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Staging, Prognosis, and Treatment of Merkel Cell Carcinoma: A Population-Based Study

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Yale University

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Staging, Prognosis, and Treatment of Merkel Cell Carcinoma:
A Population-Based Study

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

By
Douglas Michael Housman
2006
Merkel cell carcinoma (MCC) is a rare form of skin cancer, often described as the most aggressive cutaneous malignancy. Its high propensity for dermal-lymphatic invasion, local recurrence, and rapid lymphatic and distant metastasis poses a significant treatment challenge to clinicians. Combining its highly aggressive nature with its low incidence, merkel cell carcinoma is a particularly difficult cancer to study. Two major staging criteria exist for Merkel cell carcinoma.

The purpose of this study is to validate and compare the Memorial Sloan Kettering Cancer Center (MSKCC) staging criteria with the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) staging criteria for Merkel cell carcinoma (MCC) utilizing the Surveillance, Epidemiology, and End Results (SEER) database. The role of radiation therapy (RT) is also evaluated.

1556 cases of MCC from the SEER database (1988-2002) were identified and evaluated. Tumor size, lymph node status, and metastases were staged according to the MSKCC and AJCC TNM staging criteria respectively (n = 561). The primary outcome was overall survival. Covariates included: age at diagnosis, site of primary, receipt of radiation therapy, and MSKCC or AJCC stage respectively. Kaplan-Meier survival analyses and Cox proportional hazards regressions were analyzed using SAS 9.1.

The median age was 75 years (range: 22-98) with 39% of patients being female. The median follow up was 2.2 years with a range of 0.4-14.3 in the staged populations. Under the MSKCC staging criteria: five-year overall survival was 59% for stage I (n=224), 45% for stage II (n=114), 33% for stage III (n=140), and 28% for stage IV (n=83). When compared with stage I, the adjusted mortality HR was 1.44 (95% CI 1.03-2.00) for stage II, 2.14 (95% CI 1.57-2.93) for stage III, and 2.61 (95% CI 1.85-3.67) for stage IV. Under AJCC TNM staging criteria: five-year overall survival was 60% for stage I (n=223), 47% for stage II (n=107), 31% for stage III (n=148), and 28% for stage IV (n=83). When compared with stage I, the adjusted mortality HR was 1.41 (95% CI 0.99-1.99) for stage II, 2.13 (95% CI 1.57-2.89) for stage III, and 2.62 (95% CI 1.86-3.69) for stage IV. Among 478 patients with local or regional disease, 49% received radiation. After adjusting for MSKCC stage and age, radiation was not associated with survival, mortality HR 0.83 (95% CI 0.63-1.09). The interaction of radiation with stage was not significant (P=0.69). Similarly, in the AJCC TNM staged population, radiation was not associated with survival, mortality HR 0.83 (95% CI 0.63-1.09), with no interaction of radiation with stage (P=0.42).

The MSKCC staging criteria appropriately and significantly risk stratified MCC within this SEER population. Alternately, the AJCC staging criteria did not significantly risk stratify MCC within this SEER population. The MSKCC criteria appears to better risk stratify MCC than the AJCC staging criteria, within this SEER population. Radiation does not appear to confer a survival advantage among SEER patients with local or regional disease.
ACKNOWLEDGEMENTS:

I would first like to take the opportunity to dedicate my thesis to my Gramps, who passed away during my training at Yale. He has left such an indelible mark in my life. He lived his with such composure, compassion, sincerity, honesty, and love. I hope to continue to live my life under the same values he held in such high regard. He will continue to be an influential and inspiring person to me and all of those whose lives he has touched. His presence will always remain strong and deep in my heart. Thank you, Gramps.

Additionally, I would like to take a moment to recognize and remember an amazing man, Richard Kessler, who was the inspiration for this research project. His family supported him the best they could as he fought hard for any and every additional moment he could spend with them. His love is still felt and his memory a blessing to us all.

I have been blessed with a loving family, supportive friends, brilliant mentors, and amazing opportunities. I am tremendously grateful for each and every one of these major factors which have helped mold me into the physician-scientist I aspire to become. I feel completely indebted to each of these pillars of support. I am acutely aware of the many doors that have been opened by these individuals who have invested time and energy into my developing career. I realize that none of this would have been possible without these most significant contributions. As such, I intend on repaying this debt by realizing the full potential of the talent these individuals saw in me. I will commit myself to the highest standards of patient care, academic medicine, and research exemplified by my mentors and professors. I am fortunate to have been supported by such amazing mentors and master clinicians. I aspire to emulate these characteristics and perhaps one day, offer my mentorship to those who come after me.

The first group of people who I wish to recognize is my family, who in no small way made everything possible. Grandma and Grandpa Housman, Grammy and Gramps Lushan, Mom, Dad, Elizabth, Sarah, Jared, Aunt Jeanne, Aunt Nancy, Uncle Andy, Aunt Rachel, Uncle Tony, Danny, Amanda, Rebecca, Jared, Daniel, Ilana, Jacob, Aunt Hilda, Mona, my cousins and close family friends, who are essentially family members.

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1556 cases of MCC from the SEER database (1988-2002) were identified and evaluated. Tumor size, lymph node status, and metastases were staged according to the MSKCC and AJCC TNM staging criteria respectively (n = 561). The primary outcome was overall survival. Covariates included: age at diagnosis, site of primary, receipt of radiation therapy, and MSKCC or AJCC stage respectively. Kaplan-Meier survival analyses and Cox proportional hazards regressions were analyzed using SAS 9.1.

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INTRODUCTION:

Merkel cell carcinoma (MCC) is a particularly rare form of skin cancer. Derived from neuroendocrine origin, MCC has been described as the most aggressive form of cutaneous malignancy. MCC appears to have a predilection for the elderly and a propensity for dermal-lymphatic invasion along with rapid nodal and hematogenous spread. The tumor has been shown to share many similarities with small-cell carcinoma of the lung, including treatment options and metastatic potential. Although treatment regimes often include combined modality therapy, early detection and complete surgical resection remain the foundation of the best treatment outcomes. Unfortunately, MCC is a relatively poorly understood cancer. Current management tends to be based on institutional experience and convention, with limited literature to support specific treatments. The majority of literature is represented by single institution, retrospective, observational case studies with populations significantly low enough to preclude definitive conclusions. Two major factors contribute to this relatively limited fund of knowledge that exists in the current literature. Both its rarity and aggressive nature raise research challenges that few studies have been able to overcome. In addition to the limited number of treatment studies, there remains no consensus with respect to staging. The two staging systems most commonly used in the literature are the Memorial Sloan Kettering Cancer Center (MSKCC) staging system for MCC and the American Joint Committee on Cancer (AJCC) staging system for non-melanoma skin cancer. There has not been a study that compares these staging systems or validates their respective staging criteria to the knowledge of these authors. All of these factors combine, creating a multitude of treatment challenges for the clinician. (1) (2, 3)
BACKGROUND:

Discovery of the Merkel Cell:

The Merkel Cell was first described in 1875 by Frederick Merkel. He found a unique epidermal cell in the snout skin of the mole that he named, “Tastzell” (tactile), indicating his belief that this cell represented a special sensory cell of the skin. Merkel later identified this particular round cell in the basal layers of normal human epidermis. (see figure below) The human homologue to this cell is referred to as a “Merkel cell.” Merkel observed that these cells were associated with hair follicles, as a component of the tactile hair disk of Pinkus. These cells formed complexes with the terminal nerve endings, relaying information related to the perception of mechanical stimuli. The cells are purported to be slow adapting cutaneous mechanoreceptors, providing information about touch and hair movement. Merkel cells have also been found as isolated cells in the epidermis, the dermis, nail bed, and oral cavity. The cells are of neuroendocrine origin, migrating from the neural crest to the skin, whereupon they finally differentiate into mature Merkel Cells. As such, Merkel Cells express several neuronal and epithelial cell surface molecular markers. (1, 4-6)

Figure 1. Merkel cells are located in the basal layer of the epidermis.

(1)
First Case Reports of MCC:

In 1972 Toker reported on the five cases of “trabecular-cell carcinoma” of the skin, later renamed Merkel Cell Carcinoma. In this seminal article, Toker is the first to describe the pathohistological findings of hematoxylin-eosin stained surgical sections. He noted that all growths originated within the dermis or intermediate subcutis, and displayed a uniform morphology. (7) The cells were composed of solid trabeculae that lacked acini. (7) Toker observed abundant mitotic and apoptotic figures in many of the specimens. All of the cases were in an elderly population with an age range of 65-76 and median age of 70. The derivation of these cells was not clear to Toker. Originally, he believed these tumors might be cutaneous carcinoid, though they lacked carcinoidal granules. (7) He also postulated that perhaps they came from sweat glands or hair follicles, though no carcinomatous changes had ever previously been noted in the literature. (7) From this small study tumor size was observed to correlate with prognosis, with larger, faster growing tumors carrying the worst prognosis. (7) Interestingly enough, these initial case reports described as an indolent tumor of low malignant potential. (7) He also pointed out that this unique tumor carried some diagnostic confusion, as 3 of the 5 cases were misinterpreted as cutaneous metastases from visceral anaplastic tumors. (3, 7, 8)

In 1978, three more cases of trabecular carcinoma of the skin came to the attention of Tang and Toker, who subjected them to ultrastructural studies. (9) It was electron microscopy that facilitated confirmation that trabecular carcinoma of the skin was indeed a unique entity as it was ultrastructurally distinct from other diagnoses. (9) Tang and Toker proposed that the cells involved in trabecular carcinoma of the skin were of neuralcrest origin and most likely Merkel cells. (9) They described the dense core granules on electron microscopy found in all three trabecular carcinoma of the skin tumors examined in their study confirming its neuralcrest origin. (9) The ultrastructural studies conclusively excluded the possibility that trabecular carcinoma of the skin originated from other sources such as epidermis, sweat gland, and hair follicle. (9) Tang and Toker noted that trabecular cell carcinoma is most often located in the upper dermis and occasionally the epidermis. (9) Furthermore, electron microscopy allowed Tang and Toker to nominate the Merkel cell as the most likely candidate of neuralcrest derivation when the micrographs appeared consistent with prior descriptions of Merkel cells. (9) This observation was supported by Hashimoto’s theory that after separating from the Schwann cells, Merkel cells migrate through the mesenchyme in the dermis, toward epidermis, where they eventually settle. (3, 8-10)

MCC in the 1980’s:

By 1980 a total of 10 cases had been reported in the literature, and was now being referred to as neuroendocrine carcinoma of the skin, eventually throughout the 80’s and 90’s merkel cell carcinoma was eventually adopted. At that point, enough histological and ultrastructural studies of MCC had begun to elucidate the prior diagnostic
confusion, enabling epidemiological, prognostic, and treatment focused research while still maintaining the
descriptive nature of most published studies. Before the diagnosis of MCC could be made, the following
alternative diagnoses had to be systematically excluded: small-cell squamous carcinoma, malignant melanoma,
histiocytosis X, eccrine sweat gland carcinoma, metastatic small-cell carcinoma of the lung, metastatic islet cell
carcinoma, metastatic small-cell lymphoma, and either metastatic or primary cutaneous neuroblastoma. (6) In
later years, immunohistochemical staining for neuron-specific enolase and other markers improved the ability to
diagnose MCC. (11-13) By 1983, about 86 patients with trabecular carcinoma or Merkel cell tumor had been
described in the literature. The overwhelming treatment recommendation was primary surgical resection.
Recurrences were treated with radiation therapy and/or chemotherapy with varying degrees of success. (1, 4, 6,
8-10, 14-16)

Despite improving ability to diagnose this rare malignancy, information about the natural history, epidemiology,
and clinical features of MCC remained scarce because studies were hindered by the challenges related to its rare
occurrence, multiple names (trabecular carcinoma of the skin, neuroendocrine carcinoma, and finally merkel
cell carcinoma), MCC’s unclear origin, and the long differential diagnosis which contained other primary and
metastatic skin lesions. What was known about MCC was mainly derived from case series and literature
reviews that compiled previously published case studies. This led to gaps and inconsistencies with respect to
epidemiologic and survival data. (17)

