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Merkel cell carcinoma in Taiwan

A series of 24 cases and literature review

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Abstract

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine carcinoma of the skin. The available reports of MCC in Asia are limited; in this study, we report the largest series of MCC in Taiwan to date.

The series is composed by 24 pathologically proven MCC cases, which were retrospectively reviewed in Chang Gung Memorial Hospital in Taiwan between 2000 and 2018.

The tumor occurred predominantly in men (80%) and in the elderly (median 74.8 years). Twenty-one patients had locoregional MCC and 3 had metastatic MCC at the time of diagnosis. Patients with pathologically proven negative nodes by sentinel lymph node biopsy (SLNB) showed better survival time than those without SLNB in 16 clinically node-negative MCC cases undergoing primary surgery. Salvage surgery for loco-regional recurrence lengthened the survival time and possibly cured recurrent MCC. Palliative chemotherapy with cisplatin and etoposide showed a response rate of 25%, progression-free survival of 3.6 months, and overall survival of 14.8 months in 4 metastatic/recurrent MCC. Avelumab treatment was effective in 1 patient, who achieved a durable disease control.

This observational cohort of MCC patients in Taiwan suggests aggressive surgical intervention including wide excision and lymph node management, salvage operation is critical for early MCC patients, and palliative chemotherapy and immunotherapy showed their efficacy for advanced MCC patients.

Abbreviations: AJCC = American Joint Committee on Cancer, CGMH = Chang Gung Memorial Hospital, LND = lymph node dissection, MCC = Merkel cell carcinoma, MCPyV = Merkel cell polyomavirus, MSS = MCC-specific survival, OS = overall survival, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors, RFS = recurrence-free survival, SEER = Surveillance, Epidemiology, and End Results, SLN = sentinel lymph node, SLNB = sentinel lymph node biopsy, UPMCC = unknown primary MCC, UV = ultraviolet.

Keywords: avelumab, chemotherapy, Merkel cell carcinoma, sentinel lymph node biopsy

1. Introduction

Cyril Toker first described Merkel cell carcinoma (MCC) in 1972. It is a rare, but aggressive, neuroendocrine carcinoma of the skin which is associated with Merkel cell polyomavirus (MCPyV) infection, immunosuppression and ultraviolet (UV) exposure.[1,2] MCC is generally considered a chemotherapy-sensitive disease but the duration of response is limited. Recently, the immune checkpoint inhibitor avelumab, has been shown to be effective and safe in both chemotherapy-refractory[3] and chemotherapy naïve[4] MCC patients raising interest in further research of its efficacy in MCC.

Different epidemiology studies in Western and Asian countries showed a different incidence rate of malignancies such as melanoma, another aggressive skin cancer.[5] Most studies regarding MCC biologic origin, therapeutic strategies and

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outcomes were reported in Western countries, while reports for the disease in Asia are limited.[6–8] Some studies focused on epidemiology, such as prevalence of MCPyV[9] and chronic arsenicism,[10,11] but no study in Taiwan reported data about therapeutic treatments and disease outcomes. Therefore, we report here the largest series of treatment experiences on MCC in Taiwan, providing more epidemiologic data for the disease in Asia.

2. Patients and methods

2.1. Patients

Patients with a pathologically proven MCC diagnosed at Chang Gung Memorial Hospital (CGMH) in Taiwan between 2000 and 2018 were identified and their medical records were retrospectively reviewed. We recorded the following clinicopathological features: age, sex, primary locations, staging, treatment courses, and clinical outcomes. MCC patients were re-staged according to the 8th American Joint Committee on Cancer (AJCC) staging system.[12] This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (201900574B0).

2.2. Treatment options of MCC

Patients with loco-regional MCC underwent local wide excision of the primary MCC with or without lymph node management technique, such as sentinel lymph node biopsy (SLNB) or lymph node dissection (LND). SLNB was performed as we already published in cutaneous melanoma reports.[13,14] Adjuvant chemotherapy or radiotherapy were selected and performed according to physicians' judgement based on the pathologic reports. Palliative chemotherapy (cisplatin and etoposide) and immunotherapy (avelumab) was chosen for patients with inoperable MCC.

