to evaluate and review the role of radiotherapy in the management of Merkel cell carcinoma of the head and neck (MCCHN).

## 2. Background

The role of radiotherapy (XRT) in the treatment of non-melanoma skin cancers of the head and neck is well established. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the face, scalp, ear, lip, nose, and neck can be treated with radiotherapy alone, with a high cure rate, in excess of 90% in most series [3, 4]. Cosmetic outcomes are generally good or acceptable [5, 6] and the risk of severe, late toxicity such as chronic ulceration, osteoradionecrosis or chondronecrosis are very uncommon and are more likely to be associated with hypofractionated regimens which utilize a high daily radiation dose over a short number of treatments [7, 8]. There are limited data describing the use of radiotherapy for MCC of the head and neck due to the relatively low incidence and lack of prospective clinical

trials. Therefore, some overarching principles and lessons learned from decades of treatment of NMSC and SCC of the larynx/pharynx and neck may be cautiously extrapolated to help guide radiotherapy treatments for Merkel cell carcinoma of the head and neck, while recognizing that the radiobiology, patterns of spread, and natural history are unique to this neuroendocrine skin tumour.

## 3. Staging and Investigations

Clinical examination must include assessment and measurement of the primary tumour as well as palpation of the lymph node regions at risk. In addition, the physical examination must include a check of the surrounding adjacent skin to rule out "in-transit" or satellite metastases which are described in the TNM classification system [9] as "distinct from the primary lesion and located between the primary lesion and the draining regional lymph nodes, or distant to the primary lesion" and denote stage N2 disease.

Patients diagnosed with MCCHN should undergo diagnostic imaging using contrast enhanced CT or MRI to delineate the extent of local disease, assess perineural or bone invasion, and identify in-transit metastases. Regional lymph node involvement may also be assessed by standard imaging but may be insufficient for detecting small volume disease (Sentinel Lymph Node Biopsy is discussed below). Because a high proportion of patients may present with distant metastases, all patients should undergo staging CT scans of the chest and abdomen. Positron emission tomography (PET) has also been shown to be sensitive to MCC. A retrospective review of 18 patients with MCC by Concannon et al. [10] demonstrated that PET detected all tumours as small as 5 mm and that the PET scans altered staging in 33% of patients.

*3.1. Sentinel Lymph Node Biopsy (SLNBx).* SLNBx plays a critical role in the management of MCCHN. First, SLNBx has higher sensitivity for detecting microscopic lymph node metastasis. Several single institution reports demonstrate that in patients with MCC who are clinically node negative including CT imaging in some series, the SLNBx was positive in 29–50% of cases [11–14], resulting in upstaging the disease and presumably altering the management of the regional lymph nodes.

Second, the lymphatic drainage patterns of cutaneous tumours of the head and neck region are difficult to predict on the basis of the anatomic location of the primary, with a high degree of variability between patients. Klop et al. [15] compared the actual sentinel lymph node locations with the clinically predicted locations based on lymphatic mapping guidelines for 65 patients with cutaneous melanoma of the head and neck. The authors reported 23% of SLNBx locations to be discordant with the "expected" locations based on classical drainage patterns. In a similar study, Lin et al. [16] found discordance between the "clinically predicted" lymph node region and the actual SLNBx location in 49 of 114 cases (43%) of patients with melanoma of the head and neck region. In these discordant cases, the SLNBx may reveal lymph node drainage patterns that would not typically be included in standard neck dissection or radiation field, for example, postauricular nodes, inferior or posterior neck, and even contralateral nodal basins. Despite these advantages, it is also important to consider limitations of SLNBx in the head and neck region. The false negative rates in the head and neck region are known to be higher than in other anatomic sites, due to multiple pathways or aberrant drainage basins. SLNBx in a postoperative setting may also be affected by disruption of the tissues and lymphatics in the primary tumour bed. An extensive systematic review of 3442 patients included in 32 studies demonstrated a median false negative rate for nodal recurrence of 20.4% [17]. Although there are limited data examining the predicted versus actual lymphatic drainage patterns in MCCHN, it would seem reasonable to expect that these tumours may also exhibit a relatively high degree of variability.

Overall, despite those limitations described, SLNBx has the ability to improve nodal staging accuracy and guide radiotherapy or surgical treatment decisions in patients with MCCHN and is recommended for the vast majority of patients. One exception may be patients with very small tumours <1.0 cm, who are reported to be at a very low risk (4%) of regional nodal metastasis [18].

## 4. Radiotherapy for Merkel Cell Carcinoma of the Head and Neck

Merkel cell tumours are known to be highly radiosensitive and often exhibit dramatic response to moderate doses of XRT. Radiotherapy treatment of both the primary tumour site and regional lymphatics should be considered and discussed for all patients, ideally in a multidisciplinary case conference. The most common role of XRT is in the adjuvant setting but in cases where surgery is not feasible or declined, primary radiotherapy represents an alternative option for curative treatment. XRT is typically administered in a standard, conventional fractionation schedule, 1.8–2 Gy daily over 5 to 7 weeks, as normal tissue tolerances of the head and neck are well established and there is no evidence to suggest a benefit for altered fractionation. Due to the low incidence of MCC, most reports on the subject group together all anatomic locations for analysis. This more general data is presented below and when available, specific evidence pertaining to MCC of the head and neck is highlighted.

*4.1. Adjuvant Radiotherapy to the Primary Site.* To our knowledge, there are no prospective randomized studies examining the use of postoperative adjuvant radiotherapy in the setting of MCC. A large number of reports have been published on this topic, including patients who underwent wide local excision (2–5 cm margins) with and without adjuvant radiotherapy with mixed results. A relatively large, single institution study of MCC [19] including all locations found a low rate of local recurrence (8%) when negative margins were achieved and the nodal recurrence rate was as low as 11% in patients who had undergone SLNBx or

nodal dissection. Seventeen percent (41 of 237) of patients underwent adjuvant radiotherapy and the authors did not detect a significant difference in locoregional recurrence rates associated with XRT. It should be noted that the mean diameter of tumours located in the head and neck in the study was 1.3 cm and only 16% of MCCHN patients presented with clinically involved lymph nodes. In contrast, a multicentre, retrospective study of 110 patients with MCC [20] specifically located in the head and neck region found that combined modality treatment with surgery and radiotherapy was associated with better local and regional control, compared with either surgery or radiation alone. Lawenda et al. [21] also found a statistically significant improvement in local control rates associated with adjuvant XRT to the primary site compared with surgery alone (95% versus 69%, $P = 0.020$) in a series of 36 patients who all had MCCHN.

A meta-analysis of 132 studies yielded 1254 eligible patients with a single primary Merkel cell carcinoma lesion of the skin treated with surgery [22]. Approximately two thirds of patients underwent surgery alone, (the rest had surgery and adjuvant radiotherapy) and all patients included in the meta-analysis had negative margins. Patients treated with adjuvant radiotherapy had a statistically significant reduction in both local (hazard ratio, HR = 0.27, $P < 0.001$) and regional recurrence rates (HR = 0.34, $P < 0.001$). Cause specific and overall survival reached statistical significance favouring adjuvant XRT only when single case reports and studies involving a single-treatment group were excluded.

Another large review of patients with MCC was reported by Mojica et al. [23] based on the Surveillance, Epidemiological, and End Results (SEER) database. 1487 patients with MCC stage I–III, were included in the analysis and 40% of those patients had adjuvant XRT. Patients who received adjuvant radiotherapy had a statistically significant difference in overall median survival compared with those who had surgery alone (63 versus 45 months, $P = 0.0002$) despite the fact that the irradiated group had a higher incidence of regional disease at diagnosis. Subset analysis suggested that patients with tumour size >2 cm derived the greatest benefit from adjuvant XRT.

The current evidence suggests that adjuvant radiotherapy to the primary tumour bed should be recommended in most patients with MCCHN following surgery, to decrease the risk of local recurrence. It is possible that patients with small, pathologically node-negative tumours that have been widely excised with negative margins >3 cm may be at sufficiently low risk to consider observation but identification of these very low risk patients with tumours of the head and neck region is likely to be imprecise and infrequent.

*4.2. Adjuvant Radiotherapy of Regional Lymph Nodes.* MCCHN should be assessed with CT and/or MRI of the regional lymph nodes as well as sentinel lymph node biopsy. The importance of SLNBx in MCC is described above and also supported by a review of the SEER database which identified 2104 patients who had specifically MCC of the head and neck [24]. The *absence of histologic lymph node evaluation* was an independent prognostic factor for disease specific survival, suggesting that patients may have benefited from additional nodal treatments. Patients with lymph node positive disease will typically proceed to have completion neck dissection.

The role of adjuvant radiotherapy to the regional lymphatics after SLNBx or complete nodal dissection is not well defined. Veness found a high risk of regional lymph node recurrence (43%) in patients with clinically positive lymph nodes after surgical dissection alone, compared with 14% risk recurrence rate in patients undergoing dissection followed by adjuvant radiotherapy to the nodal basin [25]; in addition the authors found in a separate series of 37 patients who had exclusively head and neck MCC [26] that nodal radiotherapy was associated with a lower risk of regional relapse. Allen et al. [19] also observed a high rate of regional recurrence rate of 26% in patients with clinically node positive disease treated with surgical dissection alone. Lok and colleagues [27] also focused on the use of radiotherapy for patients with Merkel cell carcinoma of the head and neck. Only 6% of patients (3 out of 48) developed locoregional failure following surgery and radiotherapy for MCCHN with a median followup period of 51 months. All 3 regional recurrences occurred outside of the radiation field, reinforcing the importance of accurate target delineation of regions at risk.

