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RESEARCH ARTICLE

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Mesenchymal chondrosarcoma: A Japanese Musculoskeletal Oncology Group (JMOG) study on 57 patients

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Background: This study aimed to elucidate the clinical features and prognostic factors of mesenchymal chondrosarcoma (MCS) and investigate optimal treatment strategies.

Methods: Data from 57 patients with MCS were collected from a Japanese Musculoskeletal Oncology Group (JMOG) and retrospectively analyzed.

Results: Data from 29 males and 28 females were collected. Primary tumor sites were the head and neck (7 patients), trunk (35 patients), and extremities (15 patients). The tumors originating in the trunk were significantly associated with a worse OS compared with those originating at the other sites in all patients and those with localized disease ($P = 0.020$ and $P = 0.019$, respectively). In patients with localized disease, the tumors originating in the head and neck were significantly associated with better OS and MFS compared with those originating in the trunk ($P = 0.024$ and $P = 0.014$, respectively). Positive surgical margin was significantly correlated with the worse LRFS ($P = 0.018$). Adjuvant chemotherapy exhibited a clear trend toward improved OS when MCS was localized in the trunk or extremities ($P = 0.057$).

Conclusions: Adequate surgery is considered to be the mainstay of treatment for localized MCS. Prognosis was different depending on the site of tumor origin.

KEYWORDS

clinical features, mesenchymal chondrosarcoma, prognostic factors

1 | INTRODUCTION

Mesenchymal chondrosarcoma (MCS), first described by Lichtenstein and Bernstein in 1959, is a rare high-grade malignancy of the bone or soft tissues.[1] MCS exhibits a unique biphasic histology, which includes a well-differentiated cartilaginous matrix and a small, undifferentiated, round cell component. Several studies have described the clinical characteristics of MCS.[2–17] MCS differs from conventional chondrosarcoma (CCS) in terms of the patient age distribution, primary site, and prognosis. MCS typically occurs in young adults, and approximately 30% of cases occur in the soft tissues. In contrast, most CCS patients are aged ≥50 years and extraosseous CCS accounts for <1% of all cases.

The European Musculoskeletal Oncology Society (EMSOS) recently reported prognostic factors for 113 cases with MCS and concluded that a complete excision and adjuvant chemotherapy was considered to be the standard treatment for localized

This study was performed at Tokyo University.

disease.[16] However, there are only two studies to date that could analyze the clinical characteristics and prognostic factors in a sample size exceeding 50 patients with MCS.[16,18] Consequently, our understanding of MCS is still extremely limited in terms of the clinical characteristics, treatment outcome, prognostic factors, and in particular, the roles of chemotherapy and radiation therapy.

Therefore, we conducted a Nation-wide survey on patients with MCS in cooperation with the Japanese Musculoskeletal Oncology Group (JMOG). This study aimed to elucidate the clinical characteristics, treatment outcomes, prognostic factors, and roles of chemotherapy and radiation therapy in MCS.

2 | PATIENTS AND METHODS

Our study included 57 patients with histologically confirmed MCS diagnosed during 1980-2013. These patients were treated at 21 JMOG-affiliated institutions, including the National Cancer Center (nine patients), Fukushima Medical University (seven patients), Keio University (six patients), Cancer Institute Hospital (five patients), Chiba Cancer Center (four patients), and Kanazawa University (four patients). Two patients were further recruited from each of the following institutions: Hokkaido Cancer Center, Hyogo Cancer Center, Nagoya City University, Osaka University, Kobe University, Kyoto University, and Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital. One patient was recruited from each of the following institutions: Himeji Red Cross Hospital, Hiroshima University, Nagoya University, Nara Medical University, Niigata University, Teikyo University, Tokyo University, and Osaka National Hospital. This study was approved by the Institutional Review Board of each participating hospital. All diagnoses were histologically confirmed by specialist pathologists in each hospital.[19]

Patients received multi modal treatment, including surgery, radiation therapy, and chemotherapy. Excision of the primary tumor with a negative surgical margin was attempted whenever possible. The microscopic surgical margin was determined histologically using the resected specimens and was classified as either negative (no tumor cells on the inked margin) or positive (tumor cells on the inked margin). Radiation therapy was administered to patients at risk of local recurrence or to those for whom surgical excision was not indicated because of tumor progression. The tumor response for chemotherapy was assessed following the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[20]

All time-to-event endpoints were calculated using the Kaplan-Meier method. Survival analysis was calculated from the day of diagnosis, and potential prognostic factors were identified by univariate analysis using the log-rank test. Independent prognostic factors were evaluated using the Cox proportional hazards regression model. Proportions of variables among the sites of origin were compared using chi-square tests. A two-tailed probability (P) value of <0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY).