2.3. Statistical considerations

Continuous data are presented as median (range), whereas categorical data are presented as a number (percentage). Overall survival (OS) was defined as the time from diagnosis to death by any causes or to last follow-up. MCC-specific survival (MSS) was defined as the time from diagnosis to death due to MCC or to the last follow-up. Recurrence-free survival (RFS) was defined as the date from tumor excision to either recurrence of the tumor, death, or the last follow-up. Progression-free survival (PFS) was defined as the date from first day of treatment to either progression, death, or the last follow-up. The response of tumor to palliative treatment were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. Survival curves were represented using the Kaplan–Meier method. Statistical analyses were performed using GraphPad Prism 6 software.

3. Results

3.1. Patients characteristics

In this study, 24 patients with pathologically proved MCC were retrospectively analyzed. The median age at the time of diagnosis was 74.8 years with a range from 55.5 to 93.6 years. Twenty (83.3%) patients were male, while only 4 (16.7%) were female. The primary tumors' locations were extremities, trunk, and head and neck and accounted for 13 (54.2%), 3 (12.5%) and 6 (25%) patients, respectively, while 2 patients had unknown primary MCC (UPMCC). The patients were divided according to tumor stage, with stage I, II, III, IV accounting for 9 (37.5%), 8 (33.3%), 4 (16.7%) and 3 (12.5%) patients respectively, while local, nodal and metastatic MCC accounted for 17 (70.8%), 4 (16.7%), and 3 (12.5%) patients, respectively (Table 1). The different characteristics between loco-regional and metastatic MCC are summarized in Table 1. The details of staging, treatment, and outcome of 24 MCC patients are summarized in Figure 1.

Table 1

The characteristics of MCC patients (n = 24).

Characteristics	All MCC patients	Loco-Regional MCC	Metastatic MCC
Age, yr [median (range)]	74.8 (55.5–93.6)	74.7 (55.5–93.6)	77.5 (71.7–78.4)
<65	5 (20.8%)	5 (23.8%)	0
65–80	14 (58.3%)	11 (52.3%)	3 (100%)
>80	5 (20.8%)	5 (23.8%)	0
Gender			
Male	20 (83.3%)	17 (81.0%)	3 (100%)
Female	4 (16.7%)	4 (19.0%)	0
Location			
Extremities	13 (54.2%)	12 (57.1%)	1 (33.3%)
Trunk	3 (12.5%)	3 (14.3%)	0
Head and Neck	6 (25%)	5 (23.8%)	1 (33.3%)
Unknown	2 (8.3%)	1 (4.8%)	1 (33.3%)
Stage			
I	9 (37.5%)	9 (42.9%)	
II	8 (33.3%)	8 (38.1%)	
III	4 (16.7%)	4 (19.0%)	
IV	3 (12.5%)		3 (100%)

MCC = Merkel cell carcinoma.

The median follow-up time is 35.2 months with a range of 0.4 to 194.0 months until March 2019. The median OS and MSS for all 24 patients are not reached, while the estimated 5-year OS and MSS are 53.3% and 65.0%, respectively (Fig. 2). The MSS survival curves in stage I-IV is shown in Figure 3.

3.2. Surgical intervention in early MCC (stage I-III)

Of the 24 patients, 21 of them had loco-regional diseases at time of diagnosis. Two patients, due to the old age, received a supportive care only while the remaining 19 patients received primary wide excision of the tumor with or without lymph node management. Three patients underwent regional lymph node dissection for clinically lymph node-positive MCC. In 19 patients undergoing locoregional resection, the median RFS for stage II and III MCC were 15.2 and 12.8 months, respectively (Fig. 4A), while stage I MCC patients had excellent outcomes, as none of the 8 patients experienced recurrence after primary surgery. Although we found no significant difference in RFS between stage II and III patients after receiving surgery, the stage II patients had a better trend of MSS than stage III patients (Fig. 4B).