In the only prospective randomized study of radiotherapy in MCC reported to date, investigators evaluated the efficacy of "adjuvant prophylactic regional radiotherapy" in patients with Stage 1 Merkel cell carcinoma [28]. Although the trial was not completed as planned due to increasing use of sentinel lymph node biopsy, results from 83 patients were evaluated and demonstrated a significant reduction in regional recurrence (16.7% versus 0%, $P = 0.007$) favouring regional irradiation. Based on the available evidence it is useful to group the management of regional lymphatics in MCCHN into commonly encountered clinical scenarios.

(i) No histologic examination of regional LNs, no SLNBx, or dissection: if SLNBx is not technically feasible, or the patient declines then the regional lymph nodes should be irradiated. A prospective, randomized study demonstrates significant risk of nodal recurrence (16.7%) even in stage I disease and other retrospective reviews suggested a similar risk of nodal recurrence (17.6%) [13, 28].

(ii) Node negative disease after SLNBx or nodal dissection: although there is a risk of false negative results with SLNBx of the head and neck region, most patients with negative biopsy do not require full regional irradiation of the draining lymphatic basin. A reasonable approach may be to include adjacent lymph nodes that are located within the usual 3–5 cm margin from the postoperative bed. For example, adjuvant XRT for a tumour located in the pre-auricular region may include the superficial lobe of the parotid and upper jugulodigastric nodes but not extend to submandibular region or inferior neck.

(iii) Clinically positive or histologically positive: based on a high risk of regional recurrence with surgery alone and moderate radiation toxicity with intermediate doses of XRT, patients with node positive MCCHN should be recommended to undergo regional irradiation of a minimum of one echelon distal and proximal to the involved node as well as in-transit skin between the primary disease and lymph nodes if clinically feasible [25, 29].

*4.3. Primary Radiotherapy for Merkel Cell Carcinoma.* In cases where MCCHN is not treatable by primary surgery for reasons such as unacceptable deformity or defect, patient comorbidities resulting in unacceptably high perioperative risks or patient refusal of surgery, radiation alone or in combination with chemotherapy may be considered as the primary curative treatment modality.

Veness et al. reported on the Australian experience of radiotherapy alone for Merkel cell carcinoma [30]; 43 patients underwent radiotherapy as the primary treatment for either new diagnosis or gross tumour recurrence. The median age of patients was 79, and approximately half of all patients had a primary lesion of the head and neck. The in-field control rate was 75% and most recurrences occurred at distant metastatic sites. Pape et al. [31] also observed high locoregional in-field control rates in 25 patients with MCC treated exclusively with radiotherapy. After median followup of 3 years, the XRT-treated patients had no local recurrence and only 2 regional nodal relapses. These results were similar to a matched cohort of 25 patients at the same institution who underwent both surgery and radiation.

A prospective phase II study involving radiotherapy for MCC, by Poulsen et al., studied the use of concurrent chemoradiotherapy consisting of 50 Gy XRT plus carboplatin and etoposide in patients with high risk features [32]. A total of 53 patients were enrolled (22 of whom had MCCHN), 38 were treated postoperatively, and 15 patients had macroscopic disease treated with chemo-XRT without surgery. For the patients undergoing chemo-XRT alone as primary treatment, the 3 year locoregional control rate was 71% and overall survival was 45%. The prospect of radiotherapy mono-therapy has also been examined in the setting of clinically positive lymph nodes. Fang et al. examined results of patients with macroscopic lymph node disease who had either radiotherapy alone or surgery plus nodal irradiation [33]. The rate of locoregional control with XRT alone for clinically positive nodes was 78% at 2 years, compared with 73% in the cohort receiving surgery plus radiation ($P = 0.8$).

*4.4. Radiation Planning: Clinical Target Volume.* Ideally, patients with MCCHN should undergo a multidisciplinary assessment prior to surgical excision of the primary lesion. This allows for planning of the sentinel lymph node biopsy, surgical planning for the best cosmetic outcome and also radiation oncology assessment and documentation of the primary tumour location and features. Preoperative clinical photographs are also often helpful in determining the adjuvant radiotherapy field. The radiation target volume must be carefully considered on an individual case by case basis. General principles of target coverage apply to the primary site, lymphatics and perineural involvement.

(i) Adjuvant XRT for Primary Tumour Site: Target includes the scar, postoperative bed and an additional margin of 3–5 cm where clinically feasible. Adjuvant XRT to the primary site will often include the immediately adjacent nodal regions.

(ii) Regional Lymph Node XRT: at a minimum, the levels of the head and neck directly adjacent to the involved nodes (i.e., one level proximal and distal to involved regions) should be covered as well as all "in-transit" skin and dermal lymphatics between the primary tumour and draining nodal basin.

(iii) Perineural Invasion: if MCCHN involves named nerves or presents with clinical neurologic symptoms, the radiotherapy target should include the nerve pathways and associated ganglion retrograde to the base of skull foramen as described by others in the management of other cutaneous malignancies of the head and neck [34, 35].

*4.5. Radiation Dose.* The optimal radiation dose for treatment of MCCHN has not been studied in a prospective fashion. One retrospective review of 112 patients with MCC addressed the issue of dose-response in subclinical and gross disease. The authors concluded that doses of $\geq 50$ Gy could be used for microscopic disease and that gross disease should be treated to $\geq 55$ Gy, citing a decreased risk of in-field recurrence with increasing dose [29]. These authors and others have reported local recurrences just beyond the field edge, suggesting the importance of extending primary margins (4-5 cm) rather than dose escalation for microscopic residual [27, 29].

Radiation doses of up to 60–70 Gy are routinely used in the treatment of SCC of the head and neck. Based on available data, we have adopted generally accepted XRT doses for MCCHN.

(i) Microscopic, subclinical, and high risk regions: 50–56 Gy.

(ii) Primary radiation treatment of locally advanced, gross disease: 60–66 Gy.

*4.6. Radiation Treatment Toxicity.* Radiation skin toxicity is related to the total dose, volume, surface area, fractionation schedule, and patient factors such as age, vascular disease, and tumour location. Cumulative experience from the treatment of nonmelanoma skin cancer indicates virtually all patients will develop at least mild-to-moderate acute side effects such as erythema, pruritus, desquamation [36] as well as possible late radiation changes such as atrophy, change in pigmentation, telangiectasia, or fibrosis. Serious or severe complications associated with skin radiotherapy such as chronic ulceration, necrosis of the skin, bone, or cartilage requiring surgical repair are rare (approximately 1%), and

may be associated with reirradiation or hypofractionated treatment schedules [7, 8, 37].

## 5. Conclusions

Radiotherapy plays a critical role in the management of Merkel cell carcinoma of the head and neck. Local adjuvant treatment to the primary tumour site and any positive lymph node regions is associated with lower rates of locoregional recurrence. Sentinel lymph node biopsy should be considered standard of care for these patients due to the high risk of occult metastases and difficulty in accurately predicting lymph node drainage patterns. The patterns of recurrence in this challenging disease reinforce the importance of wide radiation margins and consideration of in-transit or satellite metastases. For patients with inoperable or unresectable disease, the available evidence suggests that radiotherapy as the primary therapeutic modality results in tumour control rates which are comparable to surgical series.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2012, Article ID 176173, 6 pages
doi:10.1155/2012/176173

*Review Article*

# Role of Sentinel Lymph Node Biopsy in the Management of Merkel Cell Carcinoma

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Received 4 February 2012; Revised 10 August 2012; Accepted 18 August 2012

Academic Editor: Boban M. Erovic



Merkel cell carcinoma (MCC) is a rare and typically aggressive form of skin cancer. It most commonly affects the elderly and has a predilection for the sun-exposed skin of the head and neck region. Other etiological factors include immune suppression, organ transplantation, and polyoma virus infection. MCC has a propensity to spread to regional lymphatics with a high locoregional recurrence rate. Since its discovery in 1972, treatment paradigms have shifted, with no consensus on optimal management strategies. Currently, standard of care includes surgical intervention to the primary and locoregional site with adjuvant radiotherapy for high-risk disease. In this paper, we discuss the history, pathology, and epidemiology of this rare disease with a focus on the evidentiary basis of treatment protocols. The use of sentinel lymph node biopsy as a management option will be the focus of this paper.

## 1. Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive neoplasia first described in 1972 by Toker [1]. First described as trabecular carcinoma of the skin as a consequence of its column-like growth pattern, MCC currently has many synonyms including cutaneous neuroendocrine carcinoma, and small-cell primary cutaneous carcinoma [2]. The discovery of neurosecretory granules in three of the original tumours studied by electon microscopy raised the possibility of a neuroendocrine source, and the MC was proposed as the cellular origin [3]. It has been shown that MC and MCC have overlapping electron microscopic features and immunohistochemical profiles which support the MC as the cellular origin of this aggressive tumour. The term Merkel cell carcinoma was coined by DeWoolf-Peters in 1980 and today remains the most accepted terminology [4].