3 | RESULTS

3.1 | Patient characteristics

The study group comprised 29 males (51%) and 28 females (49%) with a mean age of 33 years (range: 6-73 years) (Table 1). Thirty-three (58%) bone and 24 (42%) soft tissue tumors were identified. Seven tumors (12%) were located in the head and neck, 35 (62%) in the trunk, and 15 (26%) in the extremities. Forty patients (70%) presented with localized disease, and 17 patients (30%) presented with metastatic disease.

3.2 | Treatment

Of the 40 patients with localized disease, 34 (85%) underwent limb-sparing surgery. Of these 34 patients, information regarding the surgical margin was available in 25 patients (74%), which revealed that the margin was negative in 15 patients and positive in 10 patients. Neoadjuvant and/or adjuvant chemotherapy was administered to 13 (33%) of those 34 patients (seven patients in both neoadjuvant and adjuvant settings, five in an adjuvant setting, and one in a neoadjuvant setting). The chemotherapeutic agents administered included doxorubicin, ifosfamide, cisplatin, carboplatin, etoposide, cyclophosphamide, vincristine, methotrexate, and actinomycin-D. All 13 patients received doxorubicin, and 8/13 (62%) also received ifosfamide. Of the four patients who could be assessed for their response to neoadjuvant chemotherapy, a partial response (PR) was noted in one (25%) patient and stable disease (SD) was noted in the remaining three (75%) patients. Patients with PR or SD received doxorubicin and cisplatin with methotrexate or ifosfamide. Of the 34 patients, 10 (29%) patients received adjuvant radiation therapy. Six patients with advanced localized disease received carbon ion radiation therapy (CIRT, $n = 4$) or photon radiation therapy ($n = 2$) for primary sites without the tumor excision.

Seventeen patients exhibited an advanced stage of disease with distant metastases at diagnosis, of which 16 underwent chemotherapy. Among these patients, 15 (94%) received doxorubicin-based chemotherapy and one (6%) received high-dose ifosfamide therapy. The responses to palliative chemotherapy for the 13 assessable patients were PR in four patients (31%), SD in six patients (46%), and progressive disease (PD) in three patients (23%).

3.3 | Treatment outcomes and prognostic factors

3.3.1 | All cases

The mean follow-up time was 70 months (range: 4-306 months). The estimated 5-year and 10-year overall survival (OS) rates were 66% and 56%, respectively (Fig. 1A). The estimated 5-year and 10-year

TABLE 1 Patient characteristics

	N
Total	57
Age at diagnosis (years), mean (range)	33 (6-73)
Sex	
Male	29
Female	28
Size of tumors (cm), mean (range)	8 (3-15)
Bone or soft tissue	
Bone	33
Soft tissue	24
Site of origin	
Head and neck	7
Bone	
Skull	1
Jaw	1
Cervical spine	2
Soft tissue	
Cerebral meninge	1
Skull base	1
Paranasal cavity	1
Trunk	35
Bone	
Pelvis	9
Rib	7
Sacrum	5
Thoracic spine	2
Soft tissue	
Buttock	3
Retroperitoneum	3
Extramedullary spinal cord lesion	2
Abdominal wall	1
Posterior mediastinum	1
Pelvic cavity	1
Vaginal wall	1
Extremity	15
Bone	
Tibia	2
Fibula	1
Femur	1
Humerus	1
Ulna	1
Soft tissue	
Lower leg	5
Thigh	4
Metastasis at presentation	
Yes	17

metastasis-free survival (MFS) rates were 26% and 17%, respectively (Fig. 1B). The univariate analysis revealed that patients with metastasis at initial presentation, at tumors of trunk origin, and without neoadjuvant and/or adjuvant therapy were significantly correlated with worse OS (Table 2). Multivariate analysis revealed that metastasis at initial presentation [hazard ratio (HR) for "Yes" versus "No," 4.73; 95% confidence interval (CI): 1.63-13.76; $P = 0.004$] and trunk origin (HR for "Yes" versus "No," 3.91; 95% CI: 1.24-12.29; $P = 0.020$) were significantly associated with a worse OS.