Among 16 patients with clinically node-negative MCC undergoing surgery, SLNB was performed in 3 patients, while nodal observation alone was performed in 13 patients. While there was no recurrence in all patients undergoing SLNB, in contrast, 6 of 13 patients subjected to nodal observation experienced recurrences. SLNB procedure showed a trend of improved RFS and MSS although significance was not reached due to the limited number of cases (Fig. 5A-B).

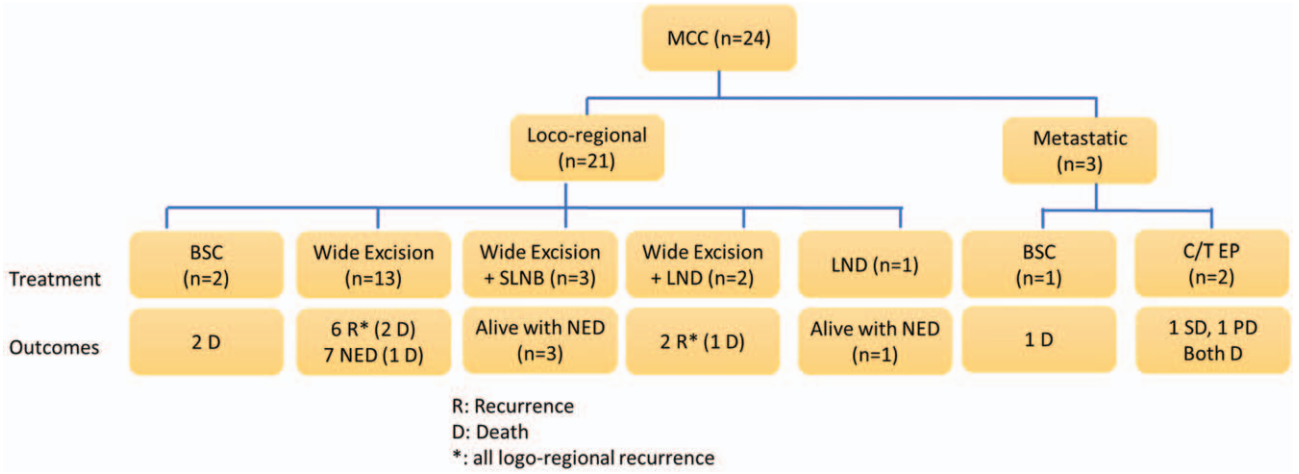

Figure 1. The staging, treatment, and outcome in 24 Merkel cell carcinoma patients. BSC = best supportive care, C/T = chemotherapy, D = death, EP = etoposide and cisplatin, LND = lymph node dissection, MCC = merkel cell carcinoma, NED = no evidence of disease, PD = progression disease, R = recurrence, SD = stable disease, SLNB = sentinel lymph node biopsy.

In the 6 patients who had recurrences, the median RFS was 11.0 months (range: 4.2–21.1 months) and all of them had loco-regional recurrences. Salvage operation was performed in selected patients and 4 of them are alive without evidence of disease until last follow-up (Fig. 1).

3.3. Palliative treatment in advanced MCC

Among 3 patients with metastatic MCC, 1 received supportive care and 2 underwent palliative chemotherapy. Among patients that underwent surgery, 2 experienced recurrence after the operation and received palliative chemotherapy. In total, 4 patients underwent palliative chemotherapy with cisplatin and etoposide in our current study, 1 patient (25%) had partial remission with a PFS of 11.9 months, 1 patient (25%) had a stable disease with a PFS of 4.4 months and 2 patients (50%) had a progressive disease with a PFS of 2.5 and 2.7 months, respectively. The estimated PFS and OS after starting palliative chemotherapy in all 4 patients were 3.6 and 14.8 months, respectively (Fig. 6). One patient has received avelumab for 10.6 months with a response of stable disease until the end of this study.

4. Discussion

Our study is the largest series of MCC in Taiwan available to date. Here, we reported 24 MCC patients, of which 21 had loco-regional disease and the 3 remaining metastatic disease. Our results suggest that an aggressive surgical intervention including wide excision and lymph node management is critical for early MCC to achieve better survival rates. Moreover, salvage operation is effective for MCC patients with loco-regional recurrence. Palliative chemotherapy with cisplatin and etoposide showed limited activity in metastatic MCC, while avelumab immunotherapy showed achieved a durable response in one patient.