**Epidemiology:**

A more efficient approach to the epidemiology of MCC has been achieved by utilizing the Survival,
Epidemiology and End Result (SEER) Program. The Surveillance, Epidemiology, and End Results (SEER)
Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence
and survival in the United States. SEER has been collecting cancer specific data over the last thirty-plus years.
Subjects with cancer registered by SEER are uniquely identified, allowing more than one cancer to be recorded
for the same individual for as long as he or she lives in a SEER area. All subjects are followed annually to
determine their vital status. SEER publishes cancer incidence and survival data from population-based cancer
registries covering approximately 26 percent of the US population. The program began collecting data on
January 1, 1973 in the following states and metropolitan cities: Connecticut, Iowa, New Mexico, Utah, Hawaii,
Detroit, and San Francisco-Oakland. Between 1974-75, Atlanta and the Seattle-Puget Sound were added to
form the SEER-9. Ten predominantly black rural counties in Georgia were added in 1978, followed by the
Native Americans living in Arizona, in 1980. Other regions participated in the SEER program prior to 1990:
1989). SEER also has been collecting information from an independent NCI tumor registry in Alaska. In 1992,
SEER expanded coverage of minority populations by adding, Los Angeles County and 4 counties in San Jose-
Monterey area. In 2001, SEER expanded again to include: Kentucky, the rest of California, and reinstated New
Jersey and Louisiana. Currently SEER coverage includes 23 percent of African Americans, 40 percent of
Hispanics, 42 percent of American Indians and Alaska Natives, 53 percent of Asians, and 70 percent of
Hawaiian/Pacific Islanders. (18)

A SEER analysis in 1999 was the first large population epidemiological studies of MCC. Miller and Rabkin
looked at 424 cases of MCC as compared with melanoma between the years of 1986-1994 from the SEER 9
registries. They found the actual age adjusted incidence of MCC to be 0.23 in 100,000 people in white
populations, with only one-twentieth of the incidence in black populations. (17) Among whites, the ratio of
MCC to melanoma was about 1 to 65. (17) The following graph represents the regional incidences of MCC
and melanoma as correlated with UVB index:

![Graph showing regional incidence rates for MCC and melanoma](image)

Regional incidence rates for both cancers increased with increasing sun exposure as measured by UVB index.
One of the most sun exposed areas of the body, the face, was the location of 36% of MCC compared with only
14% of melanoma. Both cancers were noted to have increased frequency and aggressiveness in the
immunocompromized patient. (17)

In 2003 the second SEER analysis by Agelli and Clegg identified that the incidence of MCC was markedly
higher in males (0.34) over females (0.17). Agelli and Clegg looked at 1034 cases from the time period of
Agelli and Clegg reported the following demographic characteristics of their population: (19)

- Median age: 74 (age range: 8-101)
- Mean age: 72.3
- Males: 56.3%
- Females: 43.7%
- Stage at diagnosis (According to SEER Historic Stage A*): (18)
  - Localized: 49.0%
  - Regional: 27.2%
  - Distant: 7.8%
  - Unstaged: 16.0%
- Race:
  - White: 93.6%
  - Black: 1.2%
  - Other: 3.6%
  - Unknown: 1.6%

Agelli and Clegg reported that MCC occurred mostly in whites (~94%), in people over the age of 65 (~76%), and in the head or neck region (~48%). They reported the five year survival based on SEER historic staging criteria, localized (~75%), regional (~59%) and distant (~25%). Additionally, they identified the following as positive predictors of survival: female sex, limb presentation, localized disease, and younger age. (19)

* SEER Historic Stage A description taken from the SEER Data dictionary available at www.seer.cancer.gov:
Localized — An invasive neoplasm confined entirely to the organ of origin. It may include intraluminal extension where specified. For example for colon, intraluminal extension limited to immediately contiguous segments of the large bowel is localized, if no lymph nodes are involved. Localized may exclude invasion of the serosa because of the poor survival of the patient once the serosa is invaded.
Regional — A neoplasm that has extended 1) beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) into regional lymph nodes by way of the lymphatic system; or 3) by a combination of extension and regional lymph nodes.
Distant — A neoplasm that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis (e.g., implantation or seeding) to distant organs, issues, or via the lymphatic system to distant lymph nodes.
In 2005, another SEER analysis by Hodgson, 1124 cases of MCC were identified between the years of 1986-2001 from the SEER-9 registries. Hodgson reported on the age adjusted incidence trends of MCC in relation to other cancers and within certain subgroups of the MCC population. The overall age-adjusted incidence increased from 0.15 cases per 100,000 in 1986 to 0.44 cases per 100,000 in 2001. See Figure below:

![Graph showing age-adjusted incidence rates for MCC from 1986 to 2000.](image)

Fig. 1. Age-adjusted incidence rates for the surveillance, epidemiology, and end results (SEER) program are illustrated (rates are number of cases per 100,000) for the years 1986–2000.
The estimated annual percent chance over that time period was 8.08%, indicating an incidence increase of ~8% per year, compared with melanoma which had an estimated annual percent change of 3.03% per year. (20) Hodgson reported the age-specific incidence rate trends, demonstrating an increase of incidence rates with age between 5-year age groups and within 5-year age groups from 1986 to 2001. (20) See table below:

**TABLE I. Age-Specific Incidence Rates and Counts for Merkel Cell Cancer: A Comparison of 1986 to 2001**

<table>
<thead>
<tr>
<th>Age group</th>
<th>1986, no. of cases</th>
<th>1986 rate</th>
<th>2001, no. of cases</th>
<th>2001 rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40–44</td>
<td>1</td>
<td>0.07</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45–49</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>50–54</td>
<td>1</td>
<td>0.10</td>
<td>4</td>
<td>0.50</td>
</tr>
<tr>
<td>55–59</td>
<td>4</td>
<td>0.39</td>
<td>6</td>
<td>0.37</td>
</tr>
<tr>
<td>60–64</td>
<td>4</td>
<td>0.41</td>
<td>9</td>
<td>0.40</td>
</tr>
<tr>
<td>65–69</td>
<td>7</td>
<td>0.82</td>
<td>22</td>
<td>1.83</td>
</tr>
<tr>
<td>70-74</td>
<td>2</td>
<td>0.30</td>
<td>21</td>
<td>1.71</td>
</tr>
<tr>
<td>75-79</td>
<td>5</td>
<td>1.03</td>
<td>21</td>
<td>2.56</td>
</tr>
<tr>
<td>80-84</td>
<td>6</td>
<td>1.99</td>
<td>21</td>
<td>4.24</td>
</tr>
<tr>
<td>85+</td>
<td>5</td>
<td>1.99</td>
<td>27</td>
<td>5.62</td>
</tr>
</tbody>
</table>

Hodgson also noticed an almost three-fold higher incidence in males over females. Although Hodgson accepts that the ability to diagnose disease has significantly increased for cancers like melanoma and MCC, the discrepancy between the two is most likely significant for actual and worry some increases in incidence. (20) Although with a cancer like MCC that has a particular predilection for the elderly, the growing elderly population that continues to live longer than previous generations may contribute to some of this proposed increased incidence, in addition to the increased ability to diagnose with time. (20)
Clinical Features:

At the time of diagnosis, MCC typically presents as a flesh-colored, red or violaceous intracutaneous mass with a shiny surface. The lesion is usually painless, firm, and non-tender. MCC tends to grow quite rapidly and often with overlying telangiectasias. Most commonly, the tumor is nodular but may also have plaque-like features. These tumors can resemble basal-cell carcinoma, amelanotic melanomas, squamous-cell carcinoma, and cutaneous lymphomas. (1, 3, 21, 22) (See images below)
Clinical photograph shows a dome-shaped red cutaneous nodule, which represents the typical manifestation of MCC.

Figure 1. A 55-year-old female with a 3-cm Merkel cell carcinoma of the dorsal left forearm.
Figure: Regionally metastasizing MCC with multiple cutaneous metastases accompanied by nodal disease and excessive lymphedema on the left leg
MCC tumor size ranges from 2 – 200 mm. Most common presentations have been reported as less than 20mm, though some studies maintain the median lesion size to be 20mm. (1, 3, 21, 22)
Although the most common presentation of MCC is a head and neck primary in a sun-exposed region, skin lesions can occur on the trunk, oral mucosa, genitalia, and perianal region in a random distribution. (28, 29) In the face, the eyelids are commonly involved. In 2000, a review of 661 published cases, Tai et al. described the following distribution: (22)

- Head and Neck: 47%
- Extremities: 33%
- Trunk: 10%
- Vulva: 2%
- Multiple sites: <1%

In 2001, similar distribution was described by Medina-Franco et al. in a case series and literature review of 1024 cases. (30)

- Head and Neck: 40.6%
- Extremities: 33%
- Trunk: 23%
- Unknown: 3%

In 2003, an analysis of the SEER-11 data (1973-1999), Agelli and Clegg noted the following distribution in 1034 cases: (19)

- Head and Neck: 48.3%
- Upper Extremities: 19.3%
- Lower Extremities: 16.2%
- Trunk: 11.3%
- Other: 5.2%

MCC can spread through the intricate dermal lymphatic system, resulting in the development of satellite lesions. Regional nodes are involved clinically at presentation in about a third of cases. Hematogenous spread occurs in about 50% of cases at some point in the course of the illness. Nodal status is the strongest predictor of distant involvement. (1, 3, 19, 21, 31-34) Secondary sites of involvement include: the aforementioned satellite lesions of the skin (28%), lymph nodes (27%), liver (13%), lung (10%), bone (10%), and brain (6%). (35) Some of the less common sites of metastasis include: oral mucosa, testis, and parotid gland. (35-38) Symptoms are typically limited to local effects related to rapid tumor growth and/or lymph node involvement. (1, 3, 35-37) Superior vena cava syndrome and some paraneoplastic neurological complications have been described. (1, 3, 21, 22, 31, 32, 34, 39-53)
Pathology and Histology:

MCC has been believed to arise from Merkel cells that are located in the upper dermis and frequently extend into the subcutaneous fat with the occasional involvement of basal layer of epidermis. (5, 54) Although an overwhelming majority of the literature maintains that MCC derives from the Merkel cell, there remains some controversy. (1, 3, 21, 55, 56) The fundamental assertion that MCC is of neuroendocrine origin, as established by Tang and Toker and supported many others, is not necessarily the issue. (4, 6, 9, 12, 16, 56-58) That the Merkel cell is the purported origin of MCC is the nidus of objection and suspicion. (56) Alternate hypotheses have proposed that MCC perhaps originate from immature totipotential stem cells that acquire neuroendocrine features during malignant transformation, based on the high focal concentrations of intermediate filaments and the individual concentrations of specific intermediate filaments subtypes found in MCC. (56)

The tumor consists of small blue cells, with richly heterochromatic nuclei and minimal cytoplasm. (7-9, 21) The cells are usually ovoid and up to 15 μm in diameter. (1, 54) The nuclei have fine granular chromatin, with few nucleoli. (1, 54) The tumor cells have high mitotic activity, with apoptotic figures abundant. (7-9, 21) There are three characteristics that most exemplify MCC: vesicular nuclei with small nucleoli, high mitotic activity, and apoptosis. (1, 54) Invariably the tumor demonstrates lymphovascular invasion. (6-9, 12, 16, 21, 59)

The following two images are examples of MCC cells stained by Allen et al. (54) These images appeared in their 2001 Journal of Clinical Oncology article on immunohistochemical analysis of sentinel lymph nodes. (54) The first image is a hematoxylin and eosin conventionally stained section of a MCC tumor found in the dermis. (54) Notice the hyperchromatic tumor cells. (54) The second image is of metastatic MCC found in the subcapsular sinus of a lymph node, also stained with hematoxylin and eosin. (54)
There are three main histologic patterns of MCC: trabecular type, small cell type, and intermediate type, which is most common. (1, 3, 21) No prognostic association has been linked to these different histologic subgroups, as such they have no clinical relevance as of yet. (1, 3, 21) See images below.

