Merkel cell carcinoma: long-term follow-up of a single institution series and clinical outcomes by immunological status

Constantin A Dasanu[1,2] MD PhD, Michael Del Rosario[3] MD, Ion Codreanu[4] MD PhD, Yani Lu[5] MD, Stephanie Farrell[1] RN, David M Hyams[6] MD, Steven C Plaxe[1,2] MD

Affiliations: [1]Lucy Curci Cancer Center, Eisenhower Medical Center, Rancho Mirage, California, [2]University of California San Diego, La Jolla, California, USA, [3]Department of Medicine, Eisenhower Medical Center, Rancho Mirage, California, USA, [4]Department of Radiology and Imaging, State University of Medicine and Pharmacy "Nicolae Testemitanu," Chisinau, Moldova, [5]Department of Family Medicine, Eisenhower Medical Center, Rancho Mirage, California, USA, [6]Department of Surgical Oncology, Eisenhower Medical Center, Rancho Mirage

Corresponding Author: Constantin A. Dasanu MD PhD, 6 Barnard Court, Rancho Mirage, CA, Tel: (760) 413-4371, Email: c_dasanu@yahoo.com

Abstract

Merkel cell carcinoma (MCC) usually arises in sun-exposed areas of older patients and might be more aggressive in the immunocompromised. We performed a retrospective chart review of 40 consecutive MCC patients treated at our institution between the years 2006-2017. Clinical and epidemiologic data were utilized and therapy and survival were analyzed. Compared to Surveillance, Epidemiology, and End Results (SEER) data, our population was entirely Caucasian (100% versus 95%; P=0.11) and male predominant (75% versus 63%; P=0.11). The median age was 76. The patients more often had Tumor-Node-Metastasis (TNM) stage I disease (50% versus 39%; P=0.00003) and a primary tumor size<2cm (57.5% versus 34%; P<0.01). They received more frequently lymph node dissection (70% versus 63%, P=0.002) compared with the SEER findings. We identified a subset of immunocompromised patients (n=10) who presented with more stage III disease (40% versus 33%; P=0.021). Time to death averaged 290.1 days in this subset versus 618.2 days (P<0.001) in immunocompetent patients and their likelihood of death was 5 times higher. As clinical outcomes in MCC patients vary by immunological status, a multidisciplinary tumor-board approach may better optimize individual patient management.

Keywords: Merkel cell carcinoma, immune status, survival outcomes

Introduction

First described in 1978, Merkel cell carcinoma (MCC) is a cutaneous neuroendocrine neoplasm with a propensity for lymphatic spread and subsequently, distant spread. In part owing to presentation at a late stage, MCC currently has a high case-fatality rate [1]. The advent of the ability to evaluate immunohistochemical markers improved significantly the recognition of this disease [2]. Data from Surveillance, Epidemiology, and End Results (SEER) have shown a significant and sustained increase in the MCC incidence over the last three decades [3-5]. Approximately 1,600 new cases per year are currently diagnosed in the United States.

Owing to the rarity of MCC, there have not been any large randomized clinical trials conducted in patients with this disease. Many patients with MCC are immunocompromised and might have different clinical outcomes than their immunocompetent counterparts [5]. As a result, optimal management of these patients is not yet known. We have attempted to collect the epidemiological, clinical, and laboratory characteristics of all subsequent MCC

patients treated at our cancer center in the last decade; we compare them with the SEER data and the existing published cohorts.

Methods

After our institution's IRB approval, we retrospectively reviewed the tumor registry of all patients with MCC treated at Eisenhower Lucy Curci Cancer Center in Rancho Mirage, California, U.S.A. between January 2006 and December 2017. Demographic characteristics, clinical presentation, employed diagnostic modalities, histological features, operative strategies, other therapeutic modalities, recurrence rates, associated comorbidities, disease-specific survival, and overall survival were recorded and summarized. Information regarding stage, primary tumor size, and disease course was collected and analyzed. Details of clinical presentation were obtained from patients' history and physical examination. Standard diagnostic procedures including tumor biopsy, computerized tomography (CT), and/or positron emission tomography (PET) scans were evaluated when performed. Diagnosis was confirmed either via direct skin biopsy or CT-guided fine needle aspiration cytology (FNAC) when indicated. All patients with limited disease underwent surgical resection with generous surgical margins performed by an experienced oncologic surgeon. All pathological specimens were reviewed and reclassified according to the most recent WHO criteria.