In our cohort, MCC occurred predominantly in men (80%) and the old-aged (median 74.8 years), which is consistent with previous reports in US[12,15–17] but not in Asian countries. The differences in Asian countries might result from a bias due to the

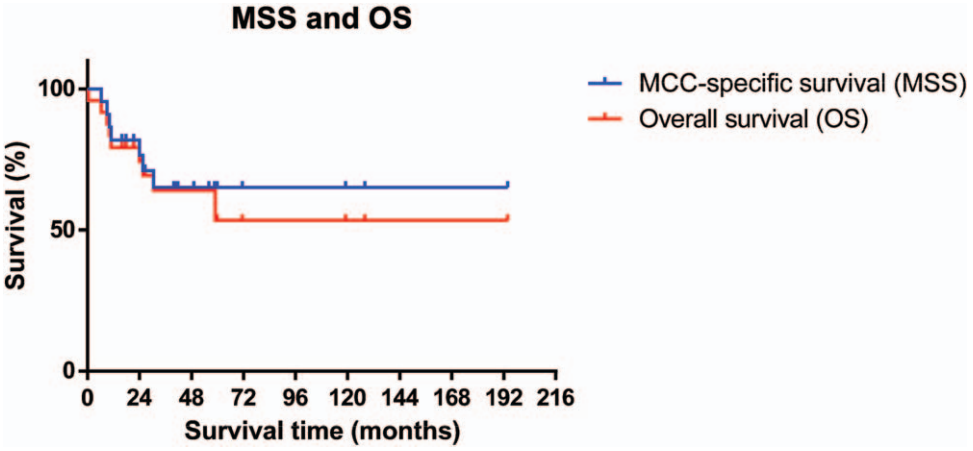

Figure 2. MCC-specific survival and overall survival in all MCC patients. MCC = Merkel cell carcinoma.

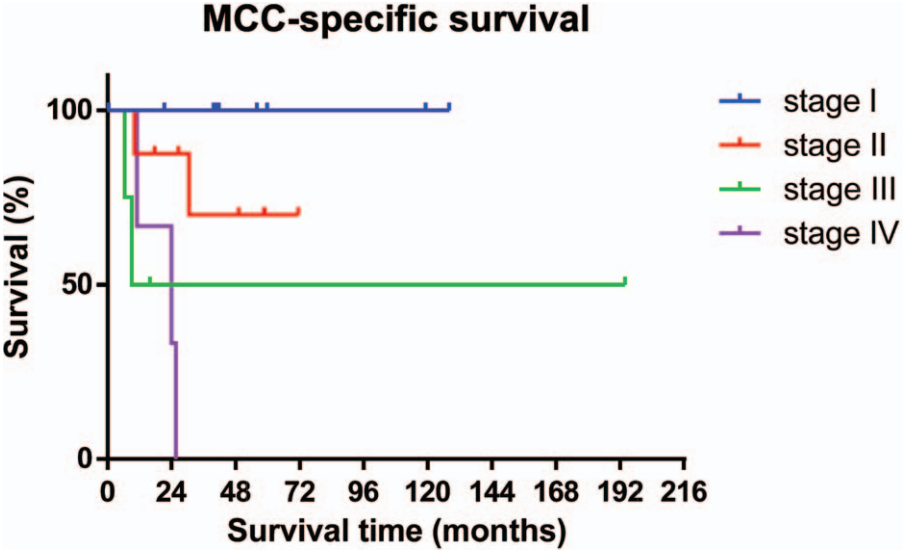

Figure 3. MCC-specific survival in stage I-IV MCC patients. MCC = Merkel cell carcinoma.

small numbers of patients analyzed in most reports. In terms of staging, the local, nodal, and metastatic diseases accounted for 70.8%, 16.7%, 12.5%, respectively, which is consistent with a large report of 9387 MCC, showing that around half of patients had local MCC and only 13.5% had metastatic MCC.[18] This finding suggests that the tumor is relatively slow growing and easily identified by inspection. Although most MCC occurred in the body extremities in our study, none of the patients developed the disease in areas where acral melanoma is frequently found, indicating a different etiology between melanoma and MCC in Asian countries.[5] MCC frequently occurred in extremities and in the head and neck area, which are typical sun exposed areas. On the other hand, the frequency of appearance in the trunk was reduced, implying that MCC might be associated with chronic sun and UV exposure in our series.