Fig 2. (A) Intermediate variant of MCC showing vesicular, basophilic nuclei with prominent nucleoli and multiple mitoses. (B) Small-cell variant, histologically indistinguishable from bronchial small-cell carcinoma. (C) Trabecular variant is rare and normally only seen as a small component of a mixed variant. (B)
Etiology:

The exact etiology of MCC is unknown. Sun exposure is believed to play a significant role though the exact mechanism remains unclear. MCC has been shown to have a higher incidence in sun exposed areas of the body. (17, 19, 33) Regional incidence rates have correlated with increasing sun exposure as measured by UVB index. (17, 19, 20) Agelli et al found a correlation between UVB index and incidence of MCC as did Miller et al. (19) See figure below:

![UVB Index vs Lograte](image)

**Fig 3.** Primary Merkel cell carcinoma of head in whites: Linear correlation of age-adjusted incidence with UVB radiation indexes (1986-1999 SEER Program studying 9 geographic areas), $r = 0.84$, $P = .005$. Lograte, Natural logarithm of age-adjusted incidence rates per 100,000 person-years. UVB indexes from Scotto et al. (19)

Co-presentation with other skin cancers for which sun exposure is a major risk factor is common. (17) MCC is associated with a high incidence of other skin tumors and hematologic malignancies. In one report by Brenner et al. 17 of 67 patients (25 %) with MCC had a second neoplasm, 50% of which were squamous cell cancers. (60) The relationship between MCC and ultraviolet (UV) radiation has been further supported by the increased incidence of MCC in populations of patients status post PUVA treatment. (3, 61)

However, etiological factors, other that sun exposure, are also likely to be involved. Many of the most deadly cases of MCC, present in areas not typically exposed to the sun. (17, 19, 20) Another possible cause of MCC may be an impaired immune system. Although no predisposing conditions have been directly and consistently identified, the incidence has been shown to be increased in immunocompromised and iatrogenically immunosuppressed patients. (3, 17, 41, 62-68) There have been several cases reported of MCC after chronic lymphocytic lymphoma (3, 67-74), in the HIV population (3, 62, 63), and in transplant patients with iatrogenic immunosuppresion (1, 3, 64-66, 75-77). Additionally, support for an immunological basis of etiology is seen in
the increased incidence of secondary malignancies in MCC patients (25%), compared with melanoma (5.8%). (17, 60) The standardized incidence ratio for a second cancer was 2.8 (95% confidence interval, 1.38 - 4.22). (60) Compared to patients with MCC only, those who developed second neoplasms had significantly higher MCC-specific mortality rate (65 versus 40 percent). (60) Additionally there have been several reports of spontaneous remission, hypothesized to be immune mediated. (3, 78, 79) These reports suggest that the immune system may play a significant role in the pathogenesis of MCC.

Pathogenesis:

There are several chromosomal abnormalities that have been described in MCC. These abnormalities may one day help elucidate the unclear pathogenesis of MCC. However, to date there have been no conclusive evidence to implicate specific tumor-suppressor genes or oncogenes. (21, 80-82) The cytogenetic abnormality that has raised much interest is the deletion of the short arm of chromosome 1 (1p36). (82-88) This deletion has been seen in melanoma and neuroblastoma and gives more weight to the neural crest origin argument. (82-88) Additionally, P73, a protein of similar structure and function to P53, has been localized to 1p36.33 and shown to have been deleted in multiple neoplasms, including those of neuroendocrine origin. (82) C to T mutations have been seen in the P73 protein leading to mis-sense and non-sense mutations, causing decreased expression and activity of P73. (82) UVB radiation has been known to cause C to T point mutations. (82) Similar mutations in P53 have been associated with more aggressive disease. Thus there exists some cytogenetic evidence to support the purported link between sunlight and MCC, in the form of UVB induced mutations to P53 and P73. (82-88)

Similarities between small-cell lung cancer and MCC have been demonstrated cytogenetically. (82-88) A common feature of small-cell lung cancer, loss of heterozygosity of the short arm of chromosome 3 (3p21), has been seen in MCC. (82-88) This region, (3p21), has been shown in lung and breast cancer to be associated with a particular tumor suppressor gene in small-cell lung cancer, a Ras association domain family 1 gene (RASSF1A). (21, 89)

A DNA-binding protein, POU4F3 – Merkel nuclear factor, has been identified in MCC. (80) The function of this transcription factor has been examined in mice. Both POU4F3 and ATOH1 have been shown to be essential to normal Merkel-cell function and for neuroendocrine differentiation. (80) The importance of these transcription factors remains unclear. (80) Several other chromosomal abnormalities have been noted, namely, trisomy of 1, 6, 11, or 18; and deletion of chromosome 7. (82-88) Loss of heterozygosity has been noted on chromosomes 13 and the long arm of 10. (82-88) Despite all of these significant findings, the relationship between these chromosomal abnormalities and a genetic basis of pathogenesis remains unclear. (82-88)
Diagnosis:

A clinical suspicion of MCC must be substantiated by biopsy. As MCC can resemble many different cutaneous neoplasms, careful effort must be made to ensure thoughtful evaluation. As described earlier by Toker (7, 8) and Tang and Toker (9), it is difficult to accurately diagnose MCC by light microscopy alone due to its similarity to other poorly differentiated small blue cell tumors, including small cell lung cancer, neuroblastoma, amelanotic melanoma, sweat gland carcinoma, Ewing’s sarcoma, cutaneous large cell lymphoma, Langerhans cell histiocytosis and various metastatic tumors i.e. metastatic carcinoid. (1, 3, 21, 31, 45, 90-95) Ultrastructural studies with electron microscopy and immunohistochemical staining are required to make a definitive diagnosis. (6, 12, 59, 94) On electron microscopy the following characteristics are typical of Merkel cells and MCC: paranuclear electron dense neurosecretory granules, 10nm filaments, and desmosomes. (12)

![Electron microscopy of MCC showing tumor cells with a prominent nucleus, several mitochondria, showing signs of increased metabolic activity (×10,400), and multiple neurosecretory granules (insert, ×19,500)](image)

Merkel cells exhibit immunohistochemical properties of both neuroendocrine and epithelial cells. As such, MCC tends to express both neuroendocrine (neuron-specific enolase, synaptophysin, chromogranin) as well as cytokeratin markers (cytokeratin 20, CAM 5.2). Immunoreactivity for various intermediate filaments, such as the subgroup of cytokeratins, help distinguish MCC from some of the other undifferentiated tumor previously mentioned. (11-13, 42, 54-56, 91, 92, 96-98) The following chart from
the 2002 review article in the Journal of Clinical Oncology by Goessling et al. summarizes the immunohistochemical staining profile of MCC and the tumors within the working differential diagnosis. (21)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>CK20</th>
<th>CK7</th>
<th>NSE</th>
<th>NFP</th>
<th>S100</th>
<th>LCA</th>
<th>CD99</th>
<th>TFF-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merkel cell tumor</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Rarely +</td>
<td>-</td>
</tr>
<tr>
<td>Small-cell carcinoma of lung</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>Rarely +</td>
<td>(cytoplasmic) +</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral primitive neuroendocrine tumor</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Rarely +</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Small-cell melanoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
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</tbody>
</table>

Abbreviations: NSE, neuron-specific enolase; NFP, neurofilament protein; LCA, leukocyte common antigen; TFF-1, thyroid transcription factor 1.

There are several cellular markers that have been identified that give MCC a unique fingerprint, improving diagnostic sensitivity and specificity. The first of these markers was identified in 1983. (19) Neuron-specific enolase (NSE) is a protein specific to neuroendocrine cells and as such, helps identify these cell types as belonging to the neuroendocrine family. (91) However, this marker is not specific to MCC and often contributes little help in narrowing the differential diagnosis. (54, 98) The second such marker is a neurofilament protein (NFP) which appears as a paranuclear dot. (1, 21, 54) Next found was CAM 5.2, an antibody that recognizes low molecular weight cytokeratins. The most significant of the markers was identified in 1992, cytokeratin 20 (CK20) which is an intermediate filament found in cutaneous epithelial cells. (19, 21, 54, 98) See the following immunohistochemical stainings of MCC found in a series of sentinel node biopsies by Allen et al. in 2001. They were stained with the following antibodies: Chromogranin, a neuroendocrine differentiation marker; Cam5.2 which recognizes low molecular weight cytokeratins; and Cytokeratin 20, a marker specific to cutaneous neuroendocrine tumors, not pulmonary variants. (54)
The MCC profile most closely resembles that of small-cell lung cancer. As these tumors share many clinical similarities, it is not surprising that their immunohistochemical profile is also similar. Notable immunohistochemical differences between small-cell lung cancer and MCC are the preferential staining of CK7 and CK20 respectively. (21, 98) CK7 is a cytokeratin that identifies bronchial small-cell carcinoma. Additionally, small-cell melanoma has a similar immunohistochemical profile to MCC, sharing the NSE cell marker. However, melanoma is CK20 negative, S100 positive, and NFP negative. (21)
These markers have lead to direct improvements of detecting MCC. Perhaps contributing to the purported increased incidence of MCC seen over the years, shown by Hodgson’s 2005 report on changing incidence trends of MCC. (20) Agelli et al. illustrated this implied relationship in their 2003 article with the following graph:

![Graph showing changes in MCC incidence over time](image)

**Fig 1.** Primary Merkel cell carcinoma: Age-adjusted incidence per 100,000 person-years according to sex and calendar year at diagnosis (1973-1999, SEER Program studying 9 geographic areas). Arrows indicate introduction of: electron microscopy (EM); neuron-specific enolase (NE); International Classification of Diseases for Oncology, first update (ICD-O); and cytokeratin (CK-20). Circles, Females; squares, males.

(19)

Official confirmatory immunohistochemical staining recommendations from the National Comprehensive Cancer Network include: NSE, chromogranin A, pancytokeratin, NFP, CK20, and thyroid transcription factor-1. (94) Additionally electron microscopy may also be helpful. (94)
Staging:

Following histologically confirmed diagnosis, proper staging should be done to help patient and clinician choose the best treatment. Proper staging is important for many reasons. Not only does staging allow assessment of prognosis, but staging also helps direct therapy and establish standards of care. There is no consensus with regard to staging system for MCC. There are two major staging systems that have been used in the literature: the Memorial Sloan Kettering Cancer Center (MSKCC) MCC staging criteria and the American Joint Committee on Cancer TNM staging criteria for non-melanoma skin cancer. The MSKCC staging criteria was first reported in the literature in 1991 by Yiengpruksawan et al. with a series of 70 cases. (34) This staging system remains the most common and is used by the National Cancer Institute. Originally the staging criteria described three stages: local, regional, and metastatic, with a sub-stratification of the local disease population. (34)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
<td>Disease confined to skin and ≤2 cm in diameter</td>
</tr>
<tr>
<td>IB</td>
<td>Disease confined to skin and &gt;2 cm in diameter</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of regional lymph nodes</td>
</tr>
<tr>
<td>III</td>
<td>Metastatic disease</td>
</tr>
</tbody>
</table>

(34)

In the original article, Yiengpruksawan et al. did not note a significant difference in outcome of Stage Ia and Stage Ib. (34) In subsequent reviews with larger numbers of cases reported, a significant difference between the outcomes of different substages. (90) However, these three stages were later revised into a four stage system. This revised staging system was published in the largest single institution (n = 251) case series (studied over a 32 year period), by Allen et al in 2005. (31)

In contrast with the MSKCC staging system, the AJCC TNM non-melanoma skin cancer staging system has one subtle difference. (Highlighted yellow below) The T-stage T4, of the AJCC TNM staging criteria, upstages tumors, regardless of size, from MSKCC stage I and MSKCC stage II, to stage III status. T4 includes direct local invasion of extradermal structures deep to the tumor (e.g., cartilage, skeletal muscle, or bone). Although a majority of the literature is based on the original or revised MSKCC staging criteria, some studies have used the non-melanoma skin cancer TNM staging criteria from the AJCC to stage and classify MCC. (1-3, 21, 31, 34, 49, 50, 54, 90)

Neither staging system, the revised MSKCC nor the AJCC TNM, has been independently validated for the use in staging MCC. Such a validation would be helpful in establishing consensus in staging such an aggressive cancer. On the following two pages, both staging systems are outlined in detail.
The MSKCC staging criteria

• **Primary tumor (T)**
  – T1: Tumor ≤ 2 cm in greatest dimension
  – T2: Tumor > 2 cm in greatest dimension

• **Regional lymph nodes (N)**
  – N0: Negative regional lymph nodes
  – N1: Positive regional lymph nodes

• **Distant metastasis (M)**
  – M0: No distant metastasis
  – M1: Distant metastasis