The primary lesion of MCC is distinguished by its absence of distinctive clinical characteristics [4]. In general, MCC occurs more commonly in sun-exposed skin and in elderly individuals. The primary lesion presents as a rapidly growing, asymptomatic, reddish-blue dermal papule or nodule that develops over the course of weeks to months (Figure 1) [4]. The mnemonic AEIOU has been used to describe its clinical appearance and demographic characteristics: asymptomatic, expanding rapidly, immune suppression, older than 50 years, and ultraviolet-exposed/fair skin [5]. Rates of lymph node metastasis can be very high which affect the treatment decisions regarding the neck.

Immunohistochemistry is one of the primary modalities used in the routine diagnostic workup of MCC to help distinguish it from other tumours in the differential diagnosis. CK20 is an intermediate filament protein that has been proposed as the most robust cytokeratin marker for distinguishing MCC from small-cell lung carcinoma and other cutaneous carcinomas [6]. Another biomarker used to differentiate these two carcinomas is thyroid transcription factor-1 (TTF-1). Often, these two biomarkers are used in conjunction because of the rare case of a CK20-negative MCC. There have been no cases of TTF-1 expression in

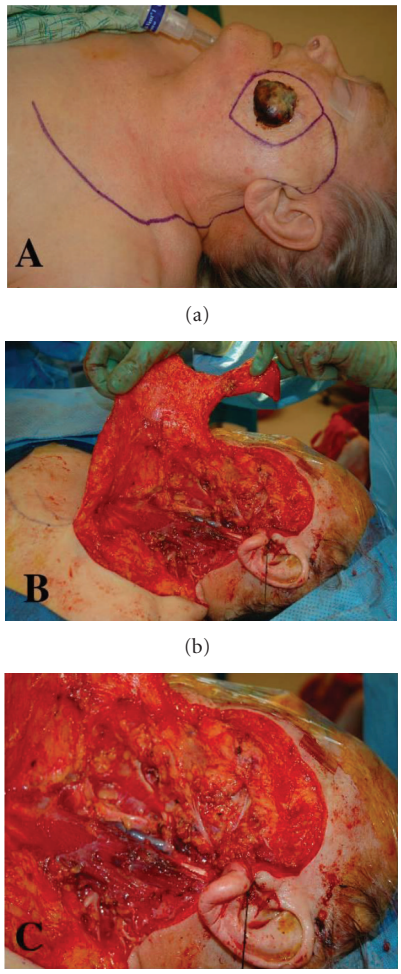


Figure 1: Macroscopic appearance of Merkel cell carcinoma. (a) Surgical photo showing red, violaceous, and firm nodule with a smooth, elevated surface. Markings depict large cervicofacial rotation flap to reconstruct the expected defect. (b) Surgical photo depicting superficial parotidectomy and level I–IV lymph node dissection. (c) Close-up picture of b.

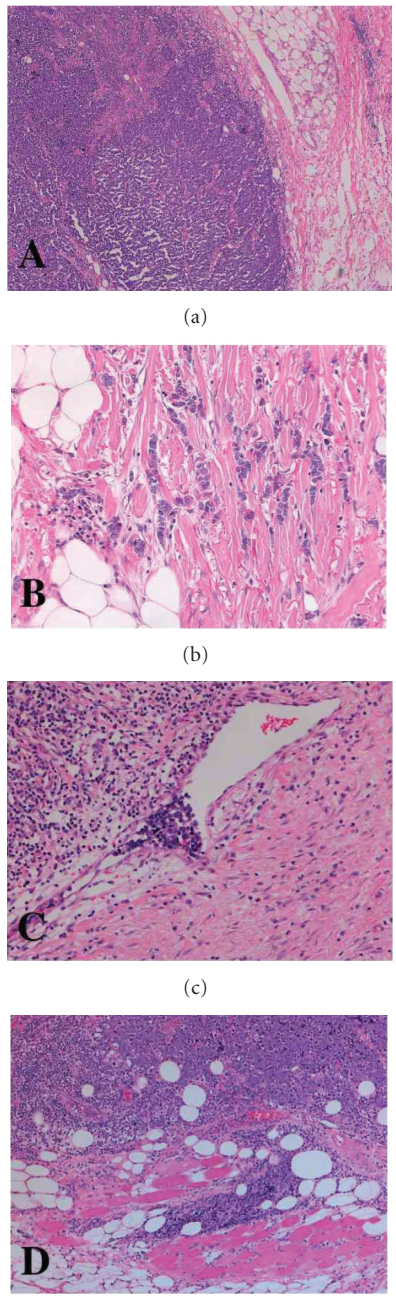


Figure 2: Microscopic appearance of Merkel cell carcinoma. Haematoxylin and eosin staining of a MCC section. (a) Nodular growth pattern. (b) Infiltrative growth pattern. (c) Lymphovascular invasion. (d) Skeletal muscle invasion.

a total of 129 MCC cases studied in the literature [7]. CM2B4 is an antibody that recognizes the Large T (LT) antigen of the Merkel cell polyomavirus (MCPV) and has shown positive reactivity in approximately 70% of MCC [8]. Despite the prominence of immunohistochemistry in the diagnostic workup of MCC, the College of American Pathologists released their 2010 recommendations in the pathological reporting of MCC of the skin. These include type of procedure, tumour site/size, margins, lymphovascular invasion, invasion of deeper soft tissues, and lymph node status (Figure 2).

## 2. Treatment

A plethora of options exist in the treatment of MCC, yet, the optimal option for this aggressive disease has yet to be found. Currently, a multimodality approach is advocated and includes in general a wide and deep local excision with regional lymph node dissection and adjuvant radiotherapy. Radiotherapy as a primary modality has been advocated in cases of inoperable disease. Sentinel lymph node biopsy can help to identify the presence of occult metastatic disease which can have prognostic implications.

## 3. Wide Local Excision

The importance of wide local excision of the primary tumour was shown by Goepfert et al. who found that inadequate surgical excision was a leading cause of local recurrence following radiotherapy [9]. Furthermore, Kokoska et al. found that early, aggressive treatment including surgical excision with margins >2.5 cm resulted in better locoregional recurrence and cumulative survival at 2 years than those patients with simple excision [10]. It was later shown by Allen et al. from Memorial Sloan-Kettering that margins >1 cm were not associated with decreased local recurrence rates [11]. Current recommendations are based on the clinical size of the primary tumour: excision with 1 cm margins for tumours <2 cm, and excision with 2 cm margins for tumours >2 cm [12].

## 4. Sentinel Lymph Node Biopsy

Generally, the progression or "cascade of metastasis" of MCC involves the local disease site, which then travels to regional lymph nodes with ultimate spread to a distant site. In the head and neck, the lymphatic system is very extensive and variable. The sentinel lymph node (SLN) is defined as the first lymph node in a regional lymphatic basin to receive lymph flow from a primary tumour site. The sentinel node is the first lymph node that tumour cells encounter as they spread through lymphatic channels. It is thought that the histologic status of this node predicts the status of the entire regional drainage basin that is at risk for metastases [13]. Therefore, if a sentinel lymph node does not contain metastatic disease, it is unlikely that other nodes in the regional lymph node basin will as well—a finding verified in patients with melanoma [14].

The concept of the sentinel node was first introduced by Cabanas for penile carcinoma in 1977 but has been used more recently in treating patients with melanoma and breast cancer [15]. Unlike in melanoma where histologic characteristics like ulceration and Breslow's thickness can help select patients for sentinel lymph node biopsy, no such characteristics are associated with prognosis that can direct patient management in MCC. Rapid transit time, close proximity of the primary site to the sentinel lymph nodes, spilling of the tracer, and the presence of multiple, contralateral or bilateral sentinel lymph nodes all pose potential difficulties with sentinel lymph node biopsy in the head and neck [16].

As the most consistent predictor of survival in MCC, the status of the regional lymph nodes has garnered much attention. It is controversial whether regional nodal disease is a governor of outcome, but it is certainly a predictor [4]. The biology of MCC is such that regional lymph node metastasis occurs frequently and early in the course of the disease. Nearly one-third of clinically node-negative patients harbour microscopic metastatic disease. Regional node involvement has been reported in up to two-thirds of patients and can be apparent at initial presentation in one-third [17]. It can take up to eight months for nodal metastases to become clinically apparent [17]. Proper identification and staging of the nodal basin could direct treatment algorithms for patients with MCC. These algorithms can include elective neck dissection or adjuvant treatment with radiation or chemotherapy.

Importantly, prophylactic dissection of the regional lymph node basin is associated with a less than 20% rate of regional failure compared to therapeutic lymph node dissection which is associated with a 60% recurrence rate [18]. This trend mirrors that of melanoma, where only 2% of cases with negative sentinel nodes develop locoregional failure [19]. Ultimately, the staging information provided by sentinel lymph node biopsy can be a primary determinate of ultimate outcome. Five year survival rates for patients with nodal disease are less than 50% compared with 80% in the absence of regional metastasis [20].

A benefit of sentinel lymph node biopsy (SLNB) is that it permits resection of a possible metastasis within the regional lymphatic basin when the tumour burden is likely to be very small [17]. Moreover, this technique can correctly identify the proper nodal basin most likely to harbor micrometastasis rather than relying on traditional anatomic drainage patterns. Up to 20% of melanoma patients undergo nonclassic lymph node dissections based on aberrant lymphoscintigraphy patterns [21].