The tumors were staged according to the 2009 American Joint Committee on Cancer (AJCC) staging system for MCC. Periodic clinical follow-up was performed every three-6 months and included a mandatory physical examination and CT scans as clinically indicated. In patients with suspected metastatic disease, additional investigations such as PET/CT scan, bone scan, and/or magnetic resonance imaging (MRI) of the brain were performed. Time to tumor recurrence and survival were calculated from the date of surgical operation in patients presenting with stages I-III.

Using the SEER program, we identified 4,256 patients with MCC from the years 2006-2013. We then compared the data in our cohort with the SEER findings. In addition, a comparison was made between our findings and other MCC series in the peer-reviewed literature.

Statistical analysis included Chi-square and Fishers' exact tests to assess the significance of associations in large and small populations, respectively. Survival analyses were performed using the Cox proportional hazards.

Results

Patient and Disease Characteristics

The records identified 40 patients with MCC diagnosed and treated between 2006-2017. Of these, 31 were men and 9 were women, with ages ranging between 61 and 93 years. We found that 90% of patients were older than 65 years of age. Median patient age was 76 in our series. Details related to demographic data and disease characteristics are provided in **Table 1**.

Compared to the SEER data, our population was entirely Caucasian (100% versus 95%; P=0.11) and male predominant (75% versus 63%; P=0.11). The patients in our cohort were diagnosed more often with TNM stage I (50% versus 39%; P=0.00003) disease and found to more often have a primary tumor size less than 2cm in the largest diameter (57.5% versus 34%; P<0.01).

Thus, more than half of the patients had a primary tumor located in the head and neck area, followed by involvement of extremities in approximately a third of patients (**Table 1**). The size of the primary tumor was less that one cm in largest diameter in nearly half of the subjects entering our study. The other half had larger primary tumors (**Table 1**).

Disease Stage and Treatment

Our patients routinely received sentinel lymph node evaluation as part of a treatment protocol. Half of them presented with early stage disease (TNM stage I-II) and another half had a more advanced stage at diagnosis (**Table 2**). Only four patients (10%) with stage III disease had palpable nodal disease; the rest of them had nodes detected via sentinel lymph node biopsy (SLNB). More than fifty percent of patients

Table 1. *Demographic data and characteristics of primary lesions.*

Characteristics	n (%)
Age at diagnosis	
≥ 65 yrs	36 (90%)
< 65 yrs	4 (10%)
Median age (range)	76 (61-93)
Gender	
Female	9 (22.5%)
Male	31 (77.5%)
Location of primary lesion	
Face	18 (45%)
Upper limb and shoulder	11 (27.5%)
Lower limb and hip	7 (17.5%)
Neck and scalp	3 (7.5%)
Trunk	1 (2.5%)
Size of primary lesion	
< 2cm	23 (57.5%)
> 2 cm	13 (32.5%)
Unknown	4 (10%)

had lymphovascular involvement present in the pathology specimens (**Table 2**).

In our patient cohort, 62.5% of patients received adjuvant radiation therapy and more than a third received chemotherapy, either in the adjuvant or metastatic setting (**Table 2**). Compared to the SEER data, our patients were more frequently treated with lymph node dissection (70% versus 63%, P=0.002). However, the frequency of radiation therapy use was not statistically different in our cohort (60% versus 50%; P=0.24).