The benefit of SLNB for clinically node-negative MCC was unknown at the beginning of our series period, so the procedure was not routinely performed in our patients. Among 16 patients with clinically node-negative MCC undergoing surgery in current study, patients undergoing SLNB had better survivals than those undergoing local surgery with nodal observation only. This result is consistent with a previous report showing that patients with clinically local-only disease and pathologically proven negative nodes had better survival outcomes than those who only underwent clinical nodal observation.[19] Moreover, another study demonstrated that SLNB procedure showed better survival than nodal observation in 1193 MCC patients from the Surveillance, Epidemiology, and End Results (SEER) registry between 2003 and 2009.[20]

In addition, in an Australian study, both microscopic and macroscopic metastatic nodal MCC did not showed significant differences in RFS and OS and were predictor of a poor prognosis.[21] Thus, our and other studies suggests that SLNB for microscopic metastasis of MCC should be performed routinely and should be a standard of care in our daily practice for clinically node-negative MCC. This practice will enable us to stage MCC accurately and to choose the following treatment. Consistently with this view, observation studies reported that pathologic

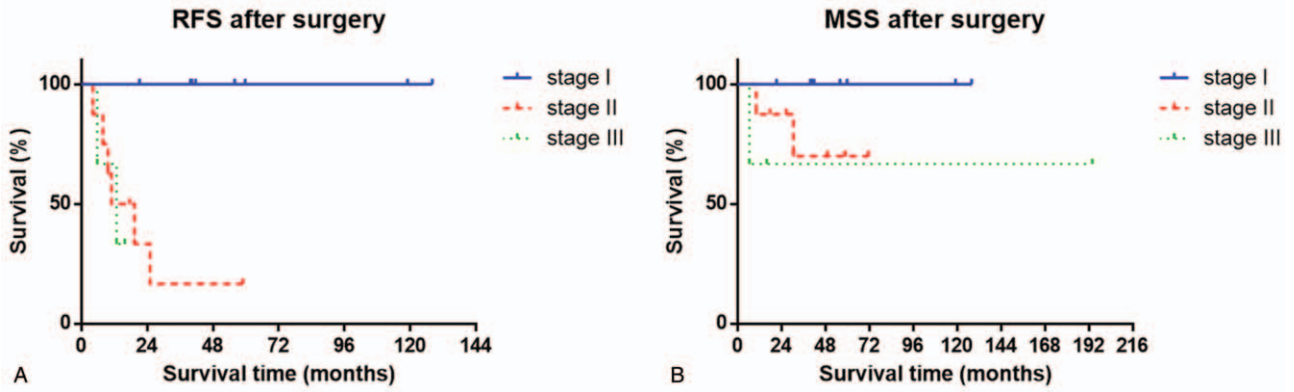

Figure 4. Recurrence-free survival (A) and MCC-specific survival (B) in stage I-III MCC patients undergoing primary surgery. (A) The median RFS for stage I, II, III MCC were not reached, 15.2, 12.8 months, respectively. (B) The median MSS was not reach in stage I, II, III MCC patients. MCC = Merkel cell carcinoma, MSS = MCC-specific survival, RFS = recurrence-free survival.