Sentinel lymph node biopsy is a minimally invasive option in patients presenting with MCC, to avoid the morbidity of elective neck dissection in the 80% of patients who are sentinel node biopsy negative. Mapping should happen at the time of wide local excision, obviating the risk of interruption of cutaneous lymphatics that could result in inaccurate localization of the sentinel node.

In some institutions, when the MCC can be completely excised with negative margins and the sentinel lymph node is negative, adjuvant therapy can be avoided [22]. As in melanoma and breast cancer, sentinel lymph node biopsy has been used to stage the nodal basin in MCC [23, 24]. The rationale for using sentinel lymph node biopsy is based on the similarities between the biology of MCC and malignant melanoma.

One of the first studies using sentinel lymph node biopsy in MCC was published in 1997. Messina et al. studied 12 patients with MCC who underwent removal of a total of 22 sentinel lymph nodes [17]. The two patients with metastatic nodes underwent completion lymph node dissection, while the remaining node-negative patients received no further surgery. The patients with node-negative disease remained free of MCC for a median followup of 10.5 months [17]. Hill et al. performed sentinel lymph node biopsies on 18 patients who underwent removal of 35 nodes [13]. Two patients had metastatic disease in the sentinel lymph nodes and with complete dissection of the nodal basin; no additional lymph nodes were positive, suggesting that the sentinel node had been properly identified [13]. A few years after these studies, Rodrigues et al. published a report on six MCC patients with clinically negative nodes who underwent successful sentinel lymph node biopsy. Three patients had a positive biopsy; all three had systemic chemotherapy and two had adjuvant radiation to the regional lymphatics [23]. Two of the node-negative patients did not have additional treatment and were alive without evidence of disease at 15 month followup [23].

The diagnostic accuracy and usefulness of sentinel lymph node biopsy in MCC have been studied in significant detail. Gupta et al. analyzed 122 patients with clinical N0 staging and found 32% harboured occult metastatic disease, compared to a 5% incidence rate in similarly staged melanoma [25]. As expected, patients with positive SLNB were 3 times more likely to develop recurrent disease than with N0 patients. This study showed that SLNB changed the stage grouping of one-third of MCC patients and in effect altering their treatment course. Many other studies have shown that SLNB can be performed reliably and safely both in the head and neck region [26] and in the extremities [27] to identify occult regional disease.

The importance in addressing the nodal status in N0 disease is highlighted in a recent Australian study that the commonest site of first relapse was in the regional nodal basin. More importantly, 68% of patients with nodal recurrence had stage I disease with untreated nodal basins [28]. This study showed a negative correlation between overall survival and the number of involved lymph nodes [28]. The authors suggest that SLNB could help select those early staged MCCs that could benefit from elective nodal treatment.

A prospective study of sentinel lymph node biopsy in MCC looking at 23 patients showed that accurate staging information can be gleaned by this technique and nodal status does have a differential effect on survival, although this did not reach significance in the study [29]. Tumour foci were found in 11 patients, 50% of which had further positive nodes on completion elective lymph node dissection. Of those patients with a negative sentinel lymph node, 33% relapsed [29]. The authors suggest that negative lymph node biopsy is not necessarily associated with a favourable prognosis and should be used in a diagnostic manner rather than for therapeutic intent. They also observed the histopathological features of the positive lymph nodes and noted that those nodes with tumour foci >2 mm in the sentinel node were more likely to have additional lymph nodes positive [29]. Thus, this technique could identify patients in further need of a complete neck dissection or radiation therapy. Despite treatment, however, the more extensive nodal disease did not seem to have any impact on the ultimate clinical course.

A study from Memorial Sloan-Kettering in New York looking at recurrence and survival in MCC patients undergoing SLNB showed that the only predictors of SLNB positivity were primary tumour size (25% <2 cm versus 45% >2 cm) and the presence of lymphovascular invasion (55% positive versus 4% negative) [30]. Interestingly, they found no difference in recurrence or death from MCC between SLNB-positive and -negative patients. Moreover, only lymphovascular invasion was associated with both recurrence and survival [30].

In a similar study, Schwartz et al. showed a statistically significant correlation between clinical size of the lesion, greatest histologic dimension, tumour thickness, mitotic rate, and growth pattern with SLNB positivity [31]. On multivariate analysis, no models were able to predict a lower than 15% likelihood of SLNB positivity. The authors posit that all patients presenting with MCC without evidence of regional lymph node disease should be considered for SLNB [31].

It is possible that the SLN might not be found due to direct extension from the primary MCC causing emboli and mechanically plugging lymphatic channels. Case reports showing infiltration of both lymph nodes and lymphatic vessels reveal unsuccessful SLNB approaches [32]. In a recent study from the University of Miami, Shnayder et al. reviewed their treatment of MCC. Fifteen patients with MCC were studied, 10 of which have wide local excision and sentinel lymph node biopsy [16]. They were successful in finding the sentinel lymph node in every patient. Those patients who were sentinel node positive received adjuvant radiation. Some of the negative sentinel node patients received radiation as well because of the invasiveness of the primary site.

Mehrany et al. performed a meta-analysis of the prognostic significance of sentinel lymph node status in MCC [33]. They reported data on 60 patients, 40 of whom had a biopsy-negative sentinel lymph node. Thirty-five of these patients had no further treatment and the remaining had completed neck dissection and adjuvant radiation or adjuvant chemoradiation [33]. One patient in this group died of metastatic disease, while the remaining patients had no recurrence at a mean of 7.3 months. The other 20 patients had biopsy-positive sentinel lymph nodes, with 15 having additional treatment. Three of the remaining five patients developed regional nodal recurrence. The risk of recurrence or metastasis was 19-fold greater in the biopsy-positive patients [33]. Only one patient with a negative sentinel lymph node experienced disease recurrence. The study authors concluded that sentinel lymph node positivity was a strong predictor of high short-term risk of recurrence and that completion of neck dissection was beneficial in alleviating this risk [33].

Warner et al. looked at their group of 11 patients who had sentinel lymph node biopsy of whom 3 were positive [34]. Two of these patients developed recurrence despite surgery and radiation. Of the eight patients who were sentinel lymph node negative, five developed recurrence of the disease [34]. This high percentage, 67%, is much higher than the average 30% seen in other studies.

They also found no correlation between depth of invasion and sentinel lymph node biopsy positivity.

Immunohistochemical analysis of sentinel lymph nodes from patients with breast carcinoma or melanoma increases the sensitivity for detection of metastases in up to 40%. Up to 40% of patients with occult MCC nodal metastasis will be missed if evaluation is limited to standard hematoxylin-eosin (H&E) staining [35, 36]. In MCC, this question was addressed by Allen et al. who studied 26 patients and found that 2 out of 5 patients with lymph node metastases were identified only after confirmation with immunohistochemical staining [37]. The addition of immunohistochemistry improves the ability to identify those patients with regional micrometastatic disease, known as "minute metastases" otherwise undetectable using traditional H&E staining.

Schmalbach et al. studied 10 patients with MCC who had sentinel lymph node biopsy and found that the two patients with positive lymph nodes appeared negative on hematoxylin-eosin staining. MCC was identified using CK20 immunostaining [38]. It should be noted that the clinical significance of submicroscopic lymph node metastases identified only by immunohistochemistry remains unclear.

Sentinel lymph node biopsy involves very little morbidity and can be used to stage the disease. In some patients, this technique helps avoid the risks of complete lymph node dissection and in others can direct further management decisions. The sentinel lymph node biopsy has the advantage of providing the pathologist with only a few samples, allowing a thorough slice-by-slice histopathological analysis. This extensive pathological evaluation would be impossible in neck dissection samples, where up to 30 lymph nodes can be included.

The high rate of regional metastases and associated poor prognosis provide an impetus to treat regional lymph node basins, like the neck, in a prophylactic manner. Although there may be a benefit in regional control and disease-free survival using elective neck dissection compared to therapeutic neck dissection, there are no reports in the literature showing any survival advantage.

Identification of any positive sentinel lymph nodes makes the initial procedure a staging one and then should be followed by a formal lymph node dissection or by adjuvant radiotherapy, especially in head and neck MCC. Patients, however, are often unwilling to undergo a second intervention [16, 29]. There remains the option of upfront elective lymph node dissection using the gamma probe as a guide. This approach would provide therapeutic treatment of the regional lymph node basin and prevent missed nodes as a result of aberrant drainage patterns. Within the head and neck, lesions in the midline may drain to either side of the neck or parotid gland.

Another option for those patients unwilling to undergo formal lymph node dissections upfront would be performing sentinel lymph node biopsy and relying on immediate frozen section results to dictate further management. A positive result would lead to immediate completion of lymphadenectomy. Patients would need to be informed about this and counseled about the probability of further treatment if there was metastatic disease identified on final pathology or immunohistochemistry.