• **Stage I**
  – T1, N0, M0

• **Stage II**
  – T2, N0, M0

• **Stage III**
  – Any T, N1, M0

• **Stage IV**
  – Any T, any N, M1
The AJCC TNM staging criteria

- **Primary tumor (T)**
  - T1: Tumor ≤ 2 cm in greatest dimension
  - T2: Tumor >2 cm but ≤ 5 cm in greatest dimension
  - T3: Tumor >5 cm in greatest dimension
  - **T4: Tumor invades deep extradermal structures**

- **Regional lymph nodes (N)**
  - N0: Negative regional lymph nodes
  - N1: Positive regional lymph nodes

- **Distant metastasis (M)**
  - M0: No distant metastasis
  - M1: Distant metastasis

- **Stage I**
  - T1, N0, M0

- **Stage II**
  - T2, N0, M0
  - T3, N0, M0

- **Stage III**
  - **T4, N0, M0**
  - Any T, N1, M0

- **Stage IV**
  - Any T, any N, M1
Staging Work-up:

After establishing a histologic diagnosis, patients should undergo further imaging for complete staging and exclude other sites as primary sources of small-cell cancer. However, before such an involved diagnostic imaging work-up, a thorough dermatological examination of the entire skin surface and draining nodes must be complete with careful attention to assess possible satellite lesions, dermal seeding, and clinical lymphadenopathy. (1, 3, 21, 31, 34, 54, 90, 94, 100) The proper staging investigations should include standard blood tests, chest x-ray, computerized tomography (CT) of the chest and abdomen, and a head CT if the patient is symptomatic. (1, 3, 21, 34, 94)

Computerized Tomography:

The CT of the chest should be performed to rule out the presence of a lung mass suspicious for either MCC metastasis or small-cell lung cancer primary. The CT of abdomen and pelvis should be assessed for evidence of metastasis. (1, 3, 21, 24, 101)
Figures 9, 10. (9) Contrast-enhanced chest CT scan shows soft-tissue metastasis from MCC in the thoracic wall (arrow). (10) Contrast-enhanced abdominal CT scan shows MCC invasion of the lower left interior chest wall and lower left rib. The chest wall mass (arrow) abuts and displaces the stomach medially (arrowhead). Note also the liver metastases with ringlike enhancement.

Figure 11. (a) Contrast-enhanced CT scan shows a soft-tissue MCC that abuts and invades the larger curvature of the stomach (arrow). (b) CT scan obtained with the patient in the right lateral decubitus position shows ulcerative MCC of the stomach (arrow).

Figure 7. Contrast-enhanced neck CT scan shows high-attenuation right parotid adenopathy from MCC (arrow).

Figure 6. Contrast-enhanced head CT scan demonstrates a soft-tissue nodule (arrow) from MCC of the left cheek.
Magnetic Resonance Imaging:

The role of magnetic resonance imaging (MRI) is clear in the evaluation of neurologically symptomatic patients and should be combined with consideration of lumbar puncture. (24)

Figure 12. (a, b) Axial (a) and coronal (b) contrast-enhanced T1-weighted MR images obtained in a patient who presented with ataxia show leptomeningeal enhancement within the posterior fossa and around the brainstem (arrows), findings that are compatible with MCC leptomeningeal metastasis. (c) Photomicrograph (original magnification, ×400; Papanicolaou stain) shows cerebrospinal fluid containing clusters of malignant cells, a finding that is consistent with MCC mixed with lymphocytes.

Figure 13. Axial T2-weighted (a) and coronal contrast-enhanced T1-weighted (b) MR images show lobulated metastasis from MCC in the brainstem (arrow). The cerebrospinal fluid tested positive for MCC cells.

(24)
MRI for the staging outside of the central nervous system (CNS) is only beginning to be assessed and remains unclear. One study thus far has sought to determine the MRI characteristic of MCC correlated with histology. Anderson et al. describes subcutaneous lymphatic reticular stranding, multiple subcutaneous masses, and lymph node metastases with retained fatty tissue—all consistent with the soft tissue lymphatic nature of MCC found on histologic sections. (102)

![Images of MRI scans and histology sections]

**Nuclear Medicine:**

Nuclear medicine has been revolutionary in staging many cancers, with positron emission tomography (PET) using fluorodeoxyglucose and combined PET/CT scans. Nuclear medicine continues to be at the forefront of diagnostic imaging for MCC and other neoplasms, with active research extending into using such specific tools to direct therapy. In particular, somatostatin-receptor scintigraphy PET, Octreoscan, has been teamed with specific targeted chemotherapy, Octreotide, with impressive results in case reports. (See Octreoscan below)
Treatment:

Due to the rarity of MCC, no prospective clinical studies with statistical significance exist that have assessed initial surgical therapy, radiation therapy, or chemotherapy. Randomized trials are virtually impossible due to MCC’s rarity, with individual centers encountering only a few cases a year. MCC’s aggressive nature and predilection for the elderly contribute to the challenges of studying this cancer and particularly to treating it. As such the literature for the management of MCC is significantly limited. There is no definitive consensus on the optimum management for early stage MCC, particularly regarding postoperative adjuvant treatment. Although chemotherapy is often a component of treatment, its use is an extension of its efficacy in other neuroendocrine tumors like small-cell lung cancer. Although the use of chemotherapy in recurrent or metastatic disease may be effective its use is often challenging in the aged population. Most management decisions are based on empirical institutional experience and convention. (1, 3, 21, 31, 54, 90)

What little consensus exists, points in the direction of supporting the primary treatment of aggressive surgical resection. (1, 3, 21, 31, 34, 44, 54, 90) Surgical excision with tumor-free, wide margins is the primary therapy for all localized disease. (1, 3, 21, 34, 53, 90, 105, 106) Most treatment guidelines recommend the margins to be between 2 to 3 cm wide and about 2 cm deep for all local excisions of the tumor. (1, 3, 21, 34, 53, 90, 105, 106) These recommendations have limited supporting data. In a series of 38 patients at MSKCC, margins of > 3cm (n=11) were without local recurrence whereas those with 2 to 3cm margins (n=27) had 4 (15%) recurrence.
They noted a local recurrence of 26% as reported in their initial study. On update, that recurrence rate increased to 55%. Several later studies found little to no benefit to survival whether margins were > or < 2cm as well as no difference even if margins are less than 1cm. The following are the current surgical guidelines for MCC from the National Comprehensive Cancer Network:

**EXCISION**

<table>
<thead>
<tr>
<th>Goal:</th>
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<tr>
<td>• Every effort should be made to achieve clear surgical margins.</td>
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</table>

**Varied Approaches:**
- Mohs technique
- Modified Mohs = Mohs technique with additional final margin for permanent section assessment.
- CCPDMA = Complete circumferential and peripheral deep margin assessment.
- 1-2 cm margins to investing fascia of muscle or pericranium with clear pathologic margins, when clinically feasible.

**Reconstruction:**
- Immediate reconstruction in most cases.
- It is preferable to delay reconstruction involving extensive undermining or flaps until negative surgical margins are assessed and certified pathologically clear.
- When primary closure is not possible, consider split thickness skin grafting (STSG) to monitor for recurrence.

Mohs micrographic surgery has been purported to be more successful at controlling local disease than traditional wide excision. One obvious advantage to Mohs surgery is the guaranteed negative margin status by histologic examination of every excised specimen. Given that MCC often demonstrated local extension into the muscle, deep margins may represent a potential site of failure, contributing to the high rate of local and regional recurrence. Boyer et al reviewed 45 cases of MCC treated with Mohs micrographic surgery with (n=20) or without (n=25) adjuvant radiation therapy (RT). There were 4 recurrences in the non-RT arm and none in the RT arm. The numbers were too small to show a significant difference between treatment arms. Aside from the small population size, a significant limitation of this study was the relatively short follow-up. The median follow-up time was 25 months for the non-RT arm and 14 for the RT arm. The role of Mohs micrographic surgery is still not proven though has some promise in treating cosmetically sensitive areas.

Pathological involvement of regional lymph nodes is present in approximately 10-30% of patients who undergo elective lymph node dissection and regional relapse in the nodal region occurs in up to 76% of cases. In some studies the incidence of micro-metastasis in elective lymph node dissection has been reported as high as 100%. As such, the role of sentinel node assessment via
lymphoscintigraphy and/or biopsy is of particular interest for this aggressive malignancy. By far the most convincing data yet to support sentinel node biopsy and other pathological nodal assessment comes from the Allen et al. paper recently published in the Journal of Clinical Oncology. Allen et al. looked at 251 patients treated at MSKCC from 1970-2002 with an average follow-up time of 40 months. In the population of clinically node negative cases (n=71), pathological staging of the draining nodal basin detected 16 (23%) cases of node positive disease. Pathological nodal staging vs. clinical node staging significantly improved stage-specific survival outcomes. Allen et al. and others have found similar findings in prior articles on sentinel node biopsy with immunohistochemical analysis. Sentinel node biopsy will likely have a more prominent role in the future of MCC staging, conferring a considerable improvement in staging accuracy without the significant morbidity of a full lymph node dissection.

Because of the aggressive nature of MCC with high local and regional recurrence following surgery, many authors have recommended postoperative radiation therapy on the basis of retrospective observational studies. However, the role of radiation therapy (RT) remains a highly contested issue. Without looking at the literature everything would seem to point to the definitive use of RT in the treatment of an aggressive cancer with high local and regional recurrence given that it has notable similarities to small-cell lung cancer, which has particular radiosensitivity. Alas the evidence remains controversial. Given the retrospective case review evidence base, current recommendations are for adjuvant RT at doses between 45 to 50 Gy administered to the primary site and involved lymph nodes following surgical resection. Radiation doses have been significantly correlated with overall survival, with doses between 45 and 50 Gy being associated with the best outcome. The results were poorer at doses greater than 50 Gy (possibly related to more aggressive tumors receiving more aggressive radiation) and the outcomes were worse with RT doses < 45 Gy, suggesting 45 Gy as the minimum effective dose. In a retrospective review of 661 mainly literature based cases, 169 received RT as a component of their initial treatment. Adjuvant RT did not have a significant impact on overall survival (p = 0.44), but was associated with significantly higher two-year disease-free interval (37 versus 24 percent) and a lower incidence of local recurrence at 18 months (21 versus 34 percent). The best support for the use of RT as adjuvant therapy in the treatment of MCC comes from the multimodality treatment meta-analysis of MCC with 1024 cases from the literature. Medina-Franco et al. included eleven case series (n = 441) in the evaluation of the post operative RT for local recurrence. The local recurrence rate with radiation was 10.5% (range, 0–33%) vs. 52.6% (range, 6–100%) without radiation (P = .00001). They concluded that surgery and adjuvant radiotherapy were associated with a reduced risk of local recurrence and appeared to provide the best local control.
In the Allen et al. 2005 Journal of Clinical Oncology article, adjuvant RT was administered to 41 (17%) of 237 patients who presented with local or regional disease, representing the largest single institution experience with MCC. (31) Although this review did not show an association with local recurrence (RT 10% v No RT 8%; P = 0.76) or nodal recurrence (RT 13% v No RT 26%; P = 0.13), the study may have been underpowered to reveal any significant difference, given the relatively small number of patients who received RT. (31, 117) When Wilson et al. raised this issue in a letter of correspondence, Allen et al. responded, “A randomized study designed to demonstrate a reduction in local or regional recurrence from 12% to 6% with the addition of RT would require 281 patients per arm (one-sided $P \leq 0.05$, power 0.8), a study that will clearly never be undertaken.” (117) Alas since none of the evidence is based on prospective randomized studies, there are significant selection biases which may be present in the retrospective observational studies and must be read with the appropriate level of caution.