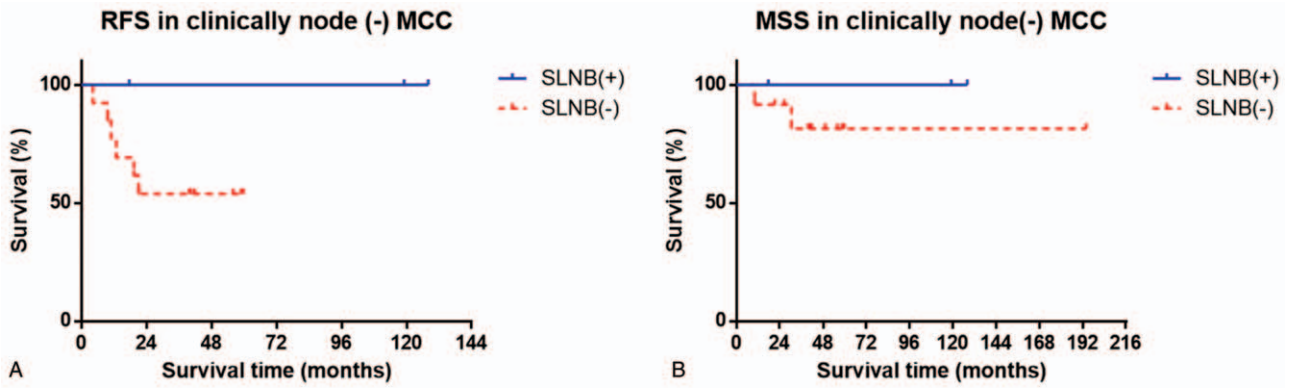

Figure 5. Recurrence-free survival (A) and MCC-specific survival (B) in stage I-III MCC patients undergoing primary surgery. (A) The median RFS for stage I, II, III MCC were not reached, 15.2, 12.8 months, respectively. (B) The median MSS was not reach in stage I, II, III MCC patients. MCC = Merkel cell carcinoma, MSS = MCC-specific survival, RFS = recurrence-free survival.

nodal evaluation is increasingly commonly performed for MCC patients.[18]

The positive rate of sentinel lymph node (SLN) in MCC patients in previous studies ranged from 11% to 57%.[22–27] This pronounced difference among the studies is probably due to the lack of routine use of immunohistochemistry, which allow the identification of micro-metastases in the SLN composed of rare single cells, which are normally missed by other routine tests, such as hematoxylin and eosin staining. Thus, the absence of immunohistochemistry staining could explain why none of the 3 patients undergoing SLNB had positive SLN. However, none of them experienced recurrence after the surgery: this indicate that the SLNB procedure is accurate and reliable in our current study.

Another issue regarding the possibility of performing SLNB is whether all MCC patients should receive it, or whether SLNB could be omitted for some patients showing a lower risk of nodal metastasis. In a study describing 95 MCC patients with 97 MCC who underwent SLNB, positive SLN was identified in 45.2% of successful SLN biopsies. The positivity was associated with a higher tumor size, thickness, and an increase rate of mitosis and infiltration. None of the subgroup showed less than 15% of positive SLN. Therefore, they concluded that SLNB should be considered in all MCC patients.[27] This recommendation was confirmed by another study enrolling 8044 MCC patients to evaluate the relationship between primary tumor sizes and nodal metastases. This study found a 14% risk of nodal metastases for small tumors (0.5 cm) and an increased risk for larger sizes of tumors, with the number of nodal involvement strongly correlating with a shorter OS, suggesting that pathologic nodal evaluation should be considered in all MCC patients.[28] In contrast, another study showed that primary tumor size could not predict nodal involvement but they supported the idea that SLNB should be performed for all primary MCC, because the tumor has metastatic potential at all sizes.[29] In conclusion, all our cited studies suggest that nodal evaluation should be performed in all MCC, regardless of the size.

In previous reports on patients with stage III MCC, patients for which the primary site was unknown had better prognosis than patients with a known primary site.[30,31] In another report, patients with stage IIIB UPMCC demonstrated a longer OS than those with MCC with a known primary site at the same stage (2-year OS: 76.9% vs 36.4%.).[32] In a larger series,

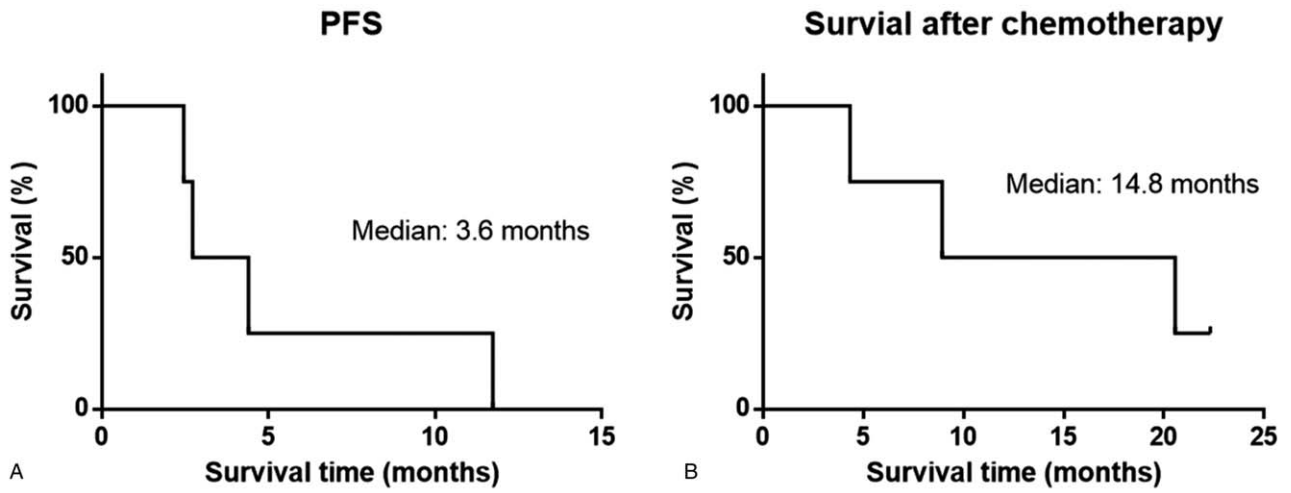

Figure 6. PFS (A) and OS (B) in 4 patients undergoing palliative chemotherapy with cisplatin and etoposide. Both PFS and OS were calculated from the first date of chemotherapy. MSS = MCC-specific survival, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival.

336 cases with UPMCC showed better OS than those with concurrent primary MCC (estimated 5-year OS: 42 vs 27%).[12] In our series, 1 patient had UPMCC and 3 had nodal-positive primary MCC. No recurrence was found in the UPMCC patient after 15.9-month follow-up. In contrast, 2 of 3 nodal-positive primary MCC patients died of MCC with OS of 9.0 and 6.4 months, respectively, while the third patient is alive but had recurrence 12.8 months after surgery. In our current study, the patient with UPMCC underwent LND followed by chemo-radiotherapy, as in the treatment of UPMCC, most of patients undergo LND followed by either radiotherapy or chemotherapy since they tend to have better outcomes than those undergoing LND only.[33]

In current study, we found salvage operation might benefit selected patients with recurrent MCC. All of 6 patients who had recurrences after wide excision and nodal observation had loco-regional recurrences, therefore, salvage operation was performed in these selected patients and 4 of them are alive without evidence of disease until last follow-up. These findings are compatible with a previous study reported by the University of Texas which encourage aggressive salvage surgery for local or nodal recurrent MCC from experience of 46 patients with recurrent MCC[34]

There are some limitations in our current study. First, as this is a retrospective study, it is accompanied by certain bias due to data collection. For example, certain patients did not follow-up regularly after the operation, and this may overestimate the RFS measure. However, we point out that the OS recorded in the current study is accurate because data from the Taiwan Cancer Registry supplemented the eventual lack of medical record. Second, the number of available MCC patients is limited due to rarity of MCC and this limit the statistical significance of the data that we present in this report, although we observe different trends in the examined patients.

In conclusion, aggressive surgical intervention including wide excision and lymph node management, such as SLNB is critical for early MCC treatment. Salvage operation is effective for MCC patients with loco-regional recurrence. Palliative chemotherapy showed limited activity in metastatic MCC and immunotherapy with avelumab achieved durable disease control in one patient.

Author contributions

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