## 5. Conclusion

Merkel cell carcinoma is a rare and aggressive cutaneous neoplasm. Advances in immunostaining are aiding in the diagnosis of this disease. With the discovery of the polyoma virus, a great deal of interest should be placed in reevaluating the role of radiotherapy in treating those virus-positive patients. Furthermore, the indications for sentinel lymph node biopsy are still being elucidated and vary between institutions. Clearly, a multidisciplinary approach to this disease is required, and the next decade should provide more insights into the best treatment of this rare disease.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2012, Article ID 742303, 6 pages
doi:10.1155/2012/742303

*Review Article*

# The Role of Free Tissue Transfer in Merkel Cell Carcinoma of the Head and Neck

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Received 30 April 2012; Accepted 8 July 2012

Academic Editor: Boban M. Erovic



Merkel cell carcinoma (MCC) is an uncommon neuroendocrine malignancy with a propensity for the head and neck. It typically presents asymptomatically in elderly Caucasians and is characterized by early local and regional spread. There is currently limited data on the appropriate algorithm for treatment of MCC. However, multimodal therapy with wide surgical excision with or without radiation therapy has become standard of care. The location of the primary tumor and intensive adjuvant therapy is often required, provides a challenge to the reconstructive head and neck surgeon. Occasionally, free tissue transfer reconstructive techniques are employed in the reconstruction of MCC defects. This paper will discuss the role of free tissue transfer as a reconstructive option after surgery for advanced head and neck MCC.

## 1. Introduction

Merkel cell carcinoma, originally described by Toker in 1972 [1], is a rare cutaneous malignancy of unknown etiology most commonly seen in the elderly Caucasian population. Incidence has been reported at 0.15 cases per 100,000 in 1986 and 0.44 cases per 100,000 in 2001, with increasing incidence attributed to longer average lifespan and advances in diagnostic technology [2]. MCC is more common in people of advanced age with history of malignancy, immunosuppression, or significant ultraviolet exposure. Recently, infection with the Merkel cell polyomavirus has been shown to be a significant risk factor as well [3–5]. Patients typically present with a firm, painless purplish nodule on the face or upper extremities. Metastatic disease at the time of presentation is rare. Diagnosis relies on tissue biopsy and examination with electron microscopy and immunohistochemical staining. Staging is based upon the traditional TNM (Tumor-node metastasis) classification system with prognostic data showing decreased overall survival with increasing stage of disease [6, 7]. Oncologic surgery within the head and neck presents unique problems, especially when treating Merkel cell carcinoma. Because of the rarity of MCC, there is limited clinical data to guide management. Currently, there are limited clinical guidelines for MCC; however most surgeon clinicians endorse multimodal therapy with wide local excision of the primary tumor and definitive treatment of any clinically significant nodal disease, either with lymphadenectomy or radiation therapy [8]. The role of chemotherapy is unclear, traditionally reserved for diffusely metastatic and/or recurrent disease. Novel targeted therapies are currently being developed and will be discussed elsewhere in this special issue on MCC. Wide excision is currently the standard of care for addressing the primary tumor. However, this can be both functionally and aesthetically devastating in larger lesions. This paper will describe the management options for advanced Merkel cell carcinoma as well as the principles of reconstruction when free tissue transfer is utilized.

## 2. Initial Management

Surgery is the current standard for locoregional disease and has been shown to confer a survival benefit in MCC [8–14]. However, controversy exists regarding the necessity for wide surgical margins, which can be problematic in the head and neck region [9]. The advent of Mohs microsurgery has made definitive oncological resection more precise. Data

regarding Mohs surgery in MCC shows comparable, if not superior, local control when compared to traditional surgical excision [15]. As MCC is predominantly found on the sun exposed areas of the head and neck, any surgical intervention will have aesthetic and functional implications. Mohs micrographic surgery provides a more conservative surgical approach while obtaining negative margins and this conserves local tissues. This allows the reconstructive surgeon more options when assessing the most appropriate reconstructive technique. In addition, it has been reported that traditional surgery for MCC frequently results in unrecognized positive deep margins. With Mohs surgery, complete excision is more likely; and local recurrence after reconstruction decreases [16]. In general, lesions on the sun-exposed areas of the face, head and neck, are typically managed with surgical excision using Mohs surgery with local tissue reconstruction. Larger primary tumors may require traditional surgical management for a variety of reasons. Mohs micrographic surgery, while accurate, is not ideal for large extensive lesions requiring general anesthetic for ablative surgery and reconstruction. Large lesions may render Mohs surgery impractical due to the length of the procedure or depth of invasion. In these situations traditional surgical excision is the preferred technique. It should be noted that the author has used a combination technique with Mohs micrographic confirmation of negative cutaneous margins prior to traditional wide local excision of the primary tumor and reconstruction. This allows for rapid excision of the primary lesion with Mohs micrographic control of the cutaneous margins, which improves accuracy and minimizes unnecessary extension of soft tissue margins. The downside to this technique is the inability to assess the deep margins via the Mohs technique and traditional frozen section must be utilized. Regardless of the surgical technique required for excision of the primary tumor, every effort should be made to obtain negative margins.

Frequently, adjuvant radiotherapy is employed in the management of advanced MCC. Large extensive lesions at risk for local recurrence should be considered for postoperative radiotherapy regardless of surgical margin status. There is data suggesting radiotherapy in addition to Mohs surgery results in improved locoregional control when compared to Mohs surgery alone [16]. Primary radiotherapy may be employed in patients with inoperable tumors or comorbidities significant enough to preclude surgery. Veness et al. presented data on 43 patients treated solely with radiation therapy to the primary tumor. They report an in-field control rate of 75%. However, the majority of patients (60%) go on to have out-of-field metastasis [17]. The determination of appropriate treatment fields for postoperative radiotherapy remains controversial and should be determined by the radiation oncologist after evaluating the patient and operative results. Additional information regarding radiotherapy for MCC will be presented elsewhere in this special issue.

At present, the recommendation for management of lymph node disease in MCC depends on clinical presentation. For clinically significant lymph node extension cervical lymphadenectomy or therapeutic radiation therapy is indicated after histological confirmation [13, 14]. The role of intervention in clinically negative regional nodal disease is controversial. There is data suggesting that the size of the primary tumor correlates with the risk of occult disease and that occult disease is unlikely with a primary tumor less than or equal to 1 cm [18]. Sentinel lymph node (SLN) biopsy has become a useful tool in attaining a reliable histological indicator of nodal spread and limited data shows decreased recurrence rates where regional management was influenced by sentinel lymph node biopsy. At present, there is insufficient data to determine standardized guidelines for SLN or elective lymph node dissection in the clinically negative neck for MCC.

## 3. Reconstructive Management

For the majority of surgical defects in the region of the head and neck, locoregional reconstruction with skin grafting or local flaps is functionally and aesthetically adequate. A comprehensive review of factors, which influence the reconstructive approach, is beyond the scope of this paper and will be reviewed elsewhere in the special issue. The extent of disease, viability and quality of surrounding tissue, involvement of the adjacent structures, and history of prior surgery or radiation therapy can make locoregional reconstruction less appealing or impossible. Given the importance of negative surgical margins in MCC, the oncologic surgeon must consider the implications of the risk of local recurrence and consider the propensity for multiple synchronous tumors as well as immune system dysfunction in elderly patients with extensive disease. In these situations, conservative surgery may not be possible, resulting in significant ablative defects of the head and neck. In these situations, free tissue transfer can provide large volume, healthy tissue for reconstruction of the surgical defect, with favorable aesthetic and functional outcomes.

The increased application of microsurgical reconstruction has resulted in several options for free tissue transfer for soft tissue defects of the head and neck. The anterolateral thigh (ALT) flap, latissimus dorsi, rectus abdominis, scapula/parascapular, and radial forearm flap (RFFF), have been employed for soft tissue reconstruction of extensive defects [19]. A variety of osteomyogenous, or osteocutaneous options exist if bone reconstruction is required. Flap selection depends on the tissue components of the defect (i.e., skin, muscle, and bone) as well as the location, size, depth, and surrounding tissue color/contour. Other aspects during reconstruction such as facial nerve involvement, availability of donor vessels, and donor site considerations such as peripheral vascular disease may alter the reconstructive plan. When considering MCC specifically, the data shows frequent local recurrence as well as a propensity for vertical invasion with positive deep margins being relatively common [20]. These considerations often result in an extensive soft tissue resection involving underlying fat and muscle. In this case, the flaps mentioned above provide a great deal of bulk, require a straightforward harvest with little donor site morbidly, and provide adequate vascular pedicles to limit the need for vein grafting. For defects in the dura, tensor

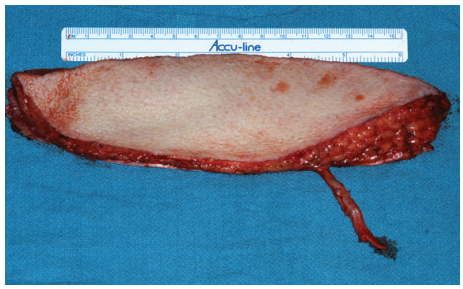



Figure 1: The anterior lateral thigh flap offers excellent soft tissue volume for reconstruction with minimal donor site morbidity. It can be harvested in multiple composite configurations with skin, fascia, and muscle as well as tensor fascia lata. Note excellent pedicle length.

fascia lata grafting is commonly employed with good results. Donor vessels commonly used are superficial temporal system, facial artery, superior thyroid artery, and transverse cervical system [21, 22]. Donor site selection involves a relatively complicated assessment of the ablative defect, the composition of the defect, and the overall condition of the patient. Options for soft tissue reconstruction will be discussed briefly; however it should be noted that a variety of other techniques (i.e., osteomyocutaneous flaps) may be employed if dictated by the defect. The ability to provide large volumes of well-vascularized composite tissue is the most significant advantage of free tissue transfer techniques, when managing large volume defects related to MCC.