Analysis by Immune Status and Survival Outcomes

Careful analysis of comorbidities in our patient cohort identified 10/40 immunocompromised patients (**Table 3**). The immunosuppressed patients included three subjects post-organ transplantation, two patients with CLL, one with metastatic skin cancer s/p post-chemotherapy, one with rheumatoid arthritis on azathioprine, one with myasthenia gravis being treated with mycophenolate mofetil, one with follicular lymphoma post-chemotherapy, and one infected with human immunodeficiency virus (HIV). As we anticipated differences in the immunocompromised subset of MCC patients, we analyzed their clinical characteristics, epidemiologic data, employed therapies, and survival separately from the immunocompetent MCC patients (Tables 3, 4).

Indeed, compared to immunocompetent MCC patients, the immunocompromised subjects displayed an absolute male predominance (100% versus 67%; P<0.01) and more TNM stage III disease (40% versus 33%; P=0.021), but less lymphovascular invasion (30% versus 7%; P<0.01), (**Table 3**).

In addition, the immunosuppressed patients received more chemotherapy (50% versus 30%; P<0.01) and radiation therapy (80% versus 57%; P<0.01), (**Table 4**). Of note, none of our patients received immunotherapy at the time of the data analysis. Importantly, overall survival was significantly worse in the immunocompromised subset. Their calculated time to death averaged 290.1 days versus 618.2 days (P<0.001), (**Figure 1**). The results also revealed a relative risk (RR) of death for immunocompromised patients of 5.01 (95% CI=1.49-16.86), indicating the likelihood of death was 5 times higher in this group.

Discussion

A relatively rare skin malignancy, MCC affects predominantly older adults. The basic demographic profile of our cohort is similar to that described in

Table 2. *Disease stage and administered therapy.*

Characteristics	n (%)
Disease stage at diagnosis	
stage I	19 (47.5%)
stage II	1 (2.5%)
stage III	14 (35%)
stage IV	6 (15%)
Lymphovascular involvement	
Yes	23 (57.5%)
No	5 (12.5%)
Unknown	12 (30%)
Chemotherapy	
Yes	14 (35%)
No	26 (65%)
Radiation therapy	
Yes	25 (62.5%)
No	15 (37.5%)

Table 3. *Demographic data of the study population and disease stage by immunocompromised versus immunocompetent status.*

Characteristics	Immunocompromised, N (%)	Immunocompetent, N (%)	P value
Age at diagnosis			
≥ 65 yrs	10 (100%)	26 (87%)	> 0.05
< 65 yrs	0 (0%)	4 (13%)	
Median age (range)	75 (66-82)	77 (61-93)	
Gender			
Female	0 (0%)	9 (30%)	< 0.01
Male	10 (100%)	21 (70%)	
Disease stage at diagnosis			
stage I	4 (40%)	15 (50%)	< 0.05
stage II	1 (10%)	0 (0%)	
stage III	4 (40%)	10 (33%)	
stage IV	1 (10%)	5 (17%)	
Lymphovascular involvement			
Yes	4 (40%)	19 (63%)	< 0.01
No	3 (30%)	2 (7%)	
Unknown	3 (30%)	9 (30%)	

other studies and the SEER database: mostly elderly, Caucasian patients, with a male predominance.

This malignancy is associated with increased sun exposure and Merkel cell polyoma virus. There is an average of 348 days of sunshine per year in our geographic area. The body area distribution of the primary MCC in our cohort favors sun exposure as a risk factor for the development of MCC, consistent with the data in the peer-reviewed literature [4]. Although sun exposure is strongly associated with MCC, this malignancy can also arise in the sun protected sites in a minority of patients.

Most affected patients receive surgical excision with sentinel lymph node biopsy (SLNB), followed by radiation therapy when indicated [6-9]. Survival benefit with the use of adjuvant chemotherapy has not been demonstrated [9]. MCC prognosis is dependent on the disease stage at presentation. The disease-specific survival rate for node-negative disease is in excess of ninety percent, and decreases to fifty percent in node positive-disease [3]. Rare but often lethal, this malignancy is much more likely to metastasize than melanoma. For remote metastatic disease, projected survival is less than ten percent at three years [1]. Therefore, early recognition of this disease may improve overall survival rates.