3.3.2 | Localized cases

The mean follow-up time in 40 patients with localized disease was 87 months (range: 4-306 months). Of these 40 patients with localized disease, 17 developed only metastatic recurrence (MR), three developed only local recurrence (LR), and nine developed both MR and LR. Among the 17 patients who developed only MR, five (29%) developed disease progression in the lung, three (18%) in the bone, and nine (53%) at multiple sites. In addition, 5/17 (29%) developed MR within the first 2 years following treatment,

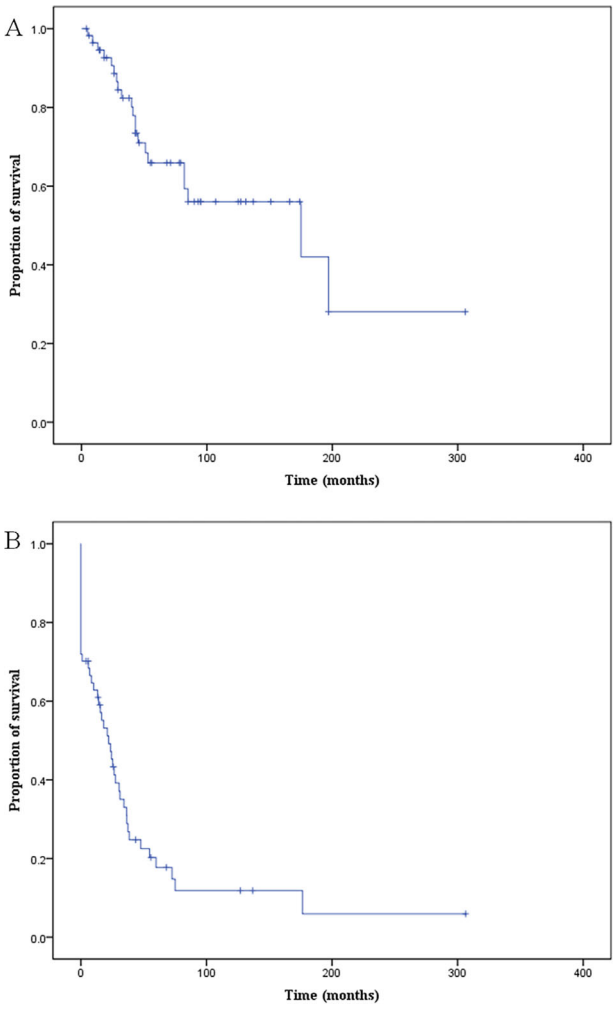

FIGURE 1 (A) Kaplan-Meier survival curve for the overall survival of all patients. (B) Kaplan-Meier survival curve for the metastatic-free survival of all patients

TABLE 2 Univariate and multivariate analysis for overall survival in all patients

			Univariate	Multivariate			
	N	5-year overall survival	*P* value	HR	95%CI		*P* value
Age at diagnosis							
≥31	31	55.5	0.157	1.41	0.56	3.51	0.466
<30	26	76.9		Reference			
Sex							
Male	29	62.1	0.928	1.67	0.67	4.21	0.274
Female	28	70.7		Reference			
Size							
≥8	21	43.8	0.227				
<8	25	67.9					
Bone or soft tissue							
Bone	33	62.0	0.604				
Soft tissue	24	71.8					
Site of origin							
Trunk	35	56.4	0.005	3.91	1.24	12.29	0.020
Other sites	22	79.4		Reference			
Metastasis at presentation							
Yes	17	28.2	<0.001	4.73	1.63	13.76	0.004
No	40	79.2		Reference			
Neoadjuvant and/or adjuvant chemotherapy							
Yes	13	90.9	0.021	0.45	0.09	2.13	0.312
No	44	57.4		Reference			

HR, hazard ratio; CI, confidence interval.

7/17 (42%) between 2 and 5 years following treatment, and 5/17 (29%) ≥5 years following treatment.

The 5-year and 10-year OS were 79% and 67%, respectively. Patients who were treated at the primary site by surgery exhibited a significantly better 5-year OS than those treated by radiation therapy (P <0.001). Multivariate and univariate analyses showed a significant association between the worse OS and trunk origin (HR for "Yes" versus "No," 12.35; 95% CI: 1.50-101.73; P = 0.019) (Table 3 and Fig. 2A). The 5-year and 10-year MFS were 37% and 24%, respectively. The univariate analysis revealed that the trunk origin have a significantly worse MFS than that at other sites (P = 0.046) (Fig. 2B). The 5-year local-recurrence free survival (LRFS) rate was 62%. The univariate analysis revealed that a tumor size of ≥8 cm and a positive surgical margin were significantly associated with a worse LRFS (P = 0.018, P = 0.009, respectively). CIRT for primary sites without excision exhibited good short-term local control ability with a 2-year LRFS of 100% in four patients. However, three of these patients (75%) finally developed LR after a mean interval of 31 months (range: 28-36 months).

The univariate analysis also revealed the neoadjuvant and/or adjuvant chemotherapy to exhibit a trend toward improvement in OS, although this was not statistically significant (P = 0.107) (Table 3) and did not correlate with significantly better MFS (P = 0.411) or LRFS (P = 0.983).

Because the head and neck origin exhibited significantly better OS and MFS than the trunk origin (P = 0.024 and 0.014, respectively) and worse LRFS than the extremity origin (P = 0.013) (Fig. 3A-C), we compared patient demographics and treatment data with the sites of origin to determine differences between the head and neck origin and other sites (Table 4). Consequently, we could demonstrate that the head and neck origin was significantly associated with a higher rate of positive surgical margin (P = 0.021) and younger age (P = 0.023). This higher rate of positive surgical margin may be one of the main reasons for the high rate of LR in patients with MCS originating in the head and neck compared with that in patients with MCS originating in other sites.

4 | DISCUSSION

The rarity of MCS makes it difficult to draw conclusive statements regarding its clinical characteristics, prognostic factors, and ideal treatment. Our data revealed that the treatment outcomes were different depending on the site of tumor origin. Tumors originating in the trunk were associated with a significantly worse OS and MFS, and those originating in the head and neck exhibited a better OS and MFS despite difficult local control. We also found that a tumor size of ≥8 cm and a positive surgical margin were significantly correlated with worse LRFS. CIRT exhibited a short-term benefit in terms of local control.

TABLE 3 Univariate and multivariate analysis for overall survival in patients with localized tumors

			Univariate	Multivariate			
	N	5-year overall survival	*P* value	HR	95%CI		*P* value
Age at diagnosis							
≥31	19	67.8	0.329	1.28	0.37	4.44	0.694
<30	21	88.5		Reference			
Sex							
Male	19	78.3	0.461	1.18	0.33	4.15	0.802
Female	21	80.4		Reference			
Size							
≥8	15	56.3	0.152				
<8	14	83.3					
Bone or soft tissue							
Bone	22	73.5	0.438				
Soft tissue	18	86.9					
Site of origin							
Trunk	24	67.5	0.002	12.35	1.50	101.73	0.019
Other sites	16	93.3		Reference			
Neoadjuvant and/or adjuvant chemotherapy							
Yes	13	90.9	0.107				
No	27	72.6					
Surgical margin							
Positive	10	88.9	0.123				
Negative	15	90.9					

HR, hazard ratio; CI, confidence interval.

In our series, the 5-year and 10-year OS rate were 66% and 56%, respectively, among all patients, which were consistent with the previously reported unsatisfactory outcomes (5-year OS rate: 51-70% and 10-year OS rate: 37-67%).[14,16,17] Among the 40 patients with localized disease, the 5-year OS was 79% and 12 (29%) patients developed LR in our cohort. These data suggest that patients with MCS can have a long survival period after LR and indicate the requirement of a long-term follow-up. Of these 40 patients, 29% developed MR ≥5 years after treatment, also indicating that a long-term follow-up is highly recommended for patients with MCS. A tumor size of ≥8 cm was a significant predictor of worse LRFS. This result indicates that an early diagnosis and treatment is important for patients with MCS. We also confirmed previously published results stating that a clear margin correlates with a better LRFS.[16] This suggests that a negative margin is an important goal to pursue for patients with localized MCS.

The impact of the tumor site on survival in patients with MCS is controversial. Better survival in patients with MCS in the jaw bone[10] and worse survival in patients with MCS in the axial origin[5] have been reported. However, the largest series from EMSOS could not demonstrate a difference in prognosis among the sites of origin.[16] In the present study, the trunk origin was a significant predictor of unfavorable OS and MFS. These results may be attributed to the larger tumor size resulting from a delay in diagnosis due to the difficulty in early detection of tumors originating in the trunk (Table 4). On the other hand, in the present study, the head and neck origin was associated with a better OS and MFS despite the high rate of LR. One of the main reasons for the high rate of LR in the head and neck in our series was a high rate of positive surgical margin, which may be due to the difficulty in achieving a clear margin at this site and the lack of awareness to resect with a sufficient margin by the treating physicians. Better OS and MFS in the head and neck origin may be explained by a smaller tumor size and earlier detection. In addition, considering the difference in the tumor backgrounds, such as younger patients with MCS in the head and neck, the biological nature may be different among the sites of origin.

This difference in clinical behavior between the head and neck origin and other sites in patients with MCS was quite similar to that observed in patients with osteosarcoma. Several reports have shown that osteosarcoma of the head and neck is associated with a better OS or MFS and worse LRFS than that of the other sites and that the clinical utility of adjuvant chemotherapy is clear in patients with osteosarcoma of the extremities or trunk but remains controversial in those with osteosarcoma of the head and neck.[21–25] Consequently, we performed additional analysis to investigate the impact of adjuvant chemotherapy on the survival of patients with localized MCS of the extremities and trunk. We could not show a significant improvement in OS potentially because of the small number of cases involved. However, there was a trend toward a better OS in patients

receiving neoadjuvant and/or adjuvant chemotherapy ($P = 0.057$, Fig. 4). Although further investigation with a greater number of cases is required, this result suggests that MCS originating in the trunk or extremities may undergo more frequent microscopic metastasis and be better adapted for adjuvant or neoadjuvant chemotherapy than MCS originating in the head and neck.

The role of chemotherapy has not been sufficiently investigated. The MD Anderson Cancer Centre analyzed 37 cases but failed to show a significant impact of adjuvant chemotherapy on OS, MFS, and LRFS.[17] In contrast, Cesari et al. and EMSOS found that chemotherapy was associated with a better OS and disease-free survival.[12,16] In the present study, neoadjuvant and/or adjuvant chemotherapy exhibited a clear trend toward improved OS when MCS was localized in the trunk or extremities. Moreover, moderate to good responses to chemotherapy were also recorded in a neoadjuvant or palliative setting (PR in five and SD in nine out of 17 patients). We believe that the establishment of an effective adjuvant chemotherapy regimen is necessary. Although doxorubicin for MCS was considered to be an attractive candidate agent in our study as well as that for other bone or soft tissue sarcomas, new agents, such as trabectedin for translocation-related sarcoma, may help improve the survival rate of MCS.[26,27]

The role of radiation therapy in patients with MCS has not been sufficiently investigated to date. Prior to the present study, there are

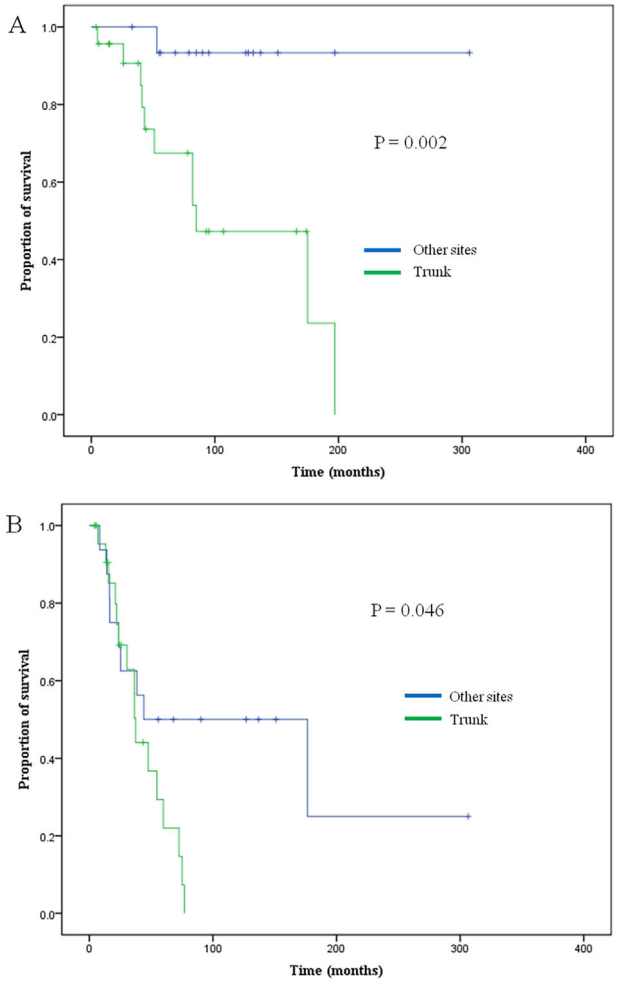

FIGURE 2 (A) Kaplan-Meier survival curve for the overall survival of localized patients comparing the tumors originating in the trunk and those originating in other sites. (B) Kaplan-Meier survival curve for the metastatic-free survival of localized patients comparing the tumors originating in the trunk and those originating in other sites

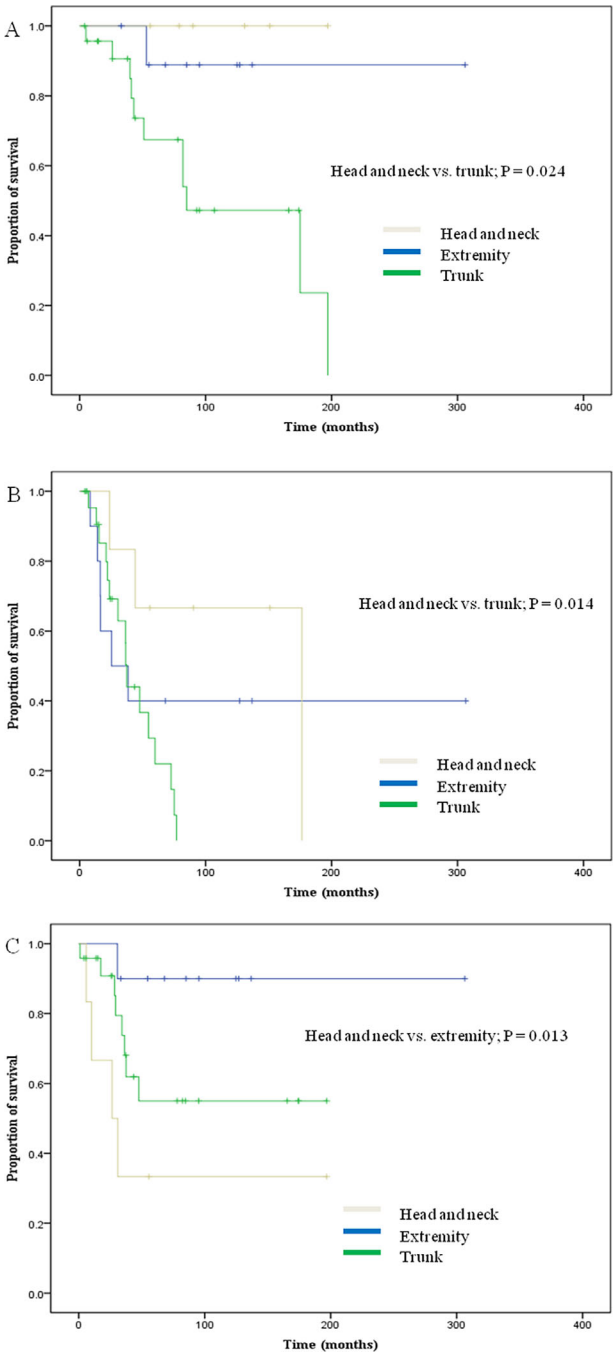

FIGURE 3 (A) Kaplan-Meier survival curve for the overall survival of localized patients comparing the sites of origin. (B) Kaplan-Meier survival curve for the metastatic-free survival of localized patients comparing the sites of origin. (C) Kaplan-Meier survival curve for the local recurrence-free survival of localized patients comparing the sites of origin

TABLE 4 Comparison among the sites of origin

	Head and neck	%	Trunk	%	Extremity	%	*P* value
Total	7		35		15		
Sex							
Male	5	71	13	37	11	73	0.246
Female	2	29	22	63	4	27	
Age							
≥31	1	14	22	63	8	53	0.023
<30	6	86	13	37	7	47	
Size							
≥8 cm	1	50	19	61	5	39	0.900
<8 cm	1	50	12	39	8	61	
Bone or soft tissue							
Bone	4	57	22	63	6	40	0.954
Soft tissue	3	43	13	37	9	60	
Metastasis at initial presentation							
Yes	1	14	11	31	5	33	0.337
No	6	86	24	69	10	67	
Surgical margin							
Positive	3	100	8	44	2	15	0.021
Negative	0	0	10	56	11	85	
Adjuvant chemotherapy							
Yes	2	29	5	14	6	40	0.698
No	5	71	30	86	9	60	
Adjuvant radiation therapy							
Yes	2	29	5	14	2	13	0.322
No	5	71	30	86	13	87	

Data on tumor size were missing from eleven patients. *P* value was calculated by comparing the head and neck with the trunk and extremity.

no reported investigations on the efficacy of CIRT for MCS. CIRT was effective and could be the first choice of curative treatment in some subtypes of sarcoma.[28,29] Our study suggests that CIRT may confer a short-term benefit for local control, particularly for patients with unresectable tumors, however, in most cases, long-term local control was not achieved. Further data is needed to investigate the long-term benefit of CIRT for MCS.

In conclusion, adequate surgery is considered to be the mainstay of treatment for localized MCS, and early diagnosis and treatment are essential. Prognosis was different depending on the site of tumor origin. We believe that the establishment of an effective adjuvant chemotherapy regimen is necessary to improve survival. Prospective collaborative studies are required to define the role of adjuvant chemotherapy or radiation therapy for MCS.

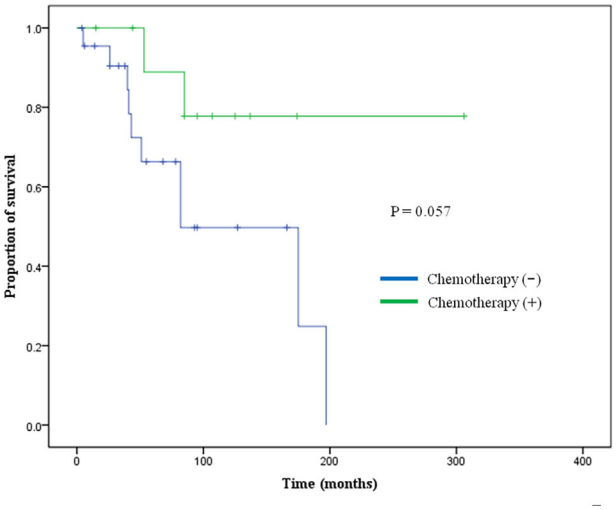

FIGURE 4 Kaplan-Meier survival curve for the overall survival of localized patients in the extremities and trunk comparing those receiving neoadjuvant and/or adjuvant chemotherapy and those not receiving neoadjuvant and/or adjuvant chemotherapy

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DISCLOSURE OF INTERESTS

We have no disclosure.

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