*3.1. Anterior Lateral Thigh Flap.* The ALT flap has become a popular reconstructive option for surgical defects within the head and neck. It is easily harvested via a two-team approach, with low donor site morbidity and provides a large softtissue volume, a long and reliable vascular pedicle. The ALT offers the option for dynamic facial nerve reconstruction via motor nerve to the vastus lateralis. The pedicle length limits the necessity for venous grafting and allows microsurgical anastomosis of vessels to occur some distance from the defect [19, 22]. The ALT flap has become the author's preferred workhorse flap for defects >100 sq cm, or in cases where thicker tissue is desired (Figure 1).

*3.2. Latissimus Dorsi Flap.* The latissimus dorsi flap has found use predominantly in reconstruction of scalp defects, especially those with exposed calvarium. It is harvested easily, provides a large surface area with excellent muscle volume and thickness. Donor site morbidity is well tolerated in most patients [21]. Atrophy of the graft provides results in close contour matching with surrounding skin and soft tissue. In most scenarios, this flap should be deepithelialized and covered with a split thickness skin graft for better aesthetic color, matching, and thickness. O'Connell et al. retrospectively evaluated 65 patients with scalp or lateral temporal bone defects, performing a total of 68 free tissue transfers. Based on their experience, the latissimus muscle-only flap with split-thickness skin graft (STSG) provides a large surface

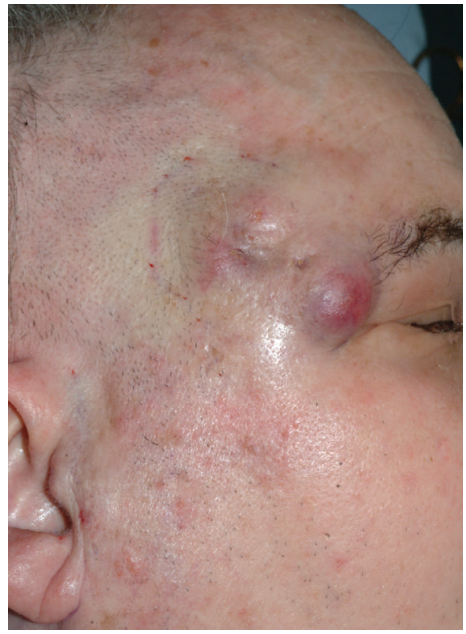
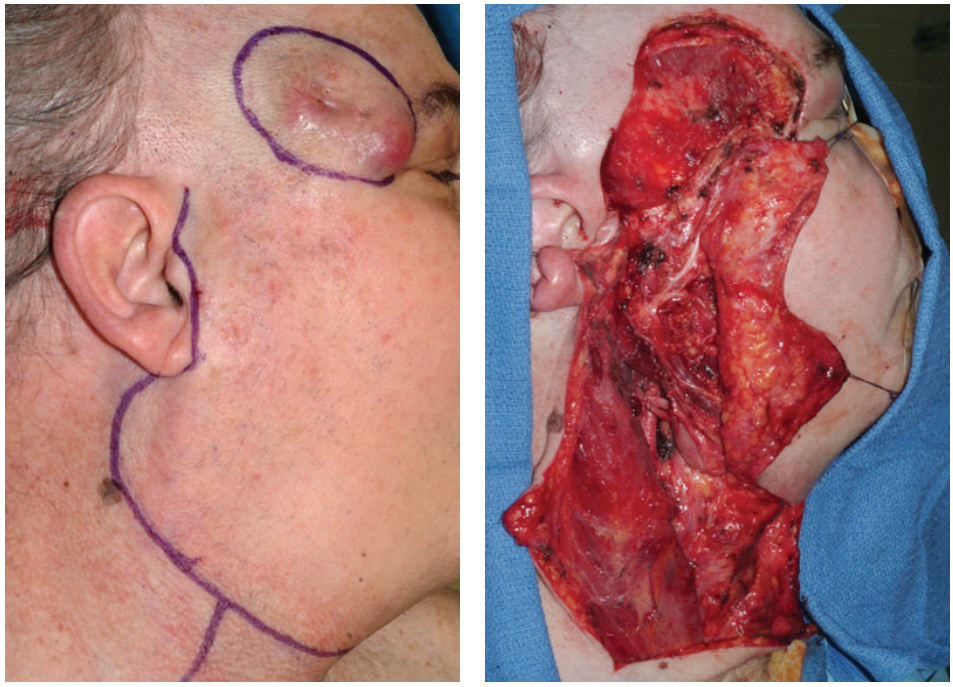


Figure 2: Right-sided Merkel cell carcinoma of the temporal region in a 63-year-old male. The lesion started as a small violaceous nodule approximately six months prior to presentation. This was excised locally at an outside institution and subsequently recurred in the region of the previous excision. The lesion subsequently enlarged and resulted in right-sided weakness in the distribution of the frontal branch of the facial nerve. Pain in the region was mild. Subsequent biopsy revealed MCC. Note multinodular cutaneous induration and anterior violaceous appearance, classic for advanced MCC.

area, adequate bulk, and an aesthetically acceptable result in a large majority of scalp defects [22]. Donor site morbidity is generally well tolerated; however in elderly patients who used stabilizing devices such as canes, walkers, or are wheelchair dependent, the ALT may be a more favorable option.

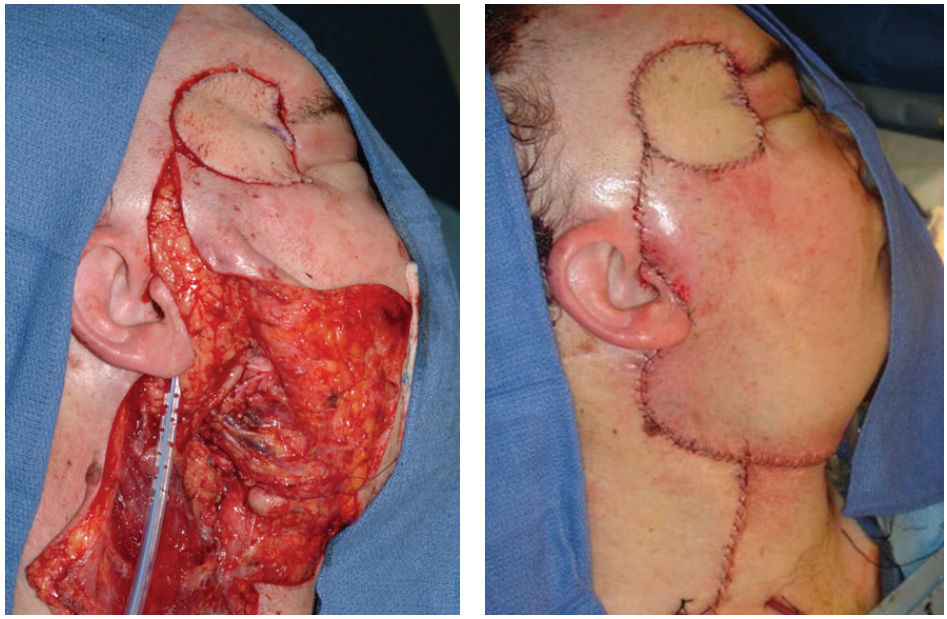
*3.3. Radial Forearm Flap.* For smaller defects requiring thin and pliable tissue, the radial forearm free flap is preferred. Primarily a fasciocutaneous flap is ideally suited to smaller defects with complex contours where it is desirable to avoid excessive bulk. The reliable pedicle length and predictability of harvest make the radial forearm free flap a commonly utilized reconstructive technique for cutaneous defects of the head and neck. In cases with vessel-depleted necks where veins are unavailable, a semifree radial forearm harvest has been described dissecting the cephalic vein proximally and performing a single arterial anastomosis, which is unique to this flap [23]. Donor site morbidity is well tolerated, however generally inferior to the anterior thigh flap [24, 25] (Figures 2, 3, and 4).

*3.4. Rectus Abdominus Flap.* The rectus abdominis flap has been used for head and neck reconstruction for cutaneous malignancies and offers the advantage of well-vascularized muscle and large amounts of soft tissue available for reconstruction. When large amounts of muscles are harvested,



(a) (b)

Figure 3: (a) Incision design to allow for wide local excision (1 cm margins) of recurrent MCC with concomitant superficial parotidectomy, selected neck dissection, and microvascular reconstruction. (b) Completion of ablative surgery and cervical lymphadenectomy, noting distal temporal facial nerve involvement. Final pathology indicated negative margin resection. There were no cervical or parotid lymph node metastasis present on final pathologic examination.



(a) (b)

Figure 4: (a) Radial forearm free tissue transfer reconstruction after microvascular anastomosis. (b) Closure. Note excellent skin color match and thin pliable soft tissue in the temporal region avoiding bulky aesthetics and unnecessary lateral canthal traction. Due to the advanced nature of the primary lesion, postoperative radiotherapy was administered to the primary site and parotid bed. At last followup, the patient was alive without evidence of distant disease or local recurrence.

donor site morbidity is increased and therefore, it is our opinion that other free tissue donor sites offer several advantages over the rectus abdominis flap in the majority of cases. Muscle sparing perforator style flaps may allow for decreased morbidity and superior control of flap thickness, and the deep inferior epigastria artery-based flaps have been shown to be a valid reliable option for head and neck reconstruction [26].