Immunosuppression is another known risk factor for MCC [10-13]. Indeed, 25% of our patients had some form of immune dysfunction, including iatrogenic suppression for solid organ transplantation, chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma, HIV, and treated autoimmune

Table 4. *Administered therapy for the study subsets.*

Characteristics	Immunocompromised, N (%)	Immunocompetent, N (%)	P value
Chemotherapy			
Yes	9 (30%)	5 (50%)	< 0.01
No	21 (70%)	5 (50%)	
Radiation therapy			
Yes	17 (57%)	8 (80%)	< 0.01
No	13 (43%)	2 (20%)	

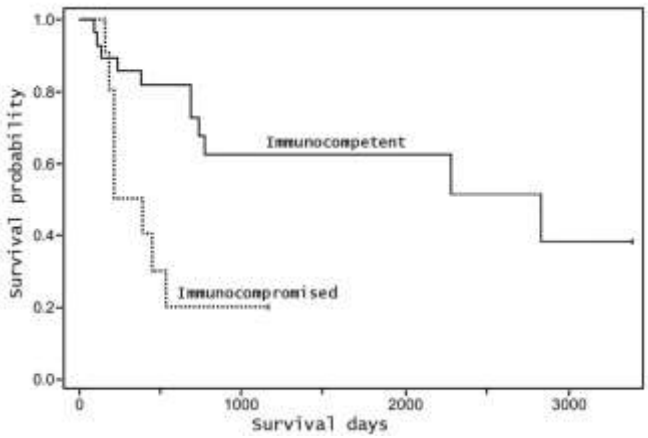

Figure 1. *Survival analysis showed an average time to death of 290.1 days in immunocompromised patients versus 618.2 days in immunocompetent subjects (P<0.001).*

conditions. Immunosuppressed patients included three subjects post-organ transplantation, two patients with CLL, one with metastatic skin cancer post-chemotherapy, one with rheumatoid arthritis on azathioprine, one with myasthenia gravis being treated with mycophenolate mofetil, one with follicular lymphoma post-chemotherapy, and one with HIV infection.

Miller et al. [14] found a 10-fold increase in the prevalence of MCC in solid organ transplant recipients. Furthermore, Friedlaender et al. [15] documented regression of MCC metastases after stopping cyclosporine in a kidney transplant patient. Engels et al. [16] identified a 13-fold increased rate of MCC in HIV-infected individuals. Several cases of MCC with an aggressive clinical course in patients with CLL have been reported [17-21]. In 2015, our center reported a case of rapidly fatal dissemination of Merkel cell carcinoma in a patient treated with alemtuzumab for CLL [22].

Several surgical MCC series were published over the last two decades. Although they have largely a retrospective design, they establish important prognostic information, especially in patients with earlier stage disease (**Table 5**).

In a study involving 251 patients, Allen et al. [23] showed that prognosis in MCC can be variable and largely dependent on the stage of disease at presentation. Pathologic nodal staging identified a group of patients with excellent long-term survival. After excision with negative margins and pathologically negative nodes in these patients, local and nodal recurrence rates were low, and overall survival – excellent [23].

A retrospective analysis of a small series by Akhtar et al. [24] suggested that distant metastases are more frequent with higher TNM stage. These authors demonstrated that a prolonged survival can be achieved after aggressively treating the loco-regional recurrences. In their study, most primary MCC lesions involved the head and neck region and extremities [24]. Half of the patients had 13 previously treated or coexisting malignant neoplasms, suggesting that additional immunosuppression was involved in these patients. In one patient, MCC developed in a previously irradiated field.

In a single institution series of consecutive patients, Bajetta et al. [25] demonstrated a disease specific survival (DSS) of 67% in all comers with MCC. A clear correlation was shown between the stage of the disease and recurrence rate. However, the 5-year DSS rate was around 80% for pathologically node-negative patients. Comparing outcomes of patients with two or less versus more than two dissected regional lymph nodes, the 5-year regional recurrence was 0% versus 39% (P=0.004) [25].