Chemotherapy is the least studied modality of treatment. MCC was initially deemed chemoresistant. (35, 38, 43, 123-125) However more recent studies investigating agents that have been shown to be helpful in small-cell lung cancer, have shown good results with chemotherapy alone or with RT. (35, 38, 43, 123-125) Among the chemotherapeutic agents, cyclophosphamide (56%), anthracyclines (49%), and cisplatin (25%) were most commonly used. (35, 123-125) Although the large meta-analysis of multimodality treatment for MCC by Medina-Franco et al found no clearly defined role for chemotherapy, other authors have reached differing conclusions. (30) In a study of chemotherapeutic use over 15 years in 107 cases, Voog et al. reported that the overall response rate was 60%. (35) The response was 69% in the setting of locally advanced disease and 57% in metastatic disease. (35) Similar findings were seen in Tai et al’s review of 204 literature based cases. (125) The TROG looked at the role of chemotherapy in combination with RT in a phase II study (TROG 96:07). (123, 124) Poulsen et al. initially reported high levels of locoregional control and survival benefit of the addition of chemotherapy to RT in patients deemed “high risk”. (124) “High risk” was defined as having one or more of the following features: recurrence after initial therapy, involved nodes, primary tumor size greater than 1 cm,
gross residual disease after surgery, or occult primary with nodes. However, this study was readdressed by Poulsen et al. in 2006. The subsequent multivariate analysis did not show a significant effect on survival in a series of 102 “high risk” patients. Patients with pathologically node-negative MCC have a good prognosis, and adjuvant chemotherapy is not recommended. For “high-risk” patients, the available data for the use of chemoradiotherapy do not support benefit from the addition of chemotherapy to RT, and adjuvant chemotherapy is not generally recommended in locoregional disease, though may be helpful in palliation. However for the treatment of metastatic disease, chemotherapy is recommended empirically based on small studies and extrapolation from its use in small-cell lung cancer. The following therapies are most commonly used to treat MCC:

<table>
<thead>
<tr>
<th>Regimen</th>
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<tbody>
<tr>
<td>Cyclophosphamide, doxorubicin, vincristine</td>
</tr>
<tr>
<td>Etoposide, cisplatin</td>
</tr>
<tr>
<td>Cyclophosphamide, epirubicin, vincristine</td>
</tr>
<tr>
<td>Cyclophosphamide, doxorubicin, vincristine alternating with etoposide,</td>
</tr>
<tr>
<td>cisplatin</td>
</tr>
<tr>
<td>Cyclophosphamide, doxorubicin, vincristine + prednisone</td>
</tr>
<tr>
<td>Doxorubicin, cisplatin ± bleomycin</td>
</tr>
<tr>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Doxorubicin/ifosfamide</td>
</tr>
<tr>
<td>Cisplatin ± doxorubicin</td>
</tr>
<tr>
<td>Mitoxantrone</td>
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</tbody>
</table>

There are some interesting therapeutic agents being currently researched in animal models. Initial reports of bcl-2 anti-sense oligonucleotides have inhibited MCC tumor growth in mice when compared with controls and chemotherapeutics. These data are interesting and may perhaps pave the way for more successful molecular-target based chemotherapeutics for future treatment of MCC.

**Follow-up:**

MCCs warrant frequent follow-up because of their aggressive nature. Follow-up should include careful total body skin examination and palpation of lymph nodes. Additionally, self-examination of the skin may also be useful for patients with MCC to look for both recurrence and other skin malignancies, as they are at increased risk for other skin cancers. Some studies have implicated serum neuron-specific enolase for
early detection of recurrence. (1, 21, 22, 94) Routine chest radiograph is indicated, while CT scans of the chest, abdomen, or head may be required in patients with symptoms suggestive of recurrence. (1, 21, 22, 94) When recurrence is found, full staging work-up should be performed. See below for NCCN MCC guidelines for recommended follow-up:

National Comprehensive Cancer Network Guidelines:

The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 20 of the world’s leading cancer centers, is dedicated to improving the quality and effectiveness of care provided to patients with cancer. (128) Through the leadership and expertise of clinical professionals at NCCN member institutions, NCCN develops resources that present valuable information to the numerous stakeholders in the health care delivery system. (128) NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers. (128) The primary goal of all NCCN initiatives is to improve the quality, effectiveness, and efficiency of oncology practice so patients can live better lives. (128) The NCCN’s Non-Melanoma Skin Cancer Panel developed a set of guidelines outlining the treatment of MCC. (94) As MCC is a rare tumor, no prospective, statistically significant data are available to verify prognostic features or treatment outcomes. (94) As such, the guidelines are based on lower level of evidence including smaller, institutional studies, meta-analysis, and clinical experience of those individuals on the panel. (94) The following are the official National Comprehensive Cancer Network (NCCN) guidelines for MCC: (94)
Clinical Presentation, Preliminary work up and clinical findings

Primary treatment of clinical N0 (MCC-2)

**PRIMARY TREATMENT AND ADJUVANT RT**

- Prior wide local excision → Radiation therapy
- Clinical N0
- No prior wide local excision → Sentinel lymph node (SLN) biopsy
  - SLN positive → SLN positive → Therapeutic lymph node dissection or radiation therapy
  - SLN negative → Radiation therapy or Consider observation
- Excision
  - Negative margins
- See Adjuvant Chemotherapy and Follow-up (MCC-5)
Primary treatment of clinical N1 (MCC-3)

**PRIMARY TREATMENT AND ADJUVANT RT**

CT chest/abdomen
Other imaging studies as clinically indicated

Positive

CT chest/abdomen
Other imaging studies as clinically indicated

M0

Excision

Therapeutic lymph node dissection + RT

M1

See Treatment of M1 disease (MCC-4)

See Adjuvant Chemotherapy and Follow-up (MCC-5)

Clinical N → FNA

Positive

Open biopsy

Negative

Follow appropriate Clinical N0 pathway (MCC-2)

Negative

(94)

Treatment of M1 Disease (MCC-4)

**TREATMENT**

Clinical M1 → Medical oncology + multidisciplinary consultation

Systemic chemotherapy

± Surgery (as indicated)

± RT (as indicated)

and

Best supportive care

(See NCCN Palliative Care Guideline)

See Follow-up (MCC-5)

(94)
Follow-up and Recurrences

Prognosis and Prognostic factors:

The natural history of MCC is variable. (1, 3, 21, 50, 52, 94, 113, 114) In some patients, localized primary tumors can be indolent and well controlled by local excision alone. (1, 19, 31, 45, 90, 129) Although most patients present with clinically localized disease, MCC is a particularly aggressive cancer with a propensity for locoregional recurrence and early lymph node metastases, giving a poor prognosis despite locally confined disease. (1, 17, 19, 21, 94) The survival rate for patients with MCC and either nodal or systemic disease parallels that of other particularly aggressive cutaneous malignancies, like melanoma. (1, 17, 19, 21, 94, 127)

Significant favorable prognostic factors for overall survival are initial localized disease, extremity site, female sex, age less than 65 years, and the absence of comorbid conditions, even after adjusting for the size of the primary lesion. (19, 22, 97, 113) The presence of nodal disease is the most powerful predictor of survival and distant metastatic disease. In one series, the median survival for patients with and without involved regional nodes was 13 versus 40 months, respectively. (122) The following negative prognostic factors are recognized by the NCCN guidelines for MCC:
The site of the primary lesion has been identified as a potential prognostic indicator. Truncal lesions, especially of the vulva or perianal region, have the worst prognosis. (1, 21, 106, 123-125) However these findings may be related more to “early” versus “late” detection of lesions than to location specific prognosis. Leg lesions are associated with a high incidence of local recurrence. (1, 21, 106, 123-125) This could be secondary to one or more challenges of treatment: the lower extremity commonly has a poor blood supply in older patients, thus limiting the role of wide surgical resection or the lower leg is poorly tolerant of high-dose irradiation. (1, 21, 106, 123-125)

The following is a summary of the adverse prognostic factors implicated in various literature reviews: (1, 17, 19-22, 30-34, 52, 94, 97, 113, 130)

- Nodal disease
- Primary > 2cm
- Tumor Site
- Male Sex
- Age greater than 60
- Positive surgical margins
- Lack of RT in treatment

The only prognostic factor associated with overall survival in the Medina-Franco et al. meta-analysis of multimodality treatment for MCC was stage at initial diagnosis. (30)
Following initial therapy, recurrences can be local, regional or distant. The risk of a local recurrence was 43% in a series of 251 treated at MSKCC. (31) However after a margin-negative excision and re-staging based on pathological nodal staging, recurrence was only 8%. (31) Local recurrence tends to develops within one year of initial therapy. (1, 21, 22, 31, 33, 45, 107, 114) Tai et al. reported in their review of 661 literature based cases, local recurrence in 29%, at a median of four months (range 1 to 96 months). (22) Nodal or distant recurrence each was a component of the recurrence 33% of cases. (22) Patients with an initial nodal recurrence had a significantly higher chance of developing subsequent distant metastases than those without a nodal recurrence. (22)

The impact of a local recurrence on survival is controversial. (1, 21, 22, 31, 33, 34, 45, 114) Tai et al. reported a median overall survival of 27 months (range 1 to 216 months) among patients who recurred and had salvage treatments. (22) Combined modality therapy (surgery, RT, chemotherapy) is associated with the best salvage potential. (1, 21, 22, 31, 125)

The median time to develop clinically detectable nodal recurrence after resection of the primary lesion is seven to eight months. Among patients with nodal involvement, either at presentation or at recurrence, 11-66% die of their disease within five years. (1, 21, 22, 31, 33, 34, 45) As with local recurrences, multimodality approaches are associated with the best outcomes following a nodal recurrence. (1, 21, 22, 31, 125)

Metastatic/systemic disease is associated with an especially bleak prognosis. (1, 21, 22, 94) The mean time to develop systemic metastases is 18 months; almost 50% of patients followed for 24 months will develop systemic recurrence and 65-75% will die of their disease. (1, 21, 22, 42, 43, 94, 107) Once diagnosed with metastatic MCC, the median survival is estimated at only 9 months. (1, 21, 22, 35, 94) All patients should be given the option of palliative care. (1, 21, 22, 35, 94)

MCC is a particularly difficult cancer to study. For the clinician, MCC provides and enormous challenge due to its highly aggressive nature. The best outcomes stem from a multidisciplinary approach to patient care with input from surgical oncology, radiation oncology, medical oncology, and pathology.
PURPOSE:

Merkel cell carcinoma (MCC) is a rare of skin cancer and is often described as the most aggressive cutaneous malignancy. Its high propensity for dermal-lymphatic invasion, local recurrence, and rapid lymphatic and distant metastasis poses a significant treatment challenge to clinicians. Combining its highly aggressive nature with its low incidence, merkel cell carcinoma is a particularly difficult cancer to study.

There is no consensus with regard to staging system for MCC. (31, 49, 50) There are two major staging systems that have been used in the literature: the Memorial Sloan Kettering Cancer Center (MSKCC) MCC staging criteria and the American Joint Committee on Cancer TNM staging criteria for non-melanoma skin cancer. Neither staging system, the MSKCC nor the AJCC TNM, has been independently validated for the use in staging MCC. Such a validation would be helpful in establishing consensus in staging such an aggressive cancer.

The primary purpose of this study is to validate and compare the Memorial Sloan Kettering Cancer Center (MSKCC) staging criteria for Merkel cell carcinoma (MCC) with the American Joint Committee on Cancer (AJCC) TNM staging criteria for non-melanoma skin cancer utilizing the Surveillance, Epidemiology, and End Results (SEER) database.

Because of the aggressive nature of MCC with high local and regional recurrence following surgery, postoperative radiation therapy is often used to maximize local and regional control. However, the role of radiation therapy (RT) remains a highly contested issue, with NCCN treatment guidelines based on limited body of evidence of retrospective observational studies. (1, 3, 21-23, 31, 34, 41, 44, 49-53, 90, 106, 108, 111-118) In response to a letter of correspondence, Allen et al. said “A randomized study designed to demonstrate a reduction in local or regional recurrence from 12% to 6% with the addition of RT would require 281 patients per arm (one-sided $P \_ .05$, power 0.8), a study that will clearly never be undertaken.” (117)

Agreeing that such a study would be nearly impossible as a randomized prospective endeavor, we sought to explore the role of RT with a retrospective cohort study design using a similar sized population. Thus, the secondary purpose of this study is to evaluate the role of RT in the curative (non-metastatic) cohort, using both MSKCC and AJCC TNM staging criteria, within the SEER dataset.
METHODS:

HIC approval of this research project and exemption from HIC review were conferred for HIC protocol number 0602001098 under federal regulation 45 CFR 46.101(b)(4). This part of the federal regulations covers research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to subjects. It is also necessary that the information obtained not be such that if disclosed outside the research, it could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects’ financial standing, employability, or reputation. As the HIC chair felt this study met these requirements, exemption and approval were conferred.

Data Source:
The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) began in 1973 and represents 26% of the US population. Currently SEER coverage includes 23 percent of African Americans, 40 percent of Hispanics, 42 percent of American Indians and Alaska Natives, 53 percent of Asians, and 70 percent of Hawaiian/Pacific Islanders. Subjects with cancer registered by SEER are uniquely identified and followed annually to determine their vital status for as long as he or she lives in a SEER area.(18)

The SEER tumor registries used in this analysis include(18):

From 1973-2002:
- Connecticut
- Iowa
- New Mexico
- Utah
- Hawaii
- Detroit
- San Francisco-Oakland

From 1974-2002:
- Atlanta
- Seattle-Puget Sound

From 1978-2002:
- 10 predominantly black rural counties in Georgia
From 1980-2002:
- Native Americans living in Arizona

- New Orleans

- New Jersey

From 1973-1989:
- Puerto Rico

From 1992-2002:
- Los Angeles County
- 4 counties in San Jose-Monterey area

From 2001-2002:
- Kentucky
- The rest of California

Additionally, SEER has been collecting information from an independent NCI tumor registry in Alaska. Data on incident malignancies and follow-up is current through 2002. (18)

Inclusion Criteria:
1. Date of diagnosis range 1988-2002
2. Cases of merkel cell carcinoma, ICD-O-3 histology code 8247/3
3. Microscopically-confirmed pathological diagnosis
4. Primary anatomic site: Skin

Although the SEER dataset registered cases as far back as the 1970’s, our analysis only evaluated data between the years of 1988 and 2002 for two major reasons: microscopic-confirmation of diagnosis was not available within the SEER dataset before 1988 and extent of disease codes were revised in 1988. (18)

One thousand six hundred and ninety seven (1697) cases of malignant merkel cell carcinoma were identified form the entire 1973-2002 SEER dataset. One thousand five hundred and sixty (1560) cases of malignant merkel cell carcinoma were identified within the SEER dataset from 1988-2002. Of these, only
microscopically-confirmed cases were included (n = 1556). Microscopic-confirmation was not available within the SEER dataset before 1988. Histology was coded according to International Classification of Disease-Oncology-Third Edition (ICD-O-3) codes (8247/3). Cases of benign or in situ MCC were beyond the scope of this analysis. Specific histological subgroups of MCC were not coded within the SEER dataset. Specific primary cutaneous site as coded by ICD-O-3 (C44.0 to C44.9) were grouped into anatomic site regions under convention of prior analyses (17, 19): Upper limb (reference category), Head, Trunk, Lower Limb, and Other. (17-20, 131, 132)

Exclusion Criteria:

1. Subjects who did not receive surgery as primary treatment for non-metastatic disease (n = 72)
2. Subjects who died within four months of diagnosis (n = 170)
3. Subjects who were not able to be staged by respective staging criteria
   a. MSKCC (n = 995)
   b. AJCC TNM (n = 863)
   c. Both (n = 995)

All subjects who did not receive surgery were excluded from the study, except for those who were found to have metastasis at initial diagnosis. The reason for this exclusion is that surgery is widely accepted as the definitive primary treatment for curative intent and according to the National Comprehensive Cancer Network guidelines the first line treatment for any non-metastatic disease. Subjects, who were found to have metastatic disease at initial diagnosis, may not have been offered or recommended surgery as a treatment option. For metastatic disease, the treatment recommendations according to the National Comprehensive Cancer Network, are to involve Medical Oncology with a multidisciplinary approach to palliative care, +/- systemic chemotherapy, +/- surgery (as indicated), and +/- radiation therapy (as indicated).

Cases of individual subjects who died within 4 months of diagnosis were excluded from this analysis for the following two reasons. According to the 1988 SEER Extent of Disease coding manual, the information pertaining to extent of disease was reported to SEER within a 4 month period following the initial diagnosis. Therefore if a subject dies within that four month period their SEER information may not be complete. And the second reason is that those who die within four months of diagnosis may represent a skewed population and not representative of the disease. They represent those who probably could not have completed a course of radiation therapy, or may have died from complications after surgery. This population could potentially skew the analysis of radiation therapy, biasing the data to appear more effective than treatments without radiation. By removing this population from the analysis, this potential bias is minimized.
The final population size that met all inclusion and exclusion criteria was 561. The subpopulation of this cohort of cases who have non-metastatic (no stage IV) disease is the curative cohort \( (n = 478) \). The role of RT will be evaluated in this curative cohort.

**The MSKCC staging criteria:** (31)

Primary tumor (T)

- T1: Tumor \( \leq 2 \) cm in greatest dimension
- T2: Tumor \( >2 \) cm in greatest dimension

Regional lymph nodes (N)

- N0: Negative regional lymph nodes
- N1: Positive regional lymph nodes

Distant metastasis (M)

- M0: No evidence of distant metastatic disease
- M1: Distant metastatic disease present

**MSKCC Stage groups**

**Stage I**

- T1, N0, M0

**Stage II**

- T2, N0, M0

**Stage III**

- Any T, N1, M0

**Stage IV**

- Any T, any N, M1
The AJCC TNM staging criteria for non-melanoma skin cancer: (99)

Primary tumor (T)
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor \( \leq 2 \) cm in greatest dimension
- T2: Tumor >2 cm but \( \leq 5 \) cm in greatest dimension
- T3: Tumor >5 cm in greatest dimension
- T4: Tumor invades deep extradermal structures (e.g., cartilage, skeletal muscle, or bone)

Regional lymph nodes (N)
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

Distant metastasis (M)
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC stage groupings

Stage 0
- Tis, N0, M0

Stage I
- T1, N0, M0

Stage II
- T2, N0, M0
- T3, N0, M0

Stage III
- T4, N0, M0
- Any T, N1, M0

Stage IV
- Any T, any N, M1
Constructing the Staging Cohorts:

In order to fit SEER cases into specific MSKCC or AJCC TNM stages, data pertaining to size, lymph node status, extension, and metastasis had to be extracted from the SEER dataset. This information is encoded within the 10 digit SEER Extent of Disease code which was revised in 1988. Below are the revised SEER codes from the SEER Extent of Disease Coding Manual (Third Edition) (18):

| C44.0 | Skin of lip, NOS (excl. vermillion surface C00_.) |
| C44.1 | Eyelid |
| C44.2 | External ear |
| C44.3 | Skin of other and unspecified parts of face |
| C44.4 | Skin of scalp and neck |
| C44.5 | Skin of trunk |
| C44.6 | Skin of upper limb and shoulder |
| C44.7 | Skin of lower limb and hip |
| C44.8 | Overlapping lesion of skin |
| C44.9 | Skin, NOS |

See also Note 3.

<-> Laterality must be coded for this site. For codes C44.3 and C44.5, if the tumor is midline (e.g., chin), code as 0, midline, in the laterality field.

**SIZE OF PRIMARY TUMOR**
(from pathology report; operative report; physical examination—in priority order)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>000</td>
<td>No mass; no tumor found</td>
</tr>
<tr>
<td>001</td>
<td>Microscopic focus or foci only</td>
</tr>
<tr>
<td>002</td>
<td>&lt;= 2 mm</td>
</tr>
<tr>
<td>003</td>
<td>3 &lt;= cm &lt;= 0.2</td>
</tr>
<tr>
<td>...</td>
<td></td>
</tr>
<tr>
<td>009</td>
<td>9 &lt;= cm &lt;= 0.9</td>
</tr>
<tr>
<td>010</td>
<td>10 &lt;= cm &lt;= 1.0</td>
</tr>
<tr>
<td>...</td>
<td></td>
</tr>
<tr>
<td>099</td>
<td>99 &lt;= cm &lt;= 9.9</td>
</tr>
<tr>
<td>100</td>
<td>100 &lt;= cm &lt;= 10.0</td>
</tr>
<tr>
<td>...</td>
<td></td>
</tr>
<tr>
<td>990</td>
<td>990 &lt;= cm &lt;= 99.0</td>
</tr>
<tr>
<td>999</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

Note 1: In the case of multiple simultaneous tumors, code tumor with greatest extension.

Note 2: Skin ulceration does not alter the Extent of Disease classification.

Note 3: Skin of genital sites is not included in this scheme. These sites are skin of vulva (C51.9-C51.2, C51.8-C51.9), skin of penis (C60.0-C60.1, C60.8, C60.9) and skin of scrotum (C63.2).
From the 1988-2002 SEER dataset, 561 cases were able to be staged with the MSKCC staging criteria. Six hundred and ninety six (696) cases fit the AJCC TNM staging criteria. There were 561 cases that could satisfy both criteria. Of this cohort, there were 478 cases of locoregional disease and 83 cases of metastatic disease.

**Covariates:**

After careful review of the literature, the following prognostic indicators were identified and included in the statistical model and analysis: age, primary anatomical site. As the role of radiation treatment within the curative population remains controversial mainly because of size limited analyses, external beam radiation therapy is included in this analysis. This study represents the largest population within which the role of radiation is examined. (17, 19, 20, 33, 131, 132)
Outcomes:

The primary outcome was overall survival and the secondary outcome was adjusted risk of death, proportional hazards ratios. SEER participants are followed annually to determine vital status. Date of death is collected at the local SEER registry and coded, matching cases to state vital statistics. The follow-up time was calculated from the month and year of the initial date of diagnosis. Overall survival (OS) was calculated with the Kaplan-Meier method, using the “proc lifetest” program in SAS version 9.1, stratified by stage. Age and RT adjusted mortality hazard ratios, were calculated with the Cox proportional hazard linear regression method, using the “proc phreg” program of SAS version 9.1.

Statistical Analysis:

Adjusted Cox proportional hazards linear regression model was constructed for the each staging system cohort. The model included the covariates: age, stage, primary anatomical site, and +/- external beam radiation therapy. The following covariates, lacking clear linear relationships with mortality, were entered as categorical (dummy) variables: stage and primary anatomic site. Interaction variables were constructed to look for interaction between [radiation treatment and stage] and [radiation treatment and age]. (133)

The adjusted Cox proportional hazards model was optimized to ensure an adequate fit of the final model. Groups were ordered according to mortality hazards ratios. Groups were consolidated if they did not contribute, with statistical significance, to clinical mortality differences of the overall model. The likelihood ratio $\chi^2$'s of the initial and consolidated models were compared to ensure an adequate fit to the final model. (133)

As this study used preexisting data without identifiers, the Yale University School of Medicine, Human Investigations Committee (HIC) granted an exemption from review (HIC protocol number: 0602001098). To protect patient identity and in accordance with SEER guidelines for presentation of public-use dataset, cell counts $\leq 5$ were suppressed in all text and tables. (18, 133)
RESULTS

Demographics of the Staging Cohort:

The staging cohort comprised of 561 patients with more men than women (ratio 1.6:1) and whites as the largest representative race (ratio to next largest race 20.1:1). The median follow-up time was 2.2 years with a range of 0.4-14.3. The median age was 75 years with a range of 22-98. The most common cutaneous primary site was head and neck (39%), followed by upper extremity (24%). There was an increasing incidence of MCC as represented by increased diagnoses from 1988 to 2002 in five year blocks, which is consistent with recent findings by Hodgson. (20) The demographic of the staging cohort (see table 1) is consistent with prior epidemiological studies. (17, 19, 20)

Baseline Demographics (Table 1)

<table>
<thead>
<tr>
<th>Size of Staging Cohort</th>
<th>n = 561 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Median Age</td>
<td>75 years</td>
</tr>
<tr>
<td>• Mean Age</td>
<td>73 years</td>
</tr>
<tr>
<td>• Standard Deviation</td>
<td>12 years</td>
</tr>
<tr>
<td>• Age Range</td>
<td>22-98 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Male</td>
<td>342</td>
<td>61%</td>
</tr>
<tr>
<td>• Female</td>
<td>219</td>
<td>39%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year of Diagnosis:</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1988-1992</td>
<td>126</td>
<td>23%</td>
</tr>
<tr>
<td>• 1993-1997</td>
<td>191</td>
<td>34%</td>
</tr>
<tr>
<td>• 1998-2002</td>
<td>299</td>
<td>53%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race:*</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• White</td>
<td>502</td>
<td>89%</td>
</tr>
<tr>
<td>• Asian/Pacific Islander</td>
<td>25</td>
<td>4%</td>
</tr>
<tr>
<td>• Hispanic</td>
<td>23</td>
<td>4%</td>
</tr>
<tr>
<td>• Black</td>
<td>6</td>
<td>1%</td>
</tr>
<tr>
<td>• Other</td>
<td>11</td>
<td>2%</td>
</tr>
</tbody>
</table>
Primary Anatomic Site:

- Head and Neck 218 39%
- Upper Extremity 133 24%
- Lower Extremity 94 17%
- Trunk 82 15%
- Other 34 5%

* in accordance with SEER guidelines to protect patient confidentiality, cell sized smaller than 5 are not reported.

The population comprised largely of the elderly, with over 75% of the cohort over the age of 60 years old. This is consistent with prior epidemiological studies as MCC has been found to have a predilection for the elderly. (17, 19, 20) (See figure 1)

This population distribution graphically demonstrated the skew of the staging cohort to the elderly consistent with prior epidemiological studies. (Figure 1)
The following two tables summarize the characteristics of the various criteria that were used to stage the SEER population to the two staging systems.

### Size Summary Statistics (Table 2)

<table>
<thead>
<tr>
<th>Size</th>
<th>n</th>
<th>Percentage</th>
<th>Mean (cm)</th>
<th>Standard Deviation</th>
<th>Range (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2cm</td>
<td>272</td>
<td>49%</td>
<td>1.22</td>
<td>0.55</td>
<td>0 - 2</td>
</tr>
<tr>
<td>&gt; 2cm</td>
<td>175</td>
<td>31%</td>
<td>4.79</td>
<td>5.19</td>
<td>2.1 – 57</td>
</tr>
<tr>
<td>Not sized</td>
<td>114</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### By MSKCC Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Percentage</th>
<th>Mean (cm)</th>
<th>Standard Deviation</th>
<th>Range (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>224</td>
<td>40%</td>
<td>1.22</td>
<td>0.54</td>
<td>0.2 - 2</td>
</tr>
<tr>
<td>Stage II</td>
<td>114</td>
<td>20%</td>
<td>4.15</td>
<td>3.36</td>
<td>2.1 - 30</td>
</tr>
<tr>
<td>Stage III*</td>
<td>140</td>
<td>25%</td>
<td>2.75</td>
<td>2.42</td>
<td>0 - 14</td>
</tr>
<tr>
<td>Stage IV*</td>
<td>83</td>
<td>15%</td>
<td>6.03</td>
<td>9.36</td>
<td>0 - 57</td>
</tr>
</tbody>
</table>

#### By AJCC TMN Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Percentage</th>
<th>Mean (cm)</th>
<th>Standard Deviation</th>
<th>Range (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>223</td>
<td>40%</td>
<td>1.22</td>
<td>0.54</td>
<td>0.2 - 2</td>
</tr>
<tr>
<td>Stage II</td>
<td>107</td>
<td>19%</td>
<td>4.17</td>
<td>3.43</td>
<td>2.1 - 30</td>
</tr>
<tr>
<td>Stage III*</td>
<td>148</td>
<td>26%</td>
<td>2.83</td>
<td>2.39</td>
<td>0 - 14</td>
</tr>
<tr>
<td>Stage IV*</td>
<td>83</td>
<td>15%</td>
<td>6.03</td>
<td>9.36</td>
<td>0 - 57</td>
</tr>
</tbody>
</table>

#### Local/regional Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>Percentage</th>
<th>Mean (cm)</th>
<th>Standard Deviation</th>
<th>Range (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td>246</td>
<td>51%</td>
<td>2.39</td>
<td>2.76</td>
<td>0 - 30</td>
</tr>
<tr>
<td>RT</td>
<td>232</td>
<td>49%</td>
<td>2.21</td>
<td>2.00</td>
<td>0 - 17</td>
</tr>
</tbody>
</table>

#### Lymph Node Status*

<table>
<thead>
<tr>
<th>Status</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative*</td>
<td>355</td>
<td>63%</td>
</tr>
<tr>
<td>Positive*</td>
<td>163</td>
<td>29%</td>
</tr>
<tr>
<td>Metastatic*</td>
<td>16</td>
<td>3%</td>
</tr>
<tr>
<td>Unknown*</td>
<td>26</td>
<td>5%</td>
</tr>
</tbody>
</table>

* many not sized
Of the entire staging cohort the median survival was 4.42 years with a range of 0.42-14.33 and 50% received post-operative RT. As all patients who either died or were lost to follow up within four months of date of diagnosis, the first death available for use in the analysis was at five months (or 0.42 years). After staging the cohort by MSKCC criteria, there were 224 patients in Stage I (40%), 114 patients in Stage II (20%), 140 patients in Stage III (25%), and 83 patients in Stage IV (15%). After staging the cohort by AJCC TNM criteria, there were 223 patients in Stage I (40%), 107 patients in Stage II (19%), 148 patients in Stage III (26%), and 83 patients in Stage IV (15%). The locoregional disease cohort (patients without metastasis at initial diagnosis) represents those patients with whom treatment was intended to be curative. Of the locoregional disease cohort staging cohort the median survival was 4.74 years with a range of 0.42-14.33 and 51% received post-operative RT. See table 4 for summary survival statistics by MSKCC and AJCC TNM stage.

### Survival Summary Statistics (Table 3)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Percentage</th>
<th>Median Survival (yrs)</th>
<th>Mean Survival (yrs)</th>
<th>Standard Error</th>
<th>Range (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>561</td>
<td></td>
<td>4.42</td>
<td>5.36</td>
<td>0.22</td>
<td>0.42-14.33</td>
</tr>
<tr>
<td><strong>By MSKCC Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Stage I</td>
<td>224</td>
<td>40%</td>
<td>6.08</td>
<td>6.48</td>
<td>0.35</td>
<td>0.42-14.33</td>
</tr>
<tr>
<td>• Stage II</td>
<td>114</td>
<td>20%</td>
<td>4.33</td>
<td>4.38</td>
<td>0.30</td>
<td>0.42-11.58</td>
</tr>
<tr>
<td>• Stage III</td>
<td>140</td>
<td>25%</td>
<td>2.91</td>
<td>4.67</td>
<td>0.42</td>
<td>0.42-11.33</td>
</tr>
<tr>
<td>• Stage IV</td>
<td>83</td>
<td>15%</td>
<td>1.50</td>
<td>2.73</td>
<td>0.28</td>
<td>0.42-12.25</td>
</tr>
<tr>
<td><strong>By AJCC TNM Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Stage I</td>
<td>223</td>
<td>40%</td>
<td>6.17</td>
<td>6.51</td>
<td>0.35</td>
<td>0.42-14.33</td>
</tr>
<tr>
<td>• Stage II</td>
<td>107</td>
<td>19%</td>
<td>4.50</td>
<td>4.45</td>
<td>0.32</td>
<td>0.42-11.58</td>
</tr>
<tr>
<td>• Stage III</td>
<td>148</td>
<td>26%</td>
<td>2.92</td>
<td>4.53</td>
<td>0.39</td>
<td>0.42-11.33</td>
</tr>
<tr>
<td>• Stage IV</td>
<td>83</td>
<td>15%</td>
<td>1.50</td>
<td>2.73</td>
<td>0.28</td>
<td>0.42-12.25</td>
</tr>
<tr>
<td><strong>Whole Cohort</strong></td>
<td>561</td>
<td></td>
<td>4.42</td>
<td>5.36</td>
<td>0.22</td>
<td>0.42-14.33</td>
</tr>
<tr>
<td>• No RT</td>
<td>280</td>
<td>50%</td>
<td>3.58</td>
<td>5.09</td>
<td>0.30</td>
<td>0.42-13.00</td>
</tr>
<tr>
<td>• RT</td>
<td>281</td>
<td>50%</td>
<td>4.50</td>
<td>5.63</td>
<td>0.31</td>
<td>0.42-14.33</td>
</tr>
<tr>
<td><strong>Local/regional Disease</strong></td>
<td>478</td>
<td></td>
<td>4.75</td>
<td>5.64</td>
<td>0.23</td>
<td>0.42-14.33</td>
</tr>
<tr>
<td>• No RT</td>
<td>246</td>
<td>51%</td>
<td>4.75</td>
<td>5.34</td>
<td>0.32</td>
<td>0.42-13.00</td>
</tr>
<tr>
<td>• RT</td>
<td>232</td>
<td>49%</td>
<td>4.67</td>
<td>5.93</td>
<td>0.34</td>
<td>0.42-14.33</td>
</tr>
</tbody>
</table>
MSKCC Staging Criteria as a Valid Staging System for MCC:

In the survival analysis of MCC by MSKCC stage, all stages demonstrated appropriate relationships to each other with stage having a better overall survival than the subsequent stage: Stage I > Stage II > Stage III > Stage IV. In the Kaplan-Meier survival plot below, Stage I is depicted in black; Stage II in red; Stage III in green; and Stage IV in blue.

The five-year overall survival was 59.3% for stage I, 44.6% for stage II, 32.5% for stage III, and 28.3% for stage IV. This data is consistent with overall survival statistics reported in the literature.
A Cox proportional hazards regression model was constructed for the MSKCC staged population using the following variables: age, RT status, MSKCC stage, and site of primary. When compared with stage I, the age and RT adjusted mortality hazard ratio (HR) was 1.44 (95% CI 1.03-2.00) for stage II, 2.14 (95% CI 1.57-2.93) for stage III, and 2.61 (95% CI 1.85-3.67) for stage IV. (See table 4)

**Age and RT Adjusted Cox Proportional Hazards Mortality Hazard Ratio by MSKCC stage (Table 4)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR</th>
<th>95% CI</th>
<th>P =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>1.00</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Stage II</td>
<td>1.44</td>
<td>1.03-2.00</td>
<td>0.0335</td>
</tr>
<tr>
<td>Stage III</td>
<td>2.14</td>
<td>1.57-2.93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2.61</td>
<td>1.85-3.67</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Bold Items were statistically different than reference values.

That each stage’s mortality HR is both greater than 1.00 and increasing with each subsequent stage, supports the prior claim that the MSKCC criteria appropriately risk stratifies this SEER cohort. Furthermore that the 95% confidence intervals do not cross 1.00 lends statistical significance with P < 0.05 for all stages in comparison with stage I. Thus, the cohort staged by the MSKCC staging criteria both appropriately and significantly risk stratified this SEER cohort.
AJCC TNM Staging Criteria as a Valid Staging System for MCC:

In the survival analysis of MCC by AJCC TNM stage, all stages demonstrated appropriate relationships to each other with stage having a better overall survival than the subsequent stage: Stage I > Stage II > Stage III > Stage IV. In the Kaplan-Meier survival plot below, Stage I is depicted in black; Stage II in red; Stage III in green; and Stage IV in blue.

The five-year overall survival was 59.7% for stage I, 47.1% for stage II, 31.0% for stage III, and 28.3% for stage IV. This data is consistent with overall survival statistics reported in the literature as well as comparable to the five-year overall survival data from the MSKCC staged cohort.
A Cox proportional hazards regression model was constructed for the AJCC TNM staged population using the following variables: age, RT status, AJCC TNM stage, and site of primary. When compared with stage I, the age and RT adjusted mortality HR was 1.41 (95% CI 0.99-1.99) for stage II, 2.13 (95% CI 1.57-2.89) for stage III, and 2.62 (95% CI 1.86-3.69) for stage IV. (See table 5)

**Age and RT Adjusted Cox Proportional hazards ratio of AJCC TNM Stages (Table 5)**

<table>
<thead>
<tr>
<th>AJCC TNM Stages (n=561)</th>
<th>Stage</th>
<th>HR</th>
<th>95% CI</th>
<th>P =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>1.00</td>
<td>Reference</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>1.41*</td>
<td>0.99-1.99*</td>
<td>0.0525</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>2.13</td>
<td>1.57-2.89</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>2.62</td>
<td>1.86-3.69</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* AJCC TNM Stage II was not statistically different from AJCC TNM Stage I (p = 0.0525)

Bold items were statistically different than reference values.

That each stage’s mortality HR is both greater than 1.00 and increasing with each subsequent stage, supports the prior claim that the AJCC TNM criteria appropriately risk stratifies this SEER cohort. However that the 95% confidence intervals cross 1.00 for stage II, implies that there is no statistical difference between AJCC TNM stages I and II with respect to survival. Although there is not statistical significant difference between stages I and II, this lack of statistical significance is small enough that a larger population analysis might show a statistically significant difference between stage I and II. That the 95% confidence intervals do not cross 1.00 for stages III and IV means that they are statistically different in comparison with stage I, with P < 0.05.

Therefore, although the cohort staged by the AJCC TNM staging criteria appropriately risk stratified this SEER cohort, it was not successful in significantly risk stratified this SEER cohort.
Comparison of Staging Systems:

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Five-year overall survival</th>
<th>n</th>
<th>Five-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>224</td>
<td>59.3%</td>
<td>223</td>
<td>59.7%</td>
</tr>
<tr>
<td>Stage II</td>
<td>114</td>
<td>44.6%</td>
<td>107</td>
<td>47.1%</td>
</tr>
<tr>
<td>Stage III</td>
<td>140</td>
<td>32.5%</td>
<td>148</td>
<td>31.0%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>83</td>
<td>28.3%</td>
<td>83</td>
<td>28.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR</th>
<th>95% CI</th>
<th>P =</th>
<th>HR</th>
<th>95% CI</th>
<th>P =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>1.44</td>
<td>1.03-2.00</td>
<td>0.0335</td>
<td>1.41*</td>
<td>0.99-1.99*</td>
<td>0.0525</td>
</tr>
<tr>
<td>Stage III</td>
<td>2.14</td>
<td>1.57-2.93</td>
<td>&lt;0.0001</td>
<td>2.13</td>
<td>1.57-2.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2.61</td>
<td>1.85-3.67</td>
<td>&lt;0.0001</td>
<td>2.62</td>
<td>1.86-3.69</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* AJCC TNM Stage II was not statistically different from AJCC TNM Stage I (p = 0.0525), though it was trending toward statistic significance (P < 0.065).

Bold Items were statistically different than reference values.

Close comparison of these two staging systems demonstrates a subtle but statistically significant difference in the way these staging criteria risk stratify the SEER cohort. Both staging systems appropriately risk stratify this SEER cohort. However, the data demonstrate a clear statistical difference for only the MSKCC staged population. As such, the MSKCC staged population is the only staging system to significantly risk stratify the SEER cohort.
The Role of Radiation Therapy in Population with Curative Intent:

The role of RT was analyzed by looking at the mortality hazard ratios of postoperative radiation therapy status in the Cox Proportional Hazard model of the SEER cohort adjusted for age and stage. The following is the summary statistical data of the curative cohort by RT status. (See table 6)

<table>
<thead>
<tr>
<th>RT Status Summary Statistics (Table 6)</th>
<th>n =</th>
<th>Percentage</th>
<th>RT Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2cm</td>
<td>272</td>
<td>49%</td>
<td>143 (53%)</td>
</tr>
<tr>
<td>&gt; 2cm</td>
<td>175</td>
<td>31%</td>
<td>89 (51%)</td>
</tr>
<tr>
<td>Not sized</td>
<td>114</td>
<td>20%</td>
<td>48 (42%)</td>
</tr>
<tr>
<td>Lymph Node Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>355</td>
<td>63%</td>
<td>200 (56%)</td>
</tr>
<tr>
<td>Positive</td>
<td>163</td>
<td>29%</td>
<td>61 (37%)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>16</td>
<td>3%</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>26</td>
<td>5%</td>
<td>10 (38%)</td>
</tr>
<tr>
<td>By MSKCC Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>224</td>
<td>40%</td>
<td>126 (56%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>114</td>
<td>20%</td>
<td>67 (59%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>140</td>
<td>25%</td>
<td>53 (38%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>83</td>
<td>15%</td>
<td>34 (41%)</td>
</tr>
<tr>
<td>By AJCC TMN Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>223</td>
<td>40%</td>
<td>125 (56%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>107</td>
<td>19%</td>
<td>64 (60%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>148</td>
<td>26%</td>
<td>57 (39%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>83</td>
<td>15%</td>
<td>34 (41%)</td>
</tr>
</tbody>
</table>
Among 478 patients with local or regional disease, 49% received radiation. The following table represents the summary survival statistics of the curative cohort by RT status. (See table 7)

<table>
<thead>
<tr>
<th>Local/regional Disease</th>
<th>n</th>
<th>Percentage</th>
<th>Median Survival (yrs)</th>
<th>Mean Survival (yrs)</th>
<th>Standard Error</th>
<th>Range (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td>246</td>
<td>51%</td>
<td>4.75</td>
<td>5.34</td>
<td>0.32</td>
<td>0.42-13.00</td>
</tr>
<tr>
<td>RT</td>
<td>232</td>
<td>49%</td>
<td>4.67</td>
<td>5.93</td>
<td>0.34</td>
<td>0.42-14.33</td>
</tr>
</tbody>
</table>

The previous graph is a plot of the Kaplan-Meier survival curves stratified by RT status. Patients who did not receive RT are represented in black; and those who received RT are represented in red. Notice that the patients who received RT tended to live longer, though this difference was not a statistically significant.
After adjusting for MSKCC stage and age, radiation did not have a statistically significant mortality HR, HR 0.83 (95% CI 0.63-1.09). Similarly, in the AJCC TNM staged population radiation did not have a statistically significant mortality HR, HR 0.83 (95% CI 0.63-1.09). (See table 8)

<table>
<thead>
<tr>
<th>Stage</th>
<th>MSKCC Stages (n=478)</th>
<th>AJCC TNM Stages (n=478)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Stage I</td>
<td>1.01</td>
<td>0.65-1.56</td>
</tr>
<tr>
<td>Stage II</td>
<td>0.82</td>
<td>0.46-1.45</td>
</tr>
<tr>
<td>Stage III</td>
<td>0.73</td>
<td>0.46-1.15</td>
</tr>
</tbody>
</table>

None were found to be significant within each stage.

A Hazard Ratio (HR) below 1.00 signifies improved survival. With HR trending downward with stage, the role of RT seems to be more beneficial to survival for the advanced staged malignancies than the early staged, though not significantly. As the HR and P values are both decreasing as stage is increasing, a trend towards significance of is noted as well as an increasing benefit from the RT as the HR decreases.

**Interaction variables:**

**MSKCC**

In the model without an interaction term, radiation is not significantly correlated with survival. The interaction between radiation and stage is not significant (P=0.69), indicating that the lack of correlation between radiation and stage is consistent across all stages.

**AJCC TNM**

In the model without an interaction term, radiation is not significantly correlated with survival. The interaction between radiation and stage is not significant (P=0.42), indicating that the lack of correlation between radiation and stage is consistent across all stages.
DISCUSSION:

Although MCC was initially described as an indolent tumor with low malignant potential, current evidence implicates MCC as one of the most aggressive cutaneous malignancies. Although there have been an increasing number of studies that have further characterized MCC, there remains much about this cancer that is unknown. By far the greatest challenge to research has been the rarity of this particular malignancy. It is the decreased incidence that limits the body of evidence to retrospective, observational, single institution studies and meta-analytical reviews of multiple studies. This study represents the largest single source cohort analysis of MCC to date. The only two other studies that have over 500 cases are literature review based. The demographic data from this study is consistent with that of prior studies.

There is no consensus with regard to staging system for MCC. Neither staging system, the MSKCC nor the AJCC TNM, has been independently validated for the use in staging MCC. The results of this study demonstrate that the MSKCC staging criteria both appropriately and significantly risk stratifies the SEER cohort for all stages. This data validates the continued use of this staging system for appropriate risk stratification of patients with MCC.

The data did not show significant risk stratification for the AJCC TNM staging criteria. However a subsequent study with a larger population may demonstrate a statistically significant difference between AJCC TNM stages I and II, as the P = 0.0525 approached statistical significance. Although the risk stratification is appropriate and approaches statistical significance, this data when compared to the data from the MSKCC staged cohort, suggest that the MSKCC staging criteria do a better job of risk stratifying.

MCC remains an enormous challenge for the clinician because these tumors have a propensity for local recurrence, nodal involvement and distant spread. The best outcomes stem from a multidisciplinary approach to patient care with input from surgical oncology, radiation oncology, medical oncology, and pathology. According to the results of this study, radiation therapy was not shown to confer a survival advantage to the curative cohort regardless of stage or staging system.

The SEER database contains a wealth of information and can be a powerful resource for studying many cancers, especially ones of profound rarity like merkel cell carcinoma. However, there are several significant limitations of the SEER dataset, which are particularly challenging for outcomes analyses based on treatment. Overall survival statistics are the most reliably reported outcome that can be analyzed through SEER. Cause specific survival, although very important in outcomes analysis, is not reliably reported for SEER, especially for a rare cancer like MCC. Such an analysis would depend on correct reporting of actual cause of death. For a poorly understood aggressive cancer like merkel cell carcinoma, the data is far less reliable. Additionally, three important factors are not reported within the SEER database: chemotherapy, margin status, and disease
progression (i.e. local, regional, or distant metastatic recurrence). Although the role of chemotherapy is unclear for MCC, some preliminary studies have reported benefit. (123-125) Margin status for any cancer whose definitive primary treatment is surgery with wide surgical margins, would play an important role in any outcomes analysis. In particular the role of radiation therapy is believed to decrease the risk of local and regional recurrence.

Radiation may play a significant role in local/regional control, though this study would not be able to address that question. As SEER does not report margin status, chemotherapy, or local/regional recurrence, the role of radiation therapy could not be completely assessed. Given the limitations of the SEER database the role of radiation for local/regional control and cause specific survival would have to be more thoroughly examined by another study. Only a large meta-analysis like those done by Tai et al and Medina-Franco et al or a single institution like MSKCC with enough cases of MCC could address a more thorough evaluation of the complete role of radiation therapy.

Additionally this study and future studies could be improved by examining the role of depth of extension as a prognostic factor. Considering that MCC shares the highly aggressive qualities as melanoma, depth may have a significant prognostic value. Given MCC’s predilection for the elderly, perhaps including medicare data on the patients that qualify, may improve scope of this project.
CONCLUSION:

MCC is a particularly rare form of skin cancer. Derived from neuroendocrine origin, MCC has been described as the most aggressive form of cutaneous malignancy. MCC appears to have a predilection for the elderly and a propensity for dermal-lymphatic invasion along with rapid nodal and hematogenous spread. The tumor has been shown to share many similarities with small-cell carcinoma of the lung, including treatment options and metastatic potential. Although treatment regimes often include combined modality therapy, early detection and complete surgical resection remain the foundation of the best treatment outcomes.

Unfortunately, MCC is a relatively poorly understood cancer. Current management tends to be based on institutional experience and convention, with limited literature to support specific treatments. The majority of literature are single institution, retrospective, observational studies with populations significantly low enough to challenge most conclusions. By far the greatest challenge to research contributing to the relatively limited fund of knowledge that exists in the current literature has been the rarity of this particular malignancy. The very low incidence of MCC limits the body of evidence to retrospective, observational, single institution studies and meta-analytical reviews of multiple studies. This study represents the largest single source cohort analysis of MCC to date. The only two other studies that have over 500 cases are literature review based.

In addition to the limited number of treatment studies, there remains no consensus with respect to staging. The two staging systems most commonly used in the literature are the MSKCC staging system for MCC and the AJCC TNM staging system for non-melanoma skin cancer. Thus far there has not been a clear independent validation study that compares these staging systems to the knowledge of these authors. All these factors combine, creating a multitude of challenges for the clinician managing the patient with MCC. The results of this study demonstrate that the MSKCC staging criteria both appropriately and significantly risk stratifies the SEER cohort for all stages. These data validate the continued use of this staging system for appropriate risk stratification of patients with MCC. The data did not show significant risk stratification for the AJCC TNM staging criteria. Although the risk stratification is appropriate and approaches statistical significance, these data, when compared with the data from the MSKCC staged cohort, suggest that the MSKCC staging criteria do a better job of risk stratifying this SEER cohort.

Radiation therapy was not shown to confer a survival advantage to the curative cohort regardless of stage or staging system. As SEER does not report margin status, chemotherapy, or local/regional recurrence, the role of radiation therapy could not be completely assessed. For a cancer as rare as MCC, the data for cause of death is not reliable; therefore cause specific survival can not be reliably calculated. Radiation may play a significant role in local/regional control, though this study would not be able to address that question. Given the limitations of the SEER database the role of radiation for local/regional control and cause specific survival would have to be more thoroughly examined by another study.
REFERENCES:


