Original Article

# Merkel cell carcinoma in Turkey: A multicentric study

Fatih Yildiz, Umut Demirci, Ahmet Küçükarda[1], Mahmut Büyüksimsek[2], Teoman Sakalar[3], Turkan Ozturk Topcu[4], Ferit Aslan, Gulnihal Tufan, Ovgu Aydin[5], Hande Turna[6], Nalan Akgul Babacan[7], Tugba Basoglu[7], Bediz Kurt[8], Birol Yildiz[9], Tülay Eren[10], Atike Gokcen Demiray[11], Ozge Gumusay[12], Cagatay Arslan[13], Nuriye Özdemir[8], Yuksel Urun[14], Meltem Baykara[15], Nedim Turan[16], Mukremin Uysal[17], Ahmet Bilici[18], Halil Kavgaci[4], İrfan Çiçin[1], Saadettin Kilickap[19], Semra Paydas[2]

Department of Medical Oncology, Dr. A. Y. Ankara Oncology Research and Education Hospital, University of Health Sciences, Yenimahalle, [8]Department of Medical Oncology, Gazi University Faculty of Medicine, [9]Department of Medical Oncology, Gulhane Education and Research Hospital, University of Health Sciences, [10]Department of

## ABSTRACT

**Background:** Merkel cell carcinoma (MCC) is a rare but highly aggressive neuroendocrine carcinoma of the skin. In this study, we aimed to evaluate the clinicopathologic characteristics, treatment outcomes, and survival of MCC cases in Turkey.

**Materials and Methods:** The patients diagnosed with MCC between 1999 and 2018 at twenty different centers in Turkey were included in the study. Patient and tumor characteristics and adjuvant and metastatis treatment outcomes were analyzed retrospectively.

**Results:** The median age of totally 89 patients was 70 (26–93). The most common primary location was lower limbs ($n = 29$, 32.5%). Immunohistochemically, CK20 positivity was present in 59 patients (66.3%). Only two patients had secondary malignancy. The majority of the patients ($n = 76$, 85.4%) were diagnosed at the localized stage. Surgery was performed for all patients in the early stage, and adjuvant radiotherapy or/and chemotherapy was applied to 52.6% ($n = 40$) of nonmetastatic patients. The median follow-up was 29 months. Recurrence developed in 21 (27.6%) of the 76 patients who presented with local or regional disease. Two-year disease-free survival (DFS) was 68.1% and 5-year DFS was 62.0% for localized stage. The 5-year DFS was similar for patients receiving adjuvant treatment (chemotherapy, radiotherapy, or sequential chemoradiotherapy) and without adjuvant therapy ($P > 0.05$). Two-year overall survival in patients who presented with localized disease was 71.3% and 18.5% in metastatic patients ($P < 0.001$). In the metastatic stage, platinum/etoposide combination was the most preferred combination regimen. Median progression-free survival (PFS) in first-line chemotherapy was 7 months (95% confidence interval: 3.5–10.5 months; standart error: 1.78).

**Conclusions:** Although MCC is rare in Turkey, the incidence is increasing. Gender, CK20 status, tumor size, lymph node involvement, and adjuvant treatment were not associated with recurrence.

**KEY WORDS:** CK20, merkel cell carcinoma, neuroendocrin carcinoma, skin carcinoma

## INTRODUCTION

Merkel cell carcinoma (MCC) is a rare primary neuroendocrine carcinoma of the skin.[1] It was first named as trabecular carcinoma of the skin in 1972 by Toker.[2] Although the incidence of MCC in the United States was 0.7/100.000, there was a 95% increase in MCC cases between 2000 and 2013.[3]

MCC is mainly seen in light-skinned and elderly people.[4] Solid organ transplant recipients, HIV-infected individuals, patients with malignancy, and patients receiving immunosuppressive therapy are at higher risk for MCC.[5-8] The most accepted factors associated with the development of MCC are Merkel cell polyomavirus, exposure to ultraviolet radiation and immunosuppression.[9,10]

The most common primary location of MCC is head and neck.[4,11-13] While 65%–75% of the patients have localized disease, 16%–26% have regional lymph node involvement and 6%–8% have distant metastasis.[12,13] Five-year overall survival rate is 60%–80% in the early stage and 11%–25% in patients with distant metastasis.[12,14,15]

Responses with conventional chemotherapies for the treatment of advanced stage MCC are

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Medical Oncology, Diskapi Yildirim Beyazit Training and Research Hospital, [14]Department of Medical Oncology, Faculty of Medicine, Ankara University, [19]Department of Medical Oncology, Faculty of Medicine, Hacettepe University, Ankara, [1]Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, [2]Department of Medical Oncology, Cukurova University Faculty of Medicine, Adana, [3]Department of Medical Oncology, Erciyes University Faculty of Medicine, Kayseri, [4]Department of Medical Oncology, Karadeniz Technical University Faculty of Medicine, Trabzon, Departments of [5]Pathology and [6]Medical Oncology, Istanbul University Cerrahpasa Medical Faculty, [7]Department of Medical Oncology, Marmara University Faculty of Medicine, [16]Department of Medical Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital, [18]Department of Medical Oncology, Medipol University, Medical Faculty, Istanbul, [11]Department of Medical Oncology, Faculty of Medicine, Pamukkale University, Denizli, [12]Department of Medical Oncology, Faculty of Medicine, Gaziosmanpasa University, Tokat, [13]Department of Medical Oncology, Medical Park Hospital, Izmir, [15]Department of Medical Oncology, Sakarya University Training and Research Hospital, Sakarya, [17]Department of Medical Oncology, Faculty of Medicine, Afyon Kocatepe University, Afyon, Turkey

**For correspondence:**
Dr. Fatih Yildiz, Department of Medical Oncology, Dr. A. Y. Ankara Oncology Research and Education Hospital, University of Health Sciences, Yenimahalle, Ankara, Turkey. E-mail: dr.fatihyildiz@hotmail.com

temporary.[16] After understanding the immunogenicity of MCC over the past 10 years, treatment strategies have focused on immune modulators.[17,18] Both the increase in incidence and achievements in immunotherapy have made MCC more remarkable.[19]

In this study, we aimed to evaluate clinicopathologic characteristics, treatment outcomes, and survival of MCC cases in Turkey.

## MATERIALS AND METHODS

This study was conducted by the Turkish Oncology Group with the participation of twenty institutions. Between 1999 and 2018, totally 89 patients with MCC were evaluated retrospectively.

Patient (sex, age at diagnosis, immunosuppression, and secondary malignancy) and tumor characteristics (anatomic location, size, nodal status, and immunohistochemical CK20 expression), treatment (adjuvant or metastatic setting) properties, and relaps or exitus status at last follow-up were investigated from the electronic registry system and patient files.

The patients were staged according to the 8$^{th}$ edition of the American Joint Committee.

Disease-free survival (DFS) was defined as the time from diagnosis to recurrence in localized disease, progression-free survival (PFS) was defined as the time from the beginning of treatment to progression in the metastatic stage, and OS was defined as the time from diagnosis to last control or death.

IBM Statistical Package for Social Sciences (SPSS®) v.23 (IBM Inc.; Armonk, NY, USA) software was used for data analysis.

The relationship between relapse and patient/tumor characteristics and adjuvant therapy was investigated by the univariate analysis.

Survival analyses were performed with Kaplan–Meier method, and the subgroups were compared with the log-rank test. A $P < 0.05$ was considered statistically significant.

## RESULTS

The median age of totally 89 patients was 70 (26–93). The patients' characteristics are shown in Table 1.

The most common primary location was lower limbs ($n = 29$, 32.5%). Majority of the patients ($n = 76$, 85.4%) had local or regional disease and 13 (14.6%) were in the metastatic stage. Eight patients (8.9%) were diagnosed between 1999 and 2008 and 91.1% ($n = 81$) were diagnosed in the past 10 years (2009–2018). Only two patients had secondary malignancy and they had used immunosuppressive therapy.

**Table 1: Patient characteristics (*n*=89)**

| | *n* (%) |
|---|---|
| Median age (year, range) | 70 (26-93) |
| Sex | |
| Female | 48 (53.9) |
| Male | 41 (46.1) |
| Primariy site | |
| Extremity | 51 (57.3) |
| Lower limbs | 29 (32.5) |
| Upper limbs | 22 (24.7) |
| Head and neck | 27 (30.3) |
| Trunk | 11 (12.4) |
| Stage | |
| I | 27 (30.3) |
| II | 27 (30.3) |
| III | 22 (24.7) |
| IV | 13 (14.6) |
| CK20 | |
| Positive | 59 (66.3) |
| Negative | 15 (16.9) |
| Unknown | 15 (16.9) |
| Secondary malignancy | 2 (2.2) |
| Immunosuppressive therapy | 2 (2.2) |
| Date of diagnosis (years) | |
| 1999-2008 | 8 (8.9) |
| 2009-2018 | 81 (91.0) |
| Exitus | 34 (38.2) |

All patients in the localized stage were R0 resected. Forty patients (52.6% of localized stage patients) received adjuvant therapy. Adjuvant therapy and relapse status according to the stages are shown in Table 2.

The median follow-up for all patients was 29 months (32 months for stage I, II, and III patients and 14 months for stage IV patients). Distant metastasis developed as a first recurrence in 14 (18.4%) and local recurrence developed in 7 (9.2%) of the 76 patients who presented with local or regional disease. Two-year DFS was 68.1% and 5-year DFS was 62% for localized stage. The 5-year DFS for patients receiving adjuvant chemotherapy or sequential chemoradiotherapy was 72.0%, 50.6% for adjuvant radiotherapy, and 62.2% for patients without adjuvant therapy [$P > 0.05$; Figure 1].

Two-year survival in patients who presented with local or regional disease was 71.3% and 18.5% in metastatic patients [$P < 0.001$; Figure 2]. Median OS at the metastatic stage was 14.8 months (1.8–36.2 months; 95% confidence interval [CI]: 8.2–21.4, standard error: 3.3).

Univariate analyses of DFS and OS are shown in Table 3. Gender, CK20 status, tumor size, lymph node involvement, and adjuvant treatment were not associated with recurrence. Only age was associated with OS.

In the metastatic setting, sisplatin or carboplatin and etoposid combination was the most preferred chemotherapy agents. Median PFS was 7 months for first-line treatment (2.3–11.4; 95% CI; 3.5–10.5, standart error: 1.7). In second-line therapy, six patients were treated with vincristine/doxorubicin/cyclophosphamide combination and two patients with avelumab.

**Table 2: Relapse status according to adjuvant treatment and stages**

| Stage | Adjuvant treatment | | Relapse, *n* (%) |
|---|---|---|---|
| | Yes | No | |
| I (*n*=27) | 11 | 16 | 6 (22.2) |
| II (*n*=27) | 13 | 14 | 11 (40.7) |
| III (*n*=22) | 16 | 6 | 4 (18.1) |

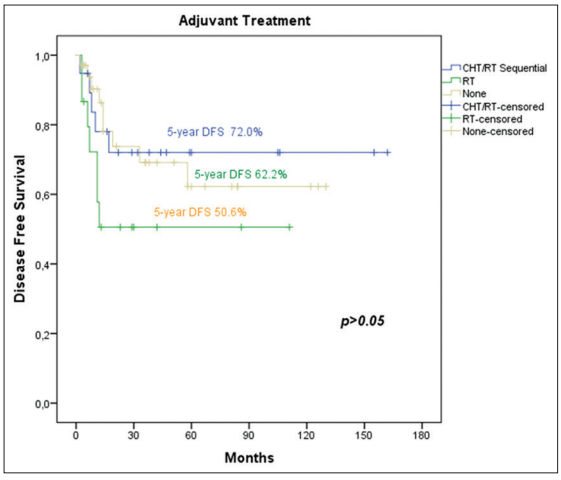


**Figure 1:** Disease-freee survival according to adjuvant treatment

## DISCUSSION

MCC is a rare but highly aggressive skin carcinoma. The incidence is increasing gradually. Most of the previous studies included European and American patients, and this is one of the rare retrospective analyses performed in our region. In this study, we aimed to evaluate the clinicopathological features and survival of MCC in Turkey retrospectively.

MCC mainly affects elderly. Previous studies which were conducted in different geographies such as the USA, Europe, and China, reported that the median age of MCC patients was between 65 and 81 years.[4,10,20-22] Similarly, the median age of the patients was 70 years in our study.

The most common anatomic location of MCC is head and neck in the Scandinavian countries, while the extremity and head-and-neck region are equally common in the USA.[4,12,22-25] In some European countries such as Italy, MCC is seen in extremities more commonly.[10] In more than half of the patients in our study, MCC lesions were located in the extremity. We think that these differences might be related to ethnic and geographical factors.

The increase in the incidence of MCC in almost all of the recent studies is remarkable. During 2000–2013, 95% increase in MCC cases was reported in the USA.[3] The epidemiological studies conducted in different countries such as France, the Netherlands, and Sweden showed that approximately 2-fold increase was observed in MCC cases in the last decade.[12,23,26] Remarkably, 89.4% of the patients in our study were diagnosed in the past 10 years (2000–2018) and 10.6% were diagnosed in previous years (1999–2008). The main reason for this

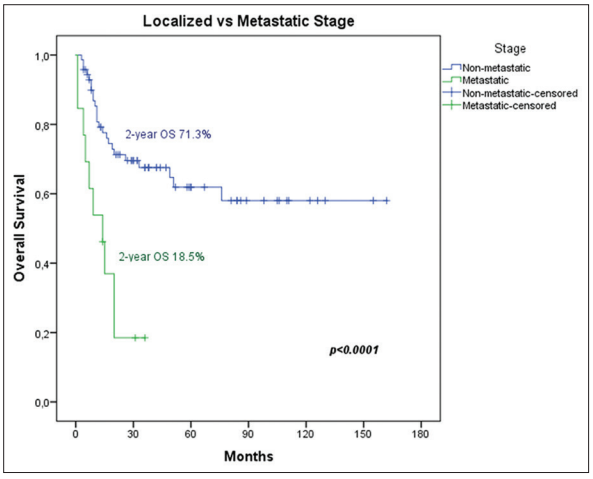


**Figure 2:** Overall survival according to the localized or advanced (metastatic) stage

**Table 3: Univariate analysis of overall survival and disease-free survival**

| | OS | | | DFS | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Male versus female | 1.56 | 0.74-3.2 | 0.24 | 1.34 | 0.84-2.1 | 0.206 |
| Age at diagnosis | 1.05 | 1.02-1.094 | 0.002 | 0.99 | 0.96-1.3 | 0.88 |
| Tumor diameter (<2 cm vs. >2 cm) | 0.634 | 0.27-1.4 | 0.286 | 0.61 | 0.23-1.6 | 0.33 |
| Nodal status (positive vs. negative) | 1.57 | 0.73-3.4 | 0.246 | 1.6 | 0.53-5 | 0.38 |
| Metastasis (yes vs. no) | 4.55 | 2-10.3 | <0.001 | | | |
| Adjuvant treatment (yes vs. no) | 0.478 | 0.184-1.2 | 0.131 | 1.09 | 0.43-2.7 | 0.85 |
| Recurrens (yes or no) | 2.58 | 1.49-4.46 | 0.001 | | | |
| CK20 (positive vs. negative) | 1.3 | 0.69-2.5 | 0.388 | 0.038 | 0.07-1.19 | 0.089 |
| Adjuvant chemotherapy (yes vs. no) | 0.47 | 0.13-16 | 0.243 | 0.43 | 0.12-1.5 | 0.191 |
| Adjuvant radiotherapy (yes vs. no) | 1.1 | 0.67-1.7 | 0.68 | 0.69 | 0.43-1.1 | 0.123 |
| Localization (extremity vs. others) | 1.54 | 0.7-3.2 | 0.24 | 1.1 | 0.45-3 | 0.74 |

DFS=Disease-free survival, OS=Overall survival, CI=Confidence interval, HR=Hazard ratio

increase in the incidence was thought to be the use of immunohistochemical tests such as CK20. In addition, the increase in HIV positivity, other malignancies, and the use of immunosuppressive treatment are other factors for the increase in the incidence of MCC worldwide.

The efficacy of adjuvant therapy in resected MCC is controversial. Adjuvant radiotherapy has been reported to significantly reduce local recurrence in most retrospective studies including meta-analyses.[27-30] However, there are also reports that adjuvant radiotherapy did not reduce recurrence.[14,21,31] There is no randomized study of the efficacy of adjuvant chemotherapy or chemoradiotherapy in MCC. In a retrospective analysis of approximately 7000 patients, neither adjuvant chemotherapy nor chemoradiotherapy had an effect on OS.[32] In other studies with fewer patients, adjuvant chemotherapy had no positive effect on relapse and OS.[29,33] In our study, 27.6% of the patients in the early stage had relapsed. Patients who received adjuvant chemotherapy or chemoradiotherapy had better 5-year DFS than those who received radiotherapy or did not receive adjuvant therapy numerically, but this difference was not statistically significant. Adjuvant treatment decisions were not similar among the participating centers included in our study. While adjuvant treatment was applied to some of the patients in stage I, some of the high-risk patients in stage III did not receive adjuvant therapy. Therefore, we could not conclude a definite conclusion about the efficacy of adjuvant therapy in this study.

A large retrospective analysis of 8044 patients revealed that tumor diameter and lymph node involvement were associated with survival.[34] In other large series, patients with small tumor size and no lymph node involvement were reported to have the longest survival group.[35] It was observed that tumor diameter, lymph node status, immunohistochemical CK20 positivity, primary location, and gender had no effect on recurrence and OS in our study. OS decreased as the age at diagnosis increased in our series. It is not correct to make a clear conclusion on this issue because of the low number of patients and heterogeneity of patient characteristics.

Our study had some limitations. First, our study was retrospective and this restricted us from accessing some data of some patients such as immunohistochemical CK20 status. Second, our study group was not homogeneous; therefore, we could not evaluate the benefit of adjuvant treatment. However, according to the best of our knowledge, this study is the largest analysis of MCC outside the USA and Europe. We believe that the multicentric study of this rare disease is very valuable in understanding the clinicopathological features of patients in our region.

## CONCLUSIONS

MCC is a very rare aggressive carcinoma. The incidence and mortality of MCC increase with age. The benefit of adjuvant therapy in early stage is not clear; prospective studies are needed on this subject.

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### Conflicts of interest

There are no conflicts of interest.

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