In a study of 153 patients from a single institution, Fields et al. [26] analyzed factors associated with SLNB positivity. SLNB identified occult nodal metastases in 29% of patients with what appeared to be localized MCC. SLNB was more likely to be positive with larger primary tumor size and presence of lymphovascular invasion (LVI). The SLNB-positive patients were more likely to receive further adjuvant radiation therapy and/or chemotherapy. Interestingly, positive sentinel lymph node status was not associated with increased recurrence rates or worse survival. By contrast, LVI was strongly associated with both higher recurrence rate and shorter survival.

Santamaria-Barria et al. [27] reported their analysis of a 161-patient series with MCC. One-third of early-stage patients had node-positive disease. Negative sentinel nodes predicted for improved but not

necessarily favorable outcome. The 5-year MCC-specific survival rates were 87, 63, 42, and 0% for stages I, II, III, and IV, respectively. Larger initial tumor size and positive nodal disease predicted for worse outcome. Adjuvant therapy did not improve recurrence or survival rates. One-third of patients died of the disease.

A study by Timmer et al. [28] showed that MCC has a high propensity for both locoregional and distant spread in the head and neck. They found that undertreatment of the lymph nodes in the neck can lead to worse outcomes as regional micrometastases are common even in T1 tumors. Future research is set to compare the outcomes of the sentinel lymph node procedure versus selective node dissection and standardize local and regional radiotherapy dosing in the head and neck region.

Establishing the clinical characteristics of MCC at diagnosis in 195 patients, Heath et al. [29] call practitioners to consider the clinical and laboratory workup for immunosuppression in patients presenting with MCC. These authors observed more

Table 5. *Long-term retrospective and prospective data in published surgical MCC series.*

Author(s) and study sites	Study years	Size (n)	Mean/ median age	5-year DSS (%)	5-year OS (%)	Prognosis and survival	Other findings
Allen et al. [23], Memorial Sloan-Kettering Cancer Center, NY, USA	1970-2002	251	71	64	NA	Prognosis correlated with MCC stage.	Negative sentinel node status predicts for excellent survival.
Akhtar et al. [24], State University of New York, Syracuse, USA	1986-1998	10	70.3	NA	NA	Advanced stage correlated with distant metastases.	Circa 50% patients had second neoplasms.
Bajetta et al. [25], Istituto Nazionale Tumori, Milan, Italy	NA	95	74	67	NA	5-yr DSS was 80% in node negative patients.	More dissected regional lymph nodes correlated with increased survival.
Fields et al. [26], Memorial Sloan-Kettering Cancer Center, NY, USA	1996-2010	153	72	NA	NA	No difference in recurrence or death rates from MCC between SLNB positive and negative patients.	LVI was strongly associated with both higher recurrence rate and shorter survival.
Santamaria-Barria et al. [27], Massachusetts General Hospital, Boston, MA, USA	1980-2010	161	74	87-stage I, 63-stage II,42-stage III,0-stage IV, respectively.	66.7	Larger initial tumor size and positive nodal disease predicted for worse survival.	Negative sentinel nodes predicted for improved but not necessarily favorable outcome.
Timmer et al. [28] Kanker Instituut, Amsterdam, Netherlands	1984-2012	47 patients with head and neck MCC	75	70	54	Under-treatment of the lymph nodes in the neck can lead to worse survival.	Regional (micro)metastases are common even in T1 tumors.
Dasanu et al. (our study) [30, 31], Eisenhower Lucy Curci Cancer Center, Rancho Mirage, CA, USA	2006-2017	40	76	NA	NA	Survival was significantly shorter in subjects with immune dysfunction.	LVI was less frequent in patients with immune dysfunction.