*3.5. Scapular/Parascapular Flap.* The scapular/parascapular flap also has excellent contour and color matching with the forehead and scalp and can typically be closed primarily after harvest with very little donor site morbidity [19, 27]. Harvest may be performed with turned supine positioning and large soft tissue flaps may be harvested. Pedicle length is generally excellent if dissection is performed to the subscapular system. Some surgeons prefer the color and thickness of the scapular/parascapular flap for head and neck reconstruction [27]. In addition, the availability of osseous harvest makes the subscapular system the most versatile flap for complex head and neck ablative defects.

## 4. Facial Nerve Involvement

Merkel cell carcinoma presents frequently on the face and the propensity for vertical invasion often puts the facial nerve at risk. Therefore, there is potential for facial nerve injury secondary to extension of the primary tumor and/or surgical excision for adequate margins (Figure 4). Facial nerve injury can result in lifelong facial asymmetry with profound physiological and psychological consequences, especially in the context of a surgical defect. A discussion of facial nerve reanimation is beyond the scope of this paper; however reconstructive flap selection in free tissue transfer may allow dynamic (latissimus, ALT) or static (ALT, radial forearm/palmaris) reconstructive procedures to be performed simultaneously [28]. Selection of free tissue donor sites should consider the desired facial nerve reanimation strategy in order to minimize additional donor sites.

## 5. Conclusion

Reconstruction after wide excision of MCC offers several unique challenges including a propensity for elderly patients with poor tissue quality and decreased immune function, large defects and a high probability of disease recurrence, and the risks inherent to adjuvant radiotherapy. For this reason, most reconstructive surgeons favor free tissue transfer as a modality for providing healthy, uninvolved tissue with an acceptable aesthetic outcome. There is clearly a need for higher quality of data in the area, as significant questions remain for the treatment for Merkel cell cancer, as well as the reconstructive methods utilized after ablative surgery. Recently, data has been published suggesting that wide surgical margins during tumor resection may not impact overall survival in patients receiving adjuvant radiotherapy [29]. This is a crucial question for the reconstructive surgeon as it may impact defect size and the probability of local recurrence. Additional data on radiotherapy and targeted chemotherapy for MCC may play a role in deciding the timing for reconstruction, as well as the selected technique. The decision on surgical approach by the reconstructive surgeon should be based on the individual patient and should take into account the details of the clinical scenario in addition to the location and size of the defect. Current free tissue transfer techniques allow the reconstructive surgeon to manage advanced MCC with acceptable functional and aesthetic results, while minimizing morbidity.

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Hindawi Publishing Corporation
Journal of Skin Cancer
Volume 2012, Article ID 654981, 5 pages
doi:10.1155/2012/654981

*Review Article*

# Radiotherapy for Metastatic Merkel Cell Carcinoma: A Review of the Literature

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Received 18 March 2012; Accepted 2 June 2012

Academic Editor: Boban M. Erovic



*Introduction.* Merkel cell carcinoma is a rare form of non-melanoma skin cancer of neuroendocrine origin. Optimal management of patients is controversial and the role of radiotherapy is unclear. *Purpose.* The purpose of this study was to review the efficacy of RT in the treatment of both local and distant metastatic disease from MCC. *Methods.* A literature search was conducted in MEDLINE (1946—January Week 1 2012) and Embase (1980–2012 Week 2). Articles of interest analyze the efficacy of radiotherapy for treatment of metastatic MCC and did not exclude case reports. *Results.* All articles except one focusing on the role of radiotherapy were of retrospective origin or case series. Significant limitations applied in all studies due to limited sample sizes and the retrospective nature of these studies. Radiotherapy improves locoregional control in the adjuvant setting, and many series suggest an improvement in overall survival. In cases where surgery is not possible, definitive radiotherapy may be an as-efficacious alternative. The radiosensitive nature of MCC coupled with existing reports suggests that treatment via current protocols for other primary tumors is adequate. *Conclusion.* Further studies should be conducted prospectively to clarify the true role of radiotherapy in metastatic MCC.

## 1. Introduction

Merkel cell carcinoma (MCC) is a rare form of non-melanoma skin cancer of neuroendocrine origin which usually is found in elderly patients, in sun exposed skin (head and neck), and an increased incidence is seen with immunosuperessed patients [1]. The incidence of MCC according to SEER has risen to 0.44 per 100 000 in 2001, from 0.15 per 100 000 in 1986 [2]. In 2008 the Merkel Carcinoma Polyomavirus was identified and its role in pathogenesis is being investigated [3].

Although approximately 70% of patients with MCC present with stage I or II disease [4–6], low 5-year survival rates (reported to be 30%–64%) [7, 8] are attributed to high rates of locoregional and distant recurrence [9]. Time to recurrence is consistently reported as occurring at a median of 8 months [4, 5, 9, 10]. Along with lymph nodes, common sites of metastases include intransit skin, lung, CNS, bone, and liver [11]. The testis, pancreas, heart, prostate, GI tract, and bladder have been reported as sites of MCC metastases in the literature [11].

Treatment of MCC is primarily surgery, with adjuvant radiotherapy (RT: to which the disease is sensitive to) becoming more common, as recent data have shown RT improves both locoregional control and survival [5, 12, 13]. In areas where resection is not possible or where surgery is refused, RT alone is offered, and though data with this respect is relatively limited high rates of local control have been reported [14–16]. Sentinel lymph node biopsy (SLNB) is becoming standard practice for patients with clinically negative nodes. For clinically node-positive disease, typically node dissection followed by radiotherapy is delivered although primary radiotherapy may again be an option. As a rare disease, randomized, prospective data of various treatments for MCC are unavailable and most data on optimal treatment in the literature are supported by retrospective studies or

case series. Further, robust data on the use of palliative RT specifically for metastases from MCC is severely lacking. The purpose of this paper is to describe the various uses of RT for managing both local and distance metastases from MCC.

## 2. Methods

A literature search was conducted in MEDLINE (1946—January Week 1 2012) and Embase (1980–2012 Week 2). Broad search terms were utilized, including "merkel cell carcinoma", "radiotherapy", ["metasta*" or "recurrence" or "palliation"]. Papers selected included those focusing on the role of radiotherapy as adjuvant treatment of local metastases and as treatment alone for local and distant metastases. Case reports were also included due to the relatively few published reports on this topic.

## 3. Results

The majority of included papers involved retrospectively analyzed data or case series. A single phase II, prospective trial of patients with MCC was found and investigated the addition of chemotherapy to adjuvant RT in stage I and II MCC. Jouary et al. prospectively compared regional adjuvant RT to observation in patients with stage I MCC [17].

*3.1. Radiation as Adjuvant Nodal Treatment.* Optimal avenues of treatment of nodal disease have been broadly divided by patients who have clinically node-negative disease versus those who are clinically node-positive. For clinically node-negative patients the rate of regional nodal relapse is high (50–66%) if untreated [17], and therefore lymph node dissection or prophylactic radiotherapy to the regional nodal bed was often recommended. Sentinel lymph node biopsy is now becoming widely accepted into routine clinical practice and is recommended in the NCCN guidelines. For patients with negative SLNB, Mehrany et al., found 97% (39/40) had no recurrence with omission of RT [18], and Gupta reported an 80% 3-year relapse free survival rate which did not alter with or without the use of RT [19]. Routine RT may be therefore be omitted in this population; however, there is a suggestion in the head and neck region that false negative SLNB may be seen due to aberrant patterns of lymphatic drainage [20]. Patients with positive SLNB traditionally undergo completion dissection followed by radiotherapy, although radiotherapy alone could be argued as an option.

Surgery is recommended for clinically node-positive disease. Compared to node dissection alone, Veness found regional control was improved 2-fold with the addition of RT (37% versus 18%) [21]. In another retrospective review by Allen et al., risk of recurrence was 14% with surgery and 13% with surgery plus RT [4]. Fang et al. reported similar rates of regional recurrence in clinically node positive patients treated with CLND ± RT of 14% [22]. In nonresectable nodal disease, RT doses up to 60 Gy are recommended [23]. Optimal dose for definitive RT has yet to be defined and there is a paucity of data on dose response rates. For palliation, NCCN guidelines suggest a dose of 30 Gy in 10 fractions, though the data on which this recommendation is based was not given [24].

*3.2. Radiation Alone for Nodal Treatment.* Only a single study to our knowledge has investigated the potential role of RT alone for treatment of nodal involvement from MCC. Fang et al. prospectively collected data from patients with MCC over a 22-year period in the United States, which included patients who received RT alone for positive nodes [22]. Stratifying by microscopically involved lymph nodes ($n = 26$) versus clinically positive lymph nodes ($n = 24$), the authors assessed the role of radiotherapy alone versus complete lymphadenectomy (CLND) ±RT. In the group with microscopic disease, 100% regional control was obtained regardless of treatment ($n_{\text{CLND}\pm\text{RT}} = 7, n_{\text{RT alone}} = 19$). In those with clinically positive lymph nodes, no significant difference was observed in 2-year recurrence free survival ± RT ($P = 0.8$). Those who received RT alone achieved a 2-year recurrence free survival of 78% ($n = 9$) versus 73% in those who received CLND ± RT ($n = 15$). The authors concluded that RT provided similar rates of local control for node metastases from MCC and may be an option for patients given clinical factors and patients' desires. Their study also affirms that early detection of MCC metastases improves local control. Although criticisms regarding the retrospective nature of the study as well as relatively low sample size have been expressed in an editorial by Bichakjian et al. [25], Fang et al. provide the best available data in the literature regarding radiotherapy alone for nodal metastases from MCC in the absence of randomized trials.

Boyle in their retrospective series reported on 16 sites in 12 patients who received RT without surgery (3 of whom also received chemotherapy) for clinically determined nodal involvement [26]. Subsequent recurrence was not reported; however, 5 sites obtained a complete response and 7 obtained a partial response. Pacella et al. describe a series of patients receiving RT for MCC [27]. Eight patients received RT alone for regional lymph node involvement with 5 that attained a complete response, 1 patient with a partial response and the other two patients with complete response.

Overall, data regarding use of RT alone for nodal involvement is sparse and limited by sample size and the retrospective nature of such studies. Similarly, much of the data was collected decades ago, demonstrating the need for current and ongoing research in this area. The question of what is the optimal dose for definitive RT was not examined in the Fang paper nor was a recommendation for dose/fractionation given. Given this is very radio responsive disease, dose escalation may not be required for bulky disease, and by defining what dose gives acceptable rates of local control in the adjuvant and definitive setting, the acute and long term toxicity of RT could be minimized.

*3.3. Radiotherapy for Bone Metastases from MCC.* Bone metastases represent approximately 10% of distant malignancy from MCC and are more commonly observed in the skull and less commonly so to the appendicular skeleton [28]. Palliation of bone metastases from MCC is efficacious

due to both the radiosensitivity of the disease, plus the general efficacy of RT for bone metastases. Similar to treatment of bone metastases from other solid tumour primary cancers, treatment schedules can vary greatly in both dose and fractions given. In a case reported by Kamijo et al., a patient presented right hip pain subsequently determined to be metastatic MCC was treated with 30 Gy in 15 fractions postoperatively [29]. Unfortunately, other case reports did not detail RT doses.

Five cases of metastatic MCC to the spine have been reported to our knowledge in the literature [30–34]. In many cases, malignancy was accompanied by neurologic deficits caused by spinal cord compression and urgent surgery was required. Radiotherapy was efficacious in a number of cases; however, all patients succumbed to rapid disease progression.

*3.4. Radiotherapy for Brain Metastases from MCC.* Feletti et al. report a case of pituitary metastasis from MCC [35]. The patient was treated with stereotactic radiosurgery with a 25 Gy total dose in 3 fractions, combined with cisplatin and VP16. The patient was alive after 8 months, but visual impairments remained. Feletti et al. also provide a review of 14 previous cases in the literature of patients with brain metastases from MCC [35]. Of the 7 that received RT, 6 received whole brain radiotherapy while one received whole brain plus radiosurgery. Surgery and chemotherapy were prescribed to two patients each for the brain metastases. The radiotherapy doses and techniques utilized in these cases are similar to the treatment courses of patients with brain metastases from other solid tumors. Similarly, surgical and chemotherapeutic methods are dependent on patient and tumor characteristics.

*3.5. Radiotherapy for Other Metastases from MCC.* Though metastases to other organs, such as, the prostate, bladder, liver, and kidneys, have been described in the literature [36] therapeutic interventions, particularly pertaining to radiotherapy specifics are rarely documented. As radiosurgery becomes more popular for treatment of metastatic disease, this certainly becomes an avenue of interest especially for such patients with relatively few visceral areas of disease, especially if surgery is not indicated.

In the case of cutaneous metastases from Merkel cell, where external beam radiotherapy may not be feasible due to size or location of the target, brachytherapy using a surface applicator maybe considered. In a case report by Cotter et al., surface-mold computer-optimized high-dose-rate brachytherapy was utilized to treat multiple cutaneous metastases in the lower extremity of a patient with a history of peripheral vascular disease. A rapid and durable treatment response was seen, a single recurrence within the treated area occurred at 25 months in the setting of diffuse metastatic disease [37].

## 4. Discussion

Treatment of primary Merkel cell carcinoma is well defined, with the mainstay being surgery accompanied by adjuvant radiotherapy [38]. Sentinel node dissection being increased used to assess regional nodal involvement [24]. As the disease progresses, guidelines become more controversial, especially pertaining to the role of radiotherapy as a primary treatment. Such data in the literature is confounded by both the retrospective nature of the studies in addition to small sample sizes, characteristic of rare diseases. Based on available studies, RT plays a key role in improving local control in nodal disease and is efficacious in palliating metastases to the bone, brain, and other organs. RT alone for management of local nodal metastases is suggested to provide similar rates of control to surgery, if the patient is not amenable to excision.

The poor life expectancy observed in patients with MCC is a result of the aggressive nature of the disease and the high rate of metastases. Though no randomized trials have been conducted, observational data supports postoperative adjuvant radiotherapy [39]. Clark et al. showed that although adjuvant radiotherapy did not confer an improvement in disease-free survival in all stages, subset analysis showed that stage II patients demonstrated both improved DFS and DSS with adjuvant radiotherapy. When divided into stage IIa and IIb, patients without nodal metastases derived the greatest benefit. There was also a nonsignificant difference in DFS for stage I disease with adjuvant radiotherapy [40]. The importance of this stage-dependent finding is that patients who may be considered to have relatively low-risk disease (stage II) and hence may not be recommended for adjuvant radiotherapy, in fact appear to be the group that derive the greatest benefit. Although (stage III) did not show a benefit this was more likely due to low numbers of these patients. Thus the authors recommended adjuvant radiotherapy in both stage II and III patients. In addition, a recent meta-analysis demonstrated that in patients who received surgery and were deemed to have clear margins, adjuvant radiotherapy significantly improved local and regional recurrence (12% versus 39% and 23% versus 56%, resp.) [13]. Though a trend in survival increase was observed, this did not reach statistical significance.

The available literature tends to support adjuvant radiotherapy in management of nodal metastases [4, 21] though NCCN guidelines suggest that sentinel node dissection ± radiotherapy is another option [24]. Though data is unclear at this point, radiotherapy alone may provide similar rates of local control compared to surgery when the latter is not an option [22]. It should be noted that in primary MCC tumors treated with RT only, Mortier et al. found no difference in overall and disease-free survival compared to patients treated with surgery and adjuvant RT [15].

Perhaps more importantly beyond these results is the importance of early treatment and detection of MCC. Stage of disease at presentation is highly prognostic, with lower tumor burden associated with better outcomes. The subgroup of patients with small primary disease and SLNB-negative disease have good outcomes (97% with no recurrence at 7.3 months median followup) [18].

An important consideration in the many uses of radiotherapy for management of MCC is the balance of expected benefit and side effects. If for example, adjuvant treatment with radiotherapy only slightly improved local control in certain cases, are the associated morbidities and side effects

worth the anticipated benefits? As MCC most commonly invades the upper regions of the body, considerations should be made regarding potential dysphagia, dental problems, xerostomia, loss of appetite, and weight loss [25]. Similarly, adjuvant irradiation of nodal metastases may result in lymphedema and cause further problems. More robust data regarding the role of radiotherapy is necessary to determine optimal strategies.

Palliation of bone, brain, and other visceral metastases from MCC is anticipated to be beneficial due to evidence from other solid tumors and the radiosensitivity of the disease; reports in the literature are based only on case reports. In patients with bone metastases, surgery may be warranted in some patients, as observed in the reports where metastatic tumors result in neurological deficits, and a wealth of guidelines exist on this topic which are likely applicable to patients with MCC especially in the absence of such data for this group. Brain metastases may similarly be resected or treated conventionally with palliative radiotherapy or more aggressively with stereotactic radiosurgery. Again, guidelines exist in the literature-depicting scenarios where one may prove more advantageous over the other.

Combination of chemotherapy with radiotherapy and surgery has also been evaluated with conflicting findings. TROG 96:07 is the only phase II, prospective trial to date that has evaluated outcomes with specific treatments for patients with MCC [41]. The authors concluded that combination carboplatin, etoposide, and RT did not improve survival in patients compared to historical control. An earlier study suggested that chemotherapy for recurrent or advanced disease may be of benefit to patients with good performance status [42]. Whether or not systemic treatments are beneficial remains to be seen, though a number of trials have been registered with a variety of interventions at time of writing.

The data presented are limited by issues common to research in rare diseases. As observed in all studies, data were retrospectively collected and therefore, other details, such as, concomitant systemic treatments were in most cases unavailable and may have confounded these results. Similarly, due to small sample sizes, a lack of robust data results in the inability to draw strong conclusions regarding optimal management. Further, smaller health centers may observe few, if any, cases of MCC, and as such, the presented data may be biased towards tertiary reports.

To conclude, radiotherapy plays an important role in the management of both local and distant metastases from MCC. It potentially improves local control as adjuvant treatment of nodal disease, or by itself when excision is not possible. Palliation of bone, brain and other systemic metastases can be primarily via radiotherapy and is assumed to be efficacious due to the radiosensitive nature of the disease and the fact that such treatment is standard when metastases result from other primary cancers. Further prospective data should be collected to better characterize the role of radiotherapy under varying circumstances.

## Conflict of Interests

The authors have no conflict of interests to declare.

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