Abbreviations: DSS, disease specific survival; OS, overall survival; LVI, lymphovascular invasion; SLNB, sentinel lymph node biopsy; NA, not available.

advanced disease at the time of presentation in immunosuppressed patients, yet the difference was not statistically significant. Their study identified several clinical profiles that may raise clinical suspicion for MCC. These include the following: asymptomatic non-tender lesions, rapidly expanding lesions in sun-exposed areas in fair-skinned persons, and immunosuppressed patients older than 50 years of age [29].

Most of the recorded characteristics involving histological features, clinical presentation, diagnostic modalities, operative strategies, other received therapy, and associated tumor-related and overall survival in our cohort are concordant with the results published by other centers. In particular, the study confirmed previous reports that the primary tumor size and nodal status represent important prognostic factors.

Compared to the general population, MCC patients treated at our institution had similar mean age at diagnosis, gender and racial distribution, and radiation treatment frequency. However, our patient population was significantly more likely to be diagnosed with stage TNM I disease, to have a smaller primary tumor size, and receive lymph node dissection [30]. Earlier stage at diagnosis recorded in our cohort appears to contrast with the SEER data. This could be explained by the heightened suspicion for skin cancer in our geographic area, likely linked with intense solar exposure. These factors could also explain a more aggressive surgical oncology approach.

The immunocompromised MCC subset in our study displayed more TNM stage III disease compared with immunocompetent patients. Unexpectedly, the immunocompromised subset demonstrated less lymphovascular invasion in their pathology specimens as opposed to immunocompetent patients. These findings warrant confirmation in further studies. In addition, the immunosuppressed patients received more chemo- and radiation therapy, presumably related to a more advance disease stage at presentation. Importantly, overall survival was significantly compromised in this group of patients. Time to death averaged 290.1 days versus 618.2 days ($P<0.001$) and the likelihood of death was 5 times higher in this group [31].

The median age in our patient cohort was higher than in other published series, which could at least in part be attributed to the somewhat older population in our community. Some degree of immune dysfunction such as decreased $CD4^+$ T-cell counts and CD4/CD8 T-cell ratio, along with diminished antibody production to various antigens, is expected in older adults [32]. This process is often referred to as immunosenescence and might account for increased MCC prevalence in older adults.

We believe that immune dysfunction might account for a rapid increase in MCC cases in the elderly in the last decade. Recent research by Paulson et al. [33] suggested that the aging population is driving significant increases in the number of new MCC cases in the U.S. They predict that the incidence of MCC in the U.S. will climb to 2,835 cases in 2020 and 3,284 cases in 2025 [22]. Besides ageing of the population, important contributing factors to this phenomenon may include increased sun exposure and expanding numbers of immunocompromised individuals in the last few years [33]. Increased numbers of immunocompromised hosts are driven by more effective immunosuppressive agents, more hematopoietic and solid tumor transplant treatments, and more effective systemic therapies for cancer and other diseases in the recent years, some of which are associated with immunosuppression. These facts warrant heightened awareness of MCC as a clinical and epidemiologic entity.

As clinical outcomes for surgically managed early-stage MCC vary, a multidisciplinary tumor-board approach is suggested to optimize individual patient management. High MCC mortality rates call for more effective adjuvant therapies and identification of more reliable markers for recurrence and treatment response. PD1/PDL1 inhibitors have recently entered the therapeutic arena in metastatic MCC and may change the outcomes of this malignancy in both immunocompetent and immunocompromised individuals with advanced disease, and hopefully, with early-stage disease in the future years [34, 35].

Study limitations

Our study has a relatively small size, which limits our ability to draw definitive conclusions and make categorical recommendations. Another limitation of the current study is its retrospective design. Although the relative rarity of MCC makes a prospective study difficult, such protocols certainly may be considered in larger centers. In addition, the study was limited to patients seen and treated at a community cancer center. Complete clinical data could not be obtained in all patients, given the relatively high rate of population migration in our geographic area. Further, this study could not assess fully the specificity of the clinical characteristics of MCC. Most of our patients were elderly and immune dysfunction is present in older adults. This might have impaired our ability to analyze the degree of immune dysfunction in the presented patient cohort. The analysis in our cohort was performed prior to the FDA approval of the PDL1 inhibitor avelumab [34]. This agent is known to improve outcomes in advanced MCC and might significantly impact survival in MCC.

Conclusion

Compared to the general population, MCC patients treated at our institution had similar mean age at diagnosis, gender and racial distribution, and radiation treatment frequency (all P values>0.05). However, our patient population was significantly more likely to be diagnosed at stage I disease, have a primary tumor size less than 2cm, and receive lymph node dissection. The earlier stage at diagnosis recorded in our cohort is in contrast with the SEER data. This could be explained by the heightened suspicion for skin cancer in our geographic area, which could also explain the more aggressive surgical oncology approach. A more advanced MCC stage and a significantly shorter survival was documented in 25% patients that were immunocompromised. We believe that immune dysfunction associated with ageing might explain a higher prevalence of MCC in seniors exceeding 70 years of age. Recently approved immunotherapies may lead to superior outcomes in both immunocompromised and immunocompetent patients with advanced and early-stages of MCC.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Schadendorf D, Lebbe C, Zur Hausen A, et al. Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. *Eur J Cancer*. 2017;71:53-69. [PMID: 27984768].
2. Goepfert H, Remmler D, Silva E, Wheeler B. Merkel cell carcinoma (endocrine carcinoma of the skin) of the head and neck. *Arch Otolaryngol*. 1984;110(11):707-12. [PMID: 6487123"]".
3. Hodgson NC. Merkel cell carcinoma: changing incidence trends. *J Surg Oncol*. 2005;89(1):1-4. [PMID: 15611998].
4. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol*. 2003;49(5):832-41. [PMID: 14576661].
5. Lemos B, Nghiem P. Merkel cell carcinoma: more deaths but still no pathway to blame. *J Invest Dermatol*. 2007;127(9):2100-3. [PMID: 17700621].
6. Gupta SG, Wang LC, Penas PF, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. *Arch Dermatol*. 2006;142(6):685-90. [PMID: 16785370].
7. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol*. 2006;142(6):693-700. [PMID: 16785371].
8. Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. *J Clin Oncol*. 2007;25(9):1043-7. [PMID: 17369567].
9. Garneski KM, Nghiem P. Merkel cell carcinoma adjuvant therapy: current data support radiation but not chemotherapy. *J Am Acad Dermatol*. 2007;57(1):166-9. [PMID: 17482714].
10. Watkins DN, Berman DM, Baylin SB. Hedgehog signaling: progenitor phenotype in small-cell lung cancer. *Cell Cycle*. 2003;2(3):196-8. [PMID: 12734424].
11. Watkins DN, Berman DM, Burkholder SG, et al. Hedgehog signalling within airway epithelial progenitors and in small-cell lung cancer. *Nature*. 2003;422(6929):313-7. [PMID: 12629553].
12. Wong DJ, Chang HY. Learning more from microarrays: insights from modules and networks. *J Invest Dermatol*. 2005;125(2):175-82. [PMID: 16098025].
13. UNAIDS/WHO Global HIV/AIDS Online Database. HIV/AIDS estimates, United States of America. Web site: http://www.who.int/hiv/strategic/db/en/
14. Miller RW, Rabkin CS. Merkel cell carcinoma and melanoma: etiological similarities and differences. *Cancer Epidemiol Biomarkers Prev*. 1999;8(2):153-8. [PMID: 10067813].
15. Friedlaender MM, Rubinger D, Rosenbaum E, Amir G, Siguencia E. Temporary regression of Merkel cell carcinoma metastases after cessation of cyclosporine. *Transplantation*. 2002;73(11):1849-50. [PMID: 12085015].
16. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. *Lancet*. 2002;359(9305):497-8. [PMID: 11853800].

17. Barroeta JE, Farkas T. Merkel cell carcinoma and chronic lymphocytic leukemia (collision tumor) of the arm: a diagnosis by fine-needle aspiration biopsy. *Diagn Cytopathol*. 2007;35(5):293-5. [PMID: 17427219].
18. Pandey U, Naraynan M, Karnik U, Sinha B. Carcinoma metastasis to unexpected synchronous lymphoproliferative disorder: report of three cases and review of literature. *J Clin Pathol*. 2003;56(12):970-1. [PMID: 14645362].
19. Papageorgiou KI, Kaniorou-Larai MG. A case report of Merkel cell carcinoma on chronic lymphocytic leukemia: differential diagnosis of coexisting lymphadenopathy and indications for early aggressive treatment. *BMC Cancer*. 2005;5:106. [PMID: 16111484].
20. Vlad R, Woodlock TJ. Merkel cell carcinoma after chronic lymphocytic leukemia: case report and literature review. *Am J Clin Oncol*. 2003;26(6):531-4. [PMID: 14663367].
21. Ziprin P, Smith S, Salerno G, Rosin RD. Two cases of merkel cell tumour arising in patients with chronic lymphocytic leukaemia. *Br J Dermatol*. 2000;142(3):525-8. [PMID: 10735964].
22. Yu KK, Dasanu CA. Rapidly Fatal Dissemination of Merkel Cell Carcinoma in a Patient Treated with Alemtuzumab for Chronic Lymphocytic Leukemia. *Conn Med*. 2016;80(6):353-8. [PMID: 27509643].
23. Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol*. 2005;23(10):2300-9. [PMID: 15800320].
24. Akhtar S, Oza KK, Wright J. Merkel cell carcinoma: report of 10 cases and review of the literature. *J Am Acad Dermatol*. 2000;43(5 Pt 1):755-67. [PMID: 11050578].
25. Bajetta E, Celio L, Platania M, et al. Single-institution series of early-stage Merkel cell carcinoma: long-term outcomes in 95 patients managed with surgery alone. *Ann Surg Oncol*. 2009;16(11):2985-93. [PMID: 19609619].
26. Fields RC, Busam KJ, Chou JF, et al. Recurrence and survival in patients undergoing sentinel lymph node biopsy for merkel cell carcinoma: analysis of 153 patients from a single institution. *Ann Surg Oncol*. 2011;18(9):2529-37. [PMID: 21431988].
27. Santamaria-Barria JA, Boland GM, Yeap BY, Nardi V, Dias-Santagata D, Cusack JC, Jr. Merkel cell carcinoma: 30-year experience from a single institution. *Ann Surg Oncol*. 2013;20(4):1365-73. [PMID: 23208132].
28. Timmer FC, Klop WM, Relyveld GN, et al. Merkel cell carcinoma of the head and neck: emphasizing the risk of undertreatment. *Eur Arch Otorhinolaryngol*. 2016;273(5):1243-51. [PMID: 25759258].
29. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol*. 2008;58(3):375-81. [PMID: 18280333].
30. Del Rosario M, Anderson E, Lu Y, et al. Clinico-epidemiologic characteristics and patterns of care in Merkel cell carcinoma: Data from a single-institution series. *J Clin Oncol*. 2017;35(15_suppl):e21049-e.
31. Del Rosario M, Anderson E, Lu Y, et al. Clinicopathologic features and survival in immunocompromised versus. immunocompetent patients with Merkel cell carcinoma: An exploratory analysis of a series of consecutive patients. *J Clin Oncol*. 2017;35(15_suppl):9568.
32. Ventura MT, Casciaro M, Gangemi S, Buquicchio R. Immunosenescence in aging: between immune cells depletion and cytokines up-regulation. *Clin Mol Allergy*. 2017;15:21. [PMID: 29259496].
33. Paulson KG, Park SY, Vandeven NA, et al. Merkel cell carcinoma: Current US incidence and projected increases based on changing demographics. *J Am Acad Dermatol*. 2018;78(3):457-63 e2. [PMID: 29102486].
34. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(10):1374-85. [PMID: 27592805].
35. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med*. 2016;374(26):2542-52. [PMID: 